NATIONAL TECHNICAL GUIDELINES ON ANTI RETROVIRAL TREATMENT

National AIDS Control Programme
Care Support and Treatment Services

October 2018

सत्यमेव जयते
Ministry of Health
Government of India

National AIDS Control Organisation
India's Voice against AIDS
Ministry of Health & Family Welfare, Government of India
www.naco.gov.in

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FOREWORD

HIV/AIDS, which was considered a virtual death sentence just a few decades ago is now a chronic manageable disease. The Key factor responsible for this transformation is introduction of "Anti Retro Viral Therapy" (ART) which has which has bought hope and confidence to the life of thousands of families.Over the years ART has become more accessible, safer and robust.

National AIDS Control Programme under Ministry of Health and Family Welfare, Government of India is committed to work towards ensuring universal access to comprehensive, equitable and stigma free HIV treatment to all people living with HIV along with standard care and psycho-social support. Programme is providing free Anti Retro viral Therapy since April 2004 and has scaled it up significantly since then. Currently more then 12 lakh PLHIV are availing standard HIV care through 540 ART centers and 1100 Link ART centers across the country.

The arena of HIV care and treatment is developing at a fast pace in light of newer scientific evidences and experiences. National AIDS Control Programme has kept its tempo with the advancements and moved in hand to hand with global recommendations. There have been regular updates in guidelines regarding "when to start", "what to start" and "how to monitor". Programme has taken landmark steps recently, keeping benefit of people living with HIV in focus. Adoption of "Test and Treat" policy, availability of simpler and safer regimens, viral load monitoring, HIV Act 2017 are few examples.

With these recent progresses, need was felt for an updated and comprehensive guideline, covering all the aspects and advances of National HIV treatment programme. I congratulate CST Division NACO and team of experts who have dedicatedly worked on this and have put together all the aspects effectively. I hope that this updated "Technical guidelines for Anti-Retroviral Treatment" will serve as a guiding document for ART centers and clinicians providing HIV care both in public as well as private sector, health care workers and programme managers.

(Sanjeeva Kumar)

सत्यमेव जयते

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Message

Since the identification of first case of HIV in year 1986, the Government of India (GOI) has achieved many remarkable milestones in the field of HIV/AIDS care with the help of strong political commitment, active engagement with the civil society and network of positive people and partner agencies. Over the years with four phases of NACP, we have been able to reverse the epidemic in most parts of country with 80% reduction in the estimated incidences of new infections since 1995 (global decline is 47%), and 71% decline also in the number of AIDS-related deaths since 2005 (global average 51%).

A major boon to the programme has been launch of free Anti- Retroviral Therapy (ART) initiative on 1st April, 2004 which has changed the face of National AIDS Control Programme. The National programme has kept pace with international guidelines and scaled programme in phased manner in light of newer evidences. India has adopted Test and Treat policy and currently we are providing free ART to more than 12 lakh PLHIVs through 540 ART centres. In addition to providing free treatment and saving lives of thousands of PLHIVs, NACO is committed to provide quality and stigma free care support and treatment services.

India is signatory to UN strategy of 90:90:90 and aims at ending HIV/AIIDS by 2030. Need of the hour is not only to identify hidden cases but to retain all those who have been initiated on ART. In view of newer initiatives and changing spectrum of disease revision of guidelines was felt across country. This revised Technical Anti-Retroviral guideline provide a comprehensive care package covering clinical monitoring, prophylaxes & treatment of opportunistic infections, ART for adolescents & adults and children. It will help health care workers, programme managers, and all stakeholders to understand the programme and provide rationale treatment to all PLHIVs which further will decrease the transmission and hence end AIDS by 2030.

(Alok Saxena)

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Preface

Starting from launch of free ART programme in April 2004, the Programme has introduced a number of new initiatives for scale up, easy access to services and improving quality of care. The journey during these three decades has been tremendous with evidences of best practices and optimal utilization of resources.
As the programme has evolved, in evidence of new scientific advancement few concepts have become obsolete while newer challenges are spiraling. Along with universal access to comprehensive, equitable, stigma-free care support and treatment services need for providing quality and client satisfaction was felt. This has emanated in to adoption of "Test and Treat "policy, simpler and safer regimens, routine viral load monitoring and differentiated care service delivery model.

These recent guidelines are the updated version of the ART technical guidelines including all recent technical updates. These technical ART guidelines will serve as a guiding tool to all service providers and healthcare professionals in public and private sector to deliver the quality care services to people living with HIV/AIDS.

Eminent experts in the field of HIV care across country from various organizations and program managers have made immense contribution in the National Technical ART guidelines. NACO acknowledges the valuable contributions made by all experts and partners and stake holders and would like to express gratitude for their unremitting support and association with the program. Thus the present updated "National ART technical guidelines" is contained in this document for implementation of ART services in our country and encourage all health care professionals to use this for delivery of ART services.

(Dr. R S Gupta)

Acknowledgement

The Technical ART guidelines serve as a guiding document which help the healthcare professionals under various settings to deliver the quality Anti-Retroviral Treatment services to PLHIV in alignment with the vision of the National Programme. With the recent changes in the treatment strategy, the program felt the need to update the guidelines for better management and sustainable care and treatment for PLHIV with improved services.

This document presents recent expansion and innovations in the ART service delivery. The development and framing of the principles for technical provisions in the guidelines has been carried under the guidance of Technical Resource Group (TRG) for ART.

National AIDS Control Organization (NACO) wishes to thank all stakeholders, experts, program managers and scientists who have contributed to the development and framing of these guiding principles for technical provisions.

The Technical Guideline was developed under the excellent leadership of Shri Sanjeeva Kumar, Addl. Secretary & DG (NACO & RNTCP) and constant support and guidance from Shri Alok Saxena, Joint Secretary, NACO. We place on record our gratitude for Dr. Naresh Goel (DDG Lab Services, IEC & Mainstreaming), Dr. S. Venkatesh (the then Addl-DG, NACO and now DGHS, Officer –In-Charge, MoHFW, Govt of India) and Dr. K S. Sachdeva (the then DDG, NCO and now DDG RNCTP) for their support during development of this Guideline. The contribution by Dr. Shobini Ranjan, (ADG, BTS) is deeply appreciated. Support received from various Programme Division, specially Dr. K. Singh Bhawani, Dr. Asha Hegde and Dr. Pradeep Kumar is highly appreciated.

The Organization is sincerely grateful to the eminent doctors/experts in the field of HIV/AIDS - Dr. S. Rajasekaran who was instrumental in providing vision and insight in drafting the revised guidelines, Dr. S. K Guha (Professor, STM, Kolkata), Dr. S Anuradha (Professor, MAMC, Delhi), Dr. Anju Seth (Professor, Kalawati Saran Children Hospital, Delhi), Dr. Sanjeeva G N (Associate Professor, IGICH, Bangalore) and Dr. Noopur Baijal (Ex- Medical Officer, Kalawati Saran Children Hospital, Delhi) for the stewardship, technical assistance and support in timely completion of the guidelines. The invaluable contribution and continued support of Dr. Sudhir Chawla (Joint Director, Gujarat SACS) and Dr. Jasjit Singh Malhi (Regional Coordinator, Northern states) in completing the guideline are also acknowledged.

National AIDS Control Programme is ever grateful to Dr. B. B Rewari (Scientist, HIV/Hepatitis, WHO, SEARO) for the technical assistance and overall guidance right from conceptualization till the completion of the guidelines. The organization also acknowledge Dr. Nicole Seguy and Dr. Vimlesh Purohit (WHO Representative) for their valuable contribution in these guidelines.

NACO is thankful to leadership of Dr. Timothy Holtz, (Captain, US Public Health Service) Director, Division of Global HIV and TB) US Centers for Disease Control and Prevention (CDC), India office, for persistent contribution in planning and printing of these technical guidelines. The critical technical guidance and assistance was provided by Dr. Reshu Agarwal (Public Health specialist, CDC India) in developing these guidelines, Dr. Sukarma Tanwar (ex-official, CDC India) and Dr. Anwar Parvez (Director Clinical Programs, I-TECH). The contribution by I-TECH team (Dr. Madhuri Mukherjee, Ms. Aarti Chettri, Dr. Malay Shah and Ms. Divya Gulati) and Dr. Rohini Gupta (Ex- Medical Advisor, I-TECH) during the various stages in completion of the guidelines is appreciated.

These guidelines were developed under the overall guidance of Dr. R. S Gupta, Deputy Director General, NACO and would not have been possible without the valuable contribution by all the members of the "CST Division" - Dr. Manish Bamrotiya, Dr. Suman, Mr. Archit Sinha, Dr. Neha Garg, Mr. Mathew Sebastian and Dr. Alice Noreen R. Marak.

Abbreviations

3SD	3 Standard Deviation
3TC	Lamivudine
4S	4 Symptoms TB screening
AAY	Antyodaya Anna Yojana
ABC	Abacavir
ADR	Acquired Drug Resistance
AEB	Accidental Exposure to Blood
AFB	Acid Fast Bacilli
AFP	Alpha-fetoprotein
AGs	Aminoglycosides
AIC	Airborne Infection Control
AIDS	Acquired Immune Deficiency Syndrome
AKI	Acute Kidney Injury
ANC	Ante-natal Care
Anti- TB	Anti- Tubercular
Anti-HBcAg	Antibodies to Hepatitis B core Antigen
anti-HBs	Antibodies to Hepatitis B surface Antigen
Anti-HCV IgG	Antibodies to Hepatitis C Virus Immunoglobulin
APV	Amprenavir
ARSH	Adolescent Reproductive and Sexual Health
ART	Anti-retroviral Treatment
ARV	Anti-retroviral
ASHA	Accredited Social Health Activists
ASPRI	Aspartate aminotransferase (AST)- to- platelet ratio index
AST	Aspartate Transaminase
ATV	Atazanavir

ATV/r	Ritonavir boosted Atazanavir
AUC	Area under the plasma drug concentration versus time curve,
AZT/ZDV	Zidovudine
BCC material	Behaviour Change Communication and Advocacy material
BCG	Bacilli Calmette Guerin
BF	Breast Feeding
BID	Twice Daily Dose
BMI	Body Mass Index
BSA	Body Surface Area
CAP	Community Acquired Pneumonia
cART	Combination ART
CBC	Complete Blood Count
CBNAAT	Cartridge Based Nucleic Acid Amplification Test
CBO	Community Based Organisations
CCC	Community Care Centres
CCR - 5	C-C chemokine receptor type 5
CD4	Cluster of Differentiation 4
CD4 T cells	Cluster of Differentiation T-lymphocyte cell
CD8	Cluster of differentiation 8
CDC	Centre for Disease Control
CG Formula	Cockcroft and Gault Formula
CHB	Chronic Hepatitis B
CKD	Chronic Kidney Disease
CLHIV	Children Living With HIV/AIDS
CMV	Cytomegalovirus infection
CNS	Central nervous system
COE	Centre of Excellence
CP	Continuation Phase
CPT	Co-trimoxazole Preventive Therapy
CrCl	Creatinine Clearance
CSC	Care and Support Centre

C-section	Caesarean section
CSF	Cerebro-Spinal fluid
CT Scan (CAT scan)	Computerized Axial tomography scan
CTX	Co-trimoxazole
CYP	Cytochrome P450
d4T	Stavudine
DAAS	Directly Acting Antivirals
DBS	Dried Blood Sample/Spot
ddC	Zalcitabine
ddI	Didanosine
DLC	Differential Leucocyte Count
DLV	Delavirdine
DNA PCR	Deoxyribonucleic Acid Polymerase Chain reaction
DPT	Diphtheria-Pertussis-Tetanus
DPV	Darunavir
DR-TB	Drug Resistant Tuberculosis
DST	Drug Sensitivity Testing
DTG	Dolutegravir
EBF	Exclusive Breast Feeding
EBV	Epstein–Barr Virus
EC1	Exposure Code-1
EC2	Exposure Code-2
EC3	Exposure Code-3
EDTA	Ethylenediaminetetraacetic acid
EFA	Essential Fatty Acids
EFV	Efavirenz
eGFR	Estimated Glomerular Filtration Rate
EID	Early Infant Diagnosis
ELISA	Enzyme-linked Immune Sorbent Assay
ERF	Exclusive Replacement Feeding
ETV	Etravirine

EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed-dose Combinations
FI	Fusion Inhibitors
FIB	A simple index for estimating hepatic fibrosis
fIPV	Fractional Inactivated Polio Vaccine
FNAC	Fine-needle Aspiration Cytology
FPV	Fosamprenavir
FS	renal Fanconi syndrome
FSW	Female Sex Worker
FTC	Emtricitabine
G6PD	Glucose-6-phosphate Dehydrogenase deficiency
GFR	Glomerular Filtration Rate
GT1	Genotype 1 of Hepatitis C
GT4	Genotype 4 of Hepatitis C
H2RA	H2 Receptor Antagonist
HAART	Highly Active ART
HAV	Hepatitis A Vaccine
Hb	Haemoglobin
HBC	Home Based Care
HBeAg	Hepatitis B e Antigen
HBIG	Hepatitis B Immunoglobulin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HBV DNA	Hepatitis B Virus DNA
HCC	Hepato Cellular Carcinoma
HCP	Health Care Personnel
HCTS	HIV Counselling and Testing Services
HCV	Hepatitis C virus
HCW	Health Care worker
HDL	High Density Lipoprotein

Hep B	Hepatitis B
Hib	Haemophilus influenza type b
HIV	Human Immunodeficiency Virus
HIV DR	HIV Drug Resistance
HIV SC1	HIV Source Code-1
HIV SC2	HIV Source Code-2
HIV-Ab	HIV Antibodies
HIV-TB	HIV and Tuberculosis co-infection
HSR	Hypersensitivity Reaction
HSS	HIV Sentinel Surveillance
HSV	Herpes Simplex Virus
IAP	Indian Academy of Paediatrics
IBBS	Integrated Biological and Behavioural Surveillance
ICDS	Integrated Child Development Services
ICF	Intensified Case Finding
ICTC	Integrated Counselling and Testing Centre
ICU	Intensive Care Unit
ID	Identification
IDU	Injecting Drug User
IEC material	Information, Education and Communication material
IMCI	Integrated Management of Childhood Illnesses
IMNCI	Integrated Management of Neonatal and Childhood Illnesses
IND	Indeterminate
INH	Isoniazid
INV	Indinavir
IP	Intensive Phase
IPT	Isoniazid Preventive Therapy
IPV	Inactivated Poliovirus Vaccine
IRIS	Immune Reconstitution Inflammatory Syndrome
JE	Japanese Encephalitis
LAC	Link ART Centre

LFT	Liver Function Tests
LFU	Lost to Follow-up
LIP	Lymphocytic interstitial pneumonia
LPV	Lopinavir
LPV/r	Ritonavir boosted Lopinavir in ratio 1:4
LPV/r+r	Ritonavir super-boosted Lopinavir in ratio 1:1
LTBI	Latent TB Infection
M.TB	Mycobacterium Tuberculosis
MAC	Mycobacterium Avium Complex
MAOI	Monoamine Oxidase Inhibitors
MCV	Measles Containing Vaccine
MDR TB	Multi-drug-resistant Tuberculosis
MOHFW	Ministry of Health and Family Welfare
MR Vaccine	Measles Rubella Vaccine
MS	Medical Superintendent
MSM	Men having Sex with Men
MTCT	Mother to Child Transmission
MTP	Medical Termination of Pregnancy
MUAC	Mid-upper-Arm circumference
NA therapy	Nucleoside Analogue Therapy
NACEP	National AIDS Clinical Expert Panel
NACP	National AIDS Control Programme
NAMs	Nucleoside Analogue Mutations
NASH	Non-alcoholic Steatohepatitis
NAT	Nucleic Acid Test
NCT	National Capital Territory
ND	Not Done
NEG	Negative
NFV	Nelfinavir
NGO	Non-governmental Organization
NITs	Non-invasive Tests

NNRTI	Non-nucleoside Reverse Transcriptase Inhibitors
NRL	National Reference Laboratories
NSAID	Nonsteroidal Anti-Inflammatory Drug
NsRTI	Nucleoside Reverse Transcriptase Inhibitors
NTM	Nontuberculous mycobacteria
NtRTI	Nucleotide Reverse Transcriptase Inhibitors
NTS	Non-typhoidal Salmonellae
NVP	Nevirapine
OHL	Oral Hairy Leucoplakia
OI	Opportunistic Infection
OK	Okay
OPV	Oral Polio Vaccine
ORS	Oral Rehydration Solution
ORW	Outreach Worker
OST	Opioid Substitution Therapy
OST	Oral Substitution Therapy
p.o.	Per Orally
PA View	Posteroanterior view
PAP	Papanicolaou test
PAS	Para aminosalicylic acid
pCOE	Paediatric Centre of Excellence
PCP	Pneumocystis Jiroveci Pneumonia
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post Exposure Prophylaxis
PGL	Persistent Glandular Lymphadenopathy
PI	Protease Inhibitors
PID No	Patient Identification Number
PITC	Provider-Initiated Testing and Counselling
PLHIV	People Living With HIV/AIDS
PML	Progressive Multifocal Leukoencephalopathy

PMTCT	Prevention of Mother To Child Transmission
POS	Positive
PPE	Papular Pruritic Eruption
	Personal Protective Equipment
PPIs	Proton Pump Inhibitors
PPSV23	Pneumococcal Polysaccharide Vaccine
PPTCT	Prevention of Parent to Child Transmission of HIV
PreP	Pre-Exposure Prophylaxis
PT	Proximal Tube
PTCT	Parent to Child Transmission
PVL	Plasma Viral Load
PWID	Persons Who Inject Drugs
QD	Once a day
QOD	Every Other Day
RAL	Raltegravir
RBF	Renal Blood Flow
RCT	Randomized Clinical Trials
RDA	Recommended Dietary Allowance
RF	Replacement Feeding
RNA	Ribonucleic Acid
RNTCP	Revised National Tuberculosis Control Programme
RPV	Rilpivirine
RT	Reverse Transcriptase
RTI	Reproductive Tract Infections
RTV	Ritonavir
RVV	Rotavirus Vaccine
SACEP	State AIDS Clinical Expert Panel
SAM	Severe Acute Malnutrition
Sd	Single Dose
SDG	Sustainable Development Goals
SGPT (ALT)	Serum Glutamic Pyruvic Transaminase (Alanine Aminotransferase)

SJS/ SJ Syndrome	Stevens Johnson syndrome
SMO/MO	Senior Medical Officer/ Medical Officer
SMX - TMP	Sulfamethoxazole- Trimethoprim
SOP	Standard Operational Procedures
SQV	Saquinavir
SRL	State Reference Laboratory
STI	Sexually Transmitted Infection
SVR	Sustained Virological Response
T-20	Enfuvirtide
TAMs	Thymidine Analogue Mutations
TB	Tuberculosis
TDF	Tenofovir
TDSC	Trivandrum Development Screening Chart
TEN	Toxic Epidermal Necrolysis
TL+ATV/r	Tenofovir + Atazanavir boosted with Ritonavir
TLC	Total Leucocyte Count
TLE	Tenofovir + Lamivudine + Efavirenz
TPV	Tipranavir
TRG	Technical Resource Group
TS/TG	Transsexual/ Transgender
T-staging	Clinical staging after starting ART
TT	Tetanus Toxoid
Tx Failure	Treatment Failure
ULN	Upper Limit of Normal
UN	United Nations
UNAIDS	United Nations Programme on HIV and AIDS
USA	United States of America
USG	Ultrasonography
VDRL	Venereal Disease Research Laboratory Test
Vit A	Vitamin A
VL	Viral load

WB	Western Blot
WBC	Whole Blood Count
WHO	World Health Organization
XDR TB	Extensively drug-resistant Tuberculosis
ZL	Zidovudine+ lamivudine
ZL+LPV/r	Zidovudine+ Lopinavir boosted with Ritonavir
ZLE	Zidovudine + Lamivudine + Efavirenz
ZLN	Zidovudine + Lamivudine + Nevirapine

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Section 1

General

1: Introduction

Since the identification of initial cases of HIV/AIDS in June 1981 in Los Angeles, USA, there have been tremendous advances in the field of HIV prevention, diagnosis, care and treatment globally. This global progress is not only limited to identification of newer molecules that are more robust and less toxic but includes a significant reduction in the cost of therapy, and innovative approaches to service delivery that increase access to treatment, literally transforming the disease from a virtual death sentence, a few years ago, to a chronic manageable disease now.

As per UNAIDS estimates, in 2016, with an adult HIV prevalence of 0.8% and considerable variation between countries, 36.7 million (30.8- 42.9 million) people were estimated to be living with HIV globally. Approximately 1.8 million new infections occurred in 2016 worldwide and approximately 1.0 million people died of AIDS-related illnesses. Currently, there are 19.5 million patients on ART globally. Albeit a great achievement, the challenge remains to put the rest on ART to reduce mortality and co-morbidities, and to prevent further transmission of HIV.

India has a low HIV prevalence of 0.22 %. The country's epidemic is concentrated among high-risk groups and is heterogeneously distributed with wide geographic variations in the vulnerabilities that drive the epidemic. Even with this low prevalence, in terms of absolute numbers, India has the third highest burden of HIV in the world with an estimated 2.14 million people living with HIV, 87,000 estimated new infections and 69,000 AIDS-related deaths annually.

The first few cases of HIV in the country were detected among female sex workers in Chennai, Tamil Nadu in 1986, followed by reports from other parts of the country. By 1987, approximately 135 more cases came to light out of which 14 had already progressed to AIDS. By the year 2006, it was estimated that there were around 5.6 million cases of HIV in the country, concentrated mainly in six states of the country, namely Maharashtra, Andhra Pradesh (AP), Karnataka, Tamil Nadu, Manipur, and Nagaland. However, by 2009, better estimation methods established the burden to be around 2.3 million.

To respond to the challenge, the Government of India established the National AIDS Committee in 1986, which set the foundation for the establishment of National AIDS Control Organization (NACO) in 1992 to oversee the policies for prevention and control of the infection. The first phase of the National AIDS Control Programme (NACP) started in 1992 and lasted until 1999. This was followed by NACP-II (2000-2005), NACP-III (2006-2011) and NACP-IV (2012-2017). The first phase contained initial interventions focused on understanding modes of transmission and on prevention, blood safety and IEC strategy to increase awareness. During NACP-II, the programme was decentralized to the states by the establishment of SACS, and focus was laid on blood safety, targeted intervention and low-cost care including management of OIs. The Antiretroviral Therapy (ART) was introduced in 2004 in the later phase of NACP II. However, the coverage of services was limited to tertiary care centres. NACP-III aimed at reversing the epidemic over the next five years and focused on targeted interventions, district-level interventions, a massive scale-up of services, and quality assurance mechanisms. Reduction in new infections by 50% was a major achievement of NACP-III. In the current phase of NACP-IV, the focus is on consolidating the

gains achieved so far, dealing with emerging vulnerabilities, and balancing between prevention and growing treatment needs. NACP-IV aims at improving integration and mainstreaming HIV care in the general health system.

The Government of India launched the free Antiretroviral Therapy (ART) initiative on the first of April 2004 in 8 tertiary level hospitals across 6 high prevalent states and the NCT of Delhi. Since then, there has been a massive scale-up and decentralization of ART services with the aim of universal access to life-saving ART for all. In addition to the evidence-based scale-up of facilities, there have been regular updates in the technical guidelines pertaining to "when to start" and "what to start", keeping pace with new evidence, global developments, and recommendations. The Government of India is committed to providing universal access to comprehensive, equitable, stigma-free, quality care, support and treatment services to all PLHIV through an integrated approach. Currently, HIV care services are being delivered through a network of 541 Antiretroviral Therapy centres and 1108 link centres along with 310 care and support centres to approximately 1.2 million PLHIV across the country. Besides government facilities, the ART technical guidelines also cater for the private institutions which can also refer to these guidelines for ART services.

India's ART programme is the second largest globally and has been acclaimed as one of the best public health programmes providing HIV care services. PLHIV have direct access to free diagnostic facilities, free first-line therapy, second and third-line ART, prevention of parent to child transmission of HIV (PPTCT) services, prevention, diagnosis and management of opportunistic infections including management of TB with daily anti-TB treatment through a single window approach. The national programme provides psycho-social support and follow-up services, individualized thematic counselling, positive living and positive prevention services with appropriate referral linkages to various social beneficiary schemes.

The impact of the programme is evident. India's gains are one of the major contributors to the global success. The adult HIV prevalence at the national level has continued its steady decline from an estimated peak of 0.38% in 2001-03 through 0.34% in 2007 and 0.28% in 2012 to 0.22% in 2017. Annual new HIV infections have declines by more than 60% since 2000.The lifesaving ART has improved millions of lives. AIDS related deaths have gone down by almost 71% since its peak in 2005, against a global average of 48%.

The success is encouraging, and gains are to be consolidated. Yet it is not the time to be complacent. Among various priorities, reaching the unreached, early diagnosis, need to improve linkages and retention across the continuum of HIV care, maintaining a high level of adherence are few key priorities. The principle of "hit hard hit early" is becoming more and more pertinent as the programme is maturing. The country is committed to achieving the SDG of ending AIDS as a public health threat by 2030 and is signatory to the UN strategy of 90-90-90 by 2020 which aims at ending AIDS epidemic by achieving that

- 90% of the estimated PLHIV know their status, of which
- 90% PLHIV are on ART, of which
- 90% PLHIV have viral suppression

To achieve this aim, standardized and uniform national ART technical guidelines remain the mainstay to standardize treatment practices and thereby improve the quality of HIV care across all sectors of health care in our country context, especially when many other guidelines with a wide spectrum of recommendations already exist.

The national guidelines for ART are written based on the national recommendations that have

been finalised grounded on national and global experiences and recommendations and taking into consideration the availability of diagnostic and treatment options in the country context. The current guidelines are being finalized based on the recommendations of the Technical Resource Group (TRG) for Antiretroviral Therapy comprising of experienced clinicians and medical practitioners from the public and private sectors, technical experts, Government of India, WHO and other UN agencies, bilateral donors, pharmaceutical industries, network of positive people and non-governmental organizations (NGOs) involved in the care and treatment of PLHIV.

These guidelines aim:

- To harmonize treatment practices between the public and the private sector since there are patients who seek care from both the sectors at the same time or at different points in time
- To consolidate various existing guidelines and incorporate recommendations for all age groups, gender, and populations
- To provide standardized guidelines for prophylaxis, prevention, screening, diagnosis and management of common opportunistic infections among PLHIV

These guidelines will continue to evolve and will be revised and updated on regular basis as per national and global evidence and recommendations.

2: Diagnosis of HIV Infection in Adults and Children

2.1 Diagnosis of HIV

HIV is now considered as a chronic manageable disease and majority of the patients with HIV remain healthy if correct and timely treatment is started. Late diagnosis is an important factor associated with HIV related morbidity and mortality. Voluntary HIV testing with informed consent should be offered and encouraged in a wide variety of settings. HIV infection in any individual beyond 18 months of age can be detected by laboratory test/s that demonstrate(s) either the virus or viral products or antibodies to the virus in the blood/serum/plasma. In children below 18 months of age, due to the persistence of maternal antibodies, diagnosis of HIV is made by PCR tests that detect HIV nucleic acid. The national programme recommends that HIV testing should be done using highly sensitive and specific rapid tests in national HIV Counselling and Testing Services (HCTS) facilities, which provide reliable and accurate results quickly, as per the prescribed quality standards.

Under the NACP, the most commonly employed rapid tests are based on the principle of enzyme immunoassay, immuno-chromatography (lateral flow), immuno-concentration / dot-blot assays (vertical flow) and particle agglutination. All these different rapid tests should have a sensitivity of ≥99.5% and specificity of ≥98%. Window period represents the period of time between infection with HIV and the time when HIV antibodies can be detected in the blood (6-12 weeks). A blood test performed during the window period may yield a negative test result for HIV antibodies. These cases may require further testing after 12 weeks.

2.2 Diagnosis of HIV infection in adults and children above the age of 18 months

Confirmatory diagnosis of HIV infection is essential for ensuring access to care and treatment services. National HIV testing strategies enable the programme to screen for HIV or confirm the diagnosis of HIV among priority populations at the nearest Integrated Counselling and Testing Centre (ICTC). In view of the low prevalence of HIV in India, it is necessary to use three different principles or antigen-based rapid tests to confirm the diagnosis. **All samples reactive in the first test should further undergo confirmatory 2nd/3rd tests based on different principles/antigens using the same serum/plasma sample as that in the 1st test.** The same blood sample is utilized for performing all the tests for identifying HIV antibodies. For indeterminate results, testing should be repeated on a second sample taken after 14-28 days.

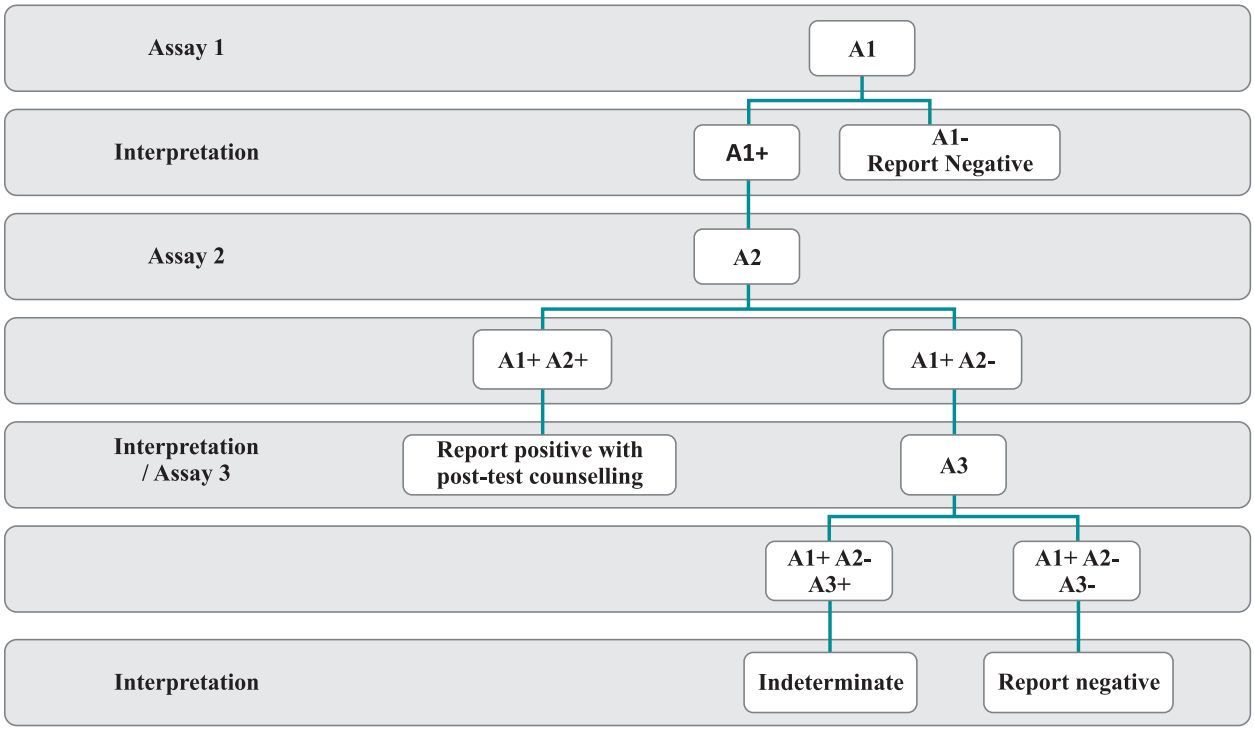
A testing strategy for diagnosis describes a testing sequence for the specific testing objective of diagnosis (as opposed to screening only), taking into consideration the presumed HIV prevalence in the population. *The national programme follows strategy I for screening and strategy II (A) for surveillance purposes whereas it uses strategy II (B) and strategy III for diagnosis in symptomatic and asymptomatic persons respectively.* The following strategies are to be used for

HIV testing and diagnosis in adults and children above the age of 18 months:

- For Clinically Symptomatic persons: the sample should be reactive with two different kits (Strategy II (B))
- For Clinically Asymptomatic persons: the sample should be reactive with three different kits (Strategy III)

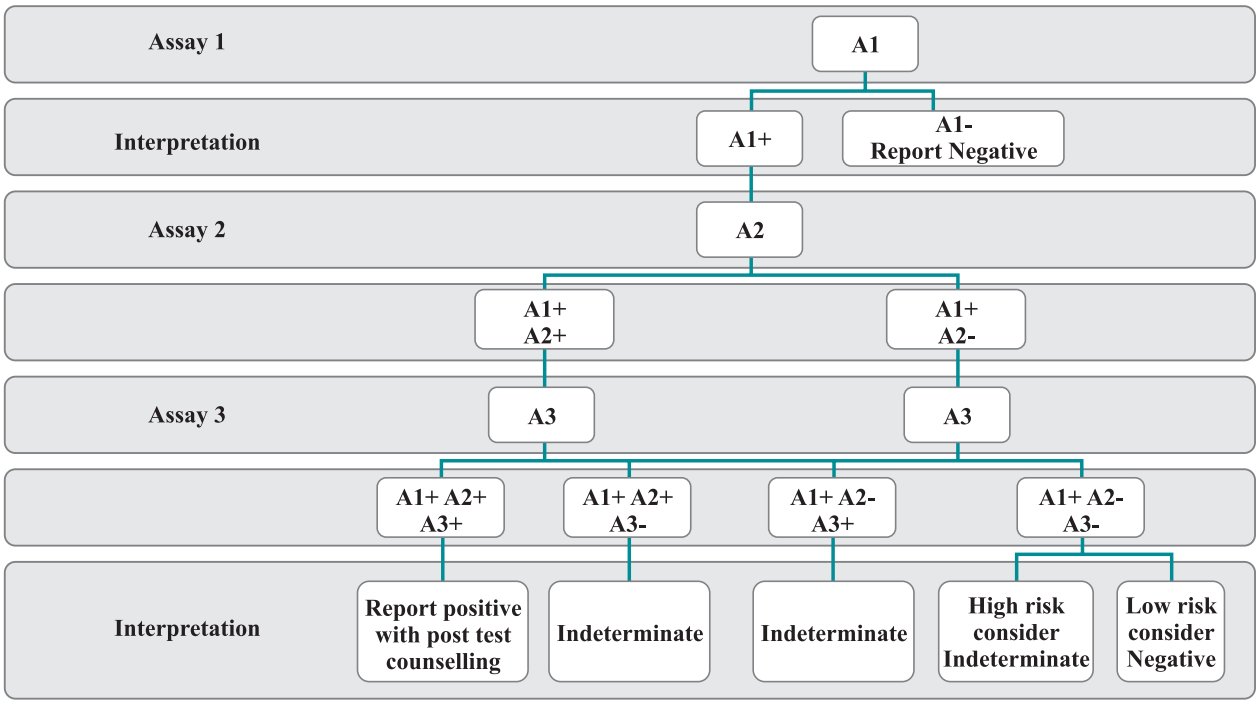
2.2.1 For Clinically Symptomatic Individuals: A patient who is clinically symptomatic and is suspected to have an AIDS indicativecondition/disease is referred to the ICTC for confirmation of the diagnosis. In this case, the same blood sample is tested twice using kits with either different antigens or principles. The patient is declared HIV-negative if the first test is non-reactive and as HIV-positive when both tests show reactive results. When there is discordance between the first two tests (first reactive and the second non-reactive), a third test is done. When the third test is also negative, it is reported as negative. When the third test is reactive, it is reported as indeterminate and the individual is retested after 14–28 days, as shown in Strategy II (B).

Strategy II (B): For diagnosis of clinically symptomatic individual



2.2.2 For Clinically Asymptomatic Individuals: Confirmation of HIV diagnosis in asymptomatic individuals is done at an ICTC using three rapid tests of three different antigens or principles. The individual is considered HIV-negative if the first test is non-reactive and as HIV-positive when all three tests show reactive results. For indeterminate results, testing should be repeated on a second sample taken after 14-28 days, as shown in Strategy III.

Strategy III: For diagnosis of clinically asymptomatic patient



All testing should follow five C's of counselling: consent, confidentiality, counselling, correct test results and immediate connection to services for HIV prevention, treatment and care. All persons should undergo pre-test and post-test counselling and confidentiality should be maintained while disclosing the results. Post-test counselling is important both for those with reactive results as well as those with negative results.

In addition to the walk-in clients and community based HIV testing, Provider-Initiated Testing and Counselling (PITC) is recommended in all health care settings for adults, adolescents or children, who present in clinical settings with signs and symptoms or medical conditions that could indicate possible HIV infection.

The spouses/partners of those with positive results and children of HIV infected mothers should also be counselled and offered HIV testing. All persons found positive for HIV should be immediately linked to appropriate HIV care services.

For more details, please refer to the national HIV Counselling and Testing Services (HCTS) Guidelines, NACO, December 2016.

2.3 Diagnosis of HIV infection in infants and children aged less than 18 months of age

Maternal HIV antibodies transferred passively to the infant during pregnancy usually persist for nearly 9-12 months in the infant. In some children, they may persist for as long as 18 months. Thus, during this period, children born to HIV-infected mothers will test positive for HIV antibodies regardless of their own infection status. A positive ELISA/Rapid test that detects antibodies to HIV, therefore, does not necessarily indicate the presence of HIV infection in the infant/child. Rather, a positive ELISA/Rapid test indicates exposure to HIV. More reliable indicators of the HIV infection status of the infant are tests that detect HIV viral RNA or antigens.

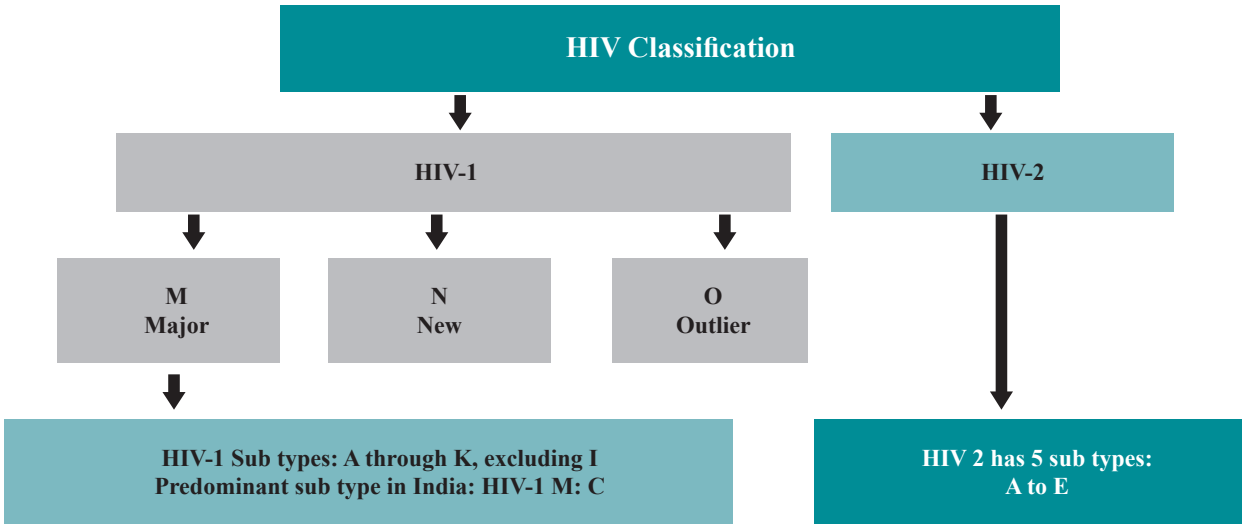
NACO recommends the use of DNA PCR test on a Dried blood sample (DBS) of the infant to

detect viral DNA for diagnosis of HIV-1 infection during infancy. This test is performed at 6 weeks of age or at the earliest opportunity until 18 months of age. At and after 6 months of age, DNA PCR must be performed after screening for HIV antibodies. It is also important to take breast-feeding into consideration in the HIV testing algorithm. Since breastfed children have an ongoing risk of HIV acquisition, they are tested (DNA PCR) 6 weeks after complete cessation of breast-feeding to reliably exclude HIV-1 infection. For more detailed information, refer to chapter 14 on "HIV Exposure in infants and young children."

Diagnosis of HIV-2

There are 2 types of Human Immunodeficiency Virus (HIV) viz. HIV type I (HIV-1) and HIV type 2 (HIV-2). The most common cause of HIV infection throughout the world is HIV-1 that comprises of several subtypes with different geographic distributions.

Information on the epidemiology of HIV-2 and dual infection in India is limited. However, cases of HIV-2 infection have been reported.



Natural history studies indicate that HIV-2 is less pathogenic than HIV-1. Those infected with HIV-2 have slower disease progression, a much longer asymptomatic stage, slower decline in CD4 count, lower rates of vertical transmission, lower viral loads while asymptomatic and smaller gains in CD4 count in response to Anti-retroviral Treatment (ART).

It is observed and well documented that infection with HIV-2 does not protect against HIV-1 or dual infection. Dually infected patients tend to present at a more advanced stage of the disease than those infected with HIV-2 only. Infection with both HIV-1 and HIV-2 generally carries the same prognosis as that of HIV-1 single infection.

Although HIV-1 and HIV-2 are related, there are important structural differences between them. Accurate diagnosis and differentiation of HIV-1 and HIV-2 is crucial for treatment, as HIV-2 is intrinsically resistant to NNRTI, the pillar of the national first-line ART regimen in adults and adolescents. This information is crucial for the treatment of infected individuals as well as for understanding the extent of HIV-2 infections in India. Rapid kits that differentiate between HIV-1 and HIV-2 are being used at ICTCs. However, test results that show HIV-2 reactivity need confirmation; confirmation cannot be done at ICTCs.

NACO has established a network of laboratories that includes ICTCs, State Reference Laboratories (SRLs) and National Reference Laboratories (NRLs). Designated NRLs and SRLs will be responsible for confirming the presence of HIV-2 infection.

Patients with a HIV-2 reactive report will be referred to the nearest ART centre by the ICTC. The guidance for HIV-2 diagnosis confirmation is as follows:

Flow chart for referring the patient for HIV-2 testing Clients/Patients

[with ICTC report "Specimen is positive for HIV antibodies

(HIV- 1 and HIV- 2 or HIV- 2 in one test only) and referral slip]

ART Centre

↓

Designated HIV-2 referral laboratory

↓

Collect fresh blood specimen

↓

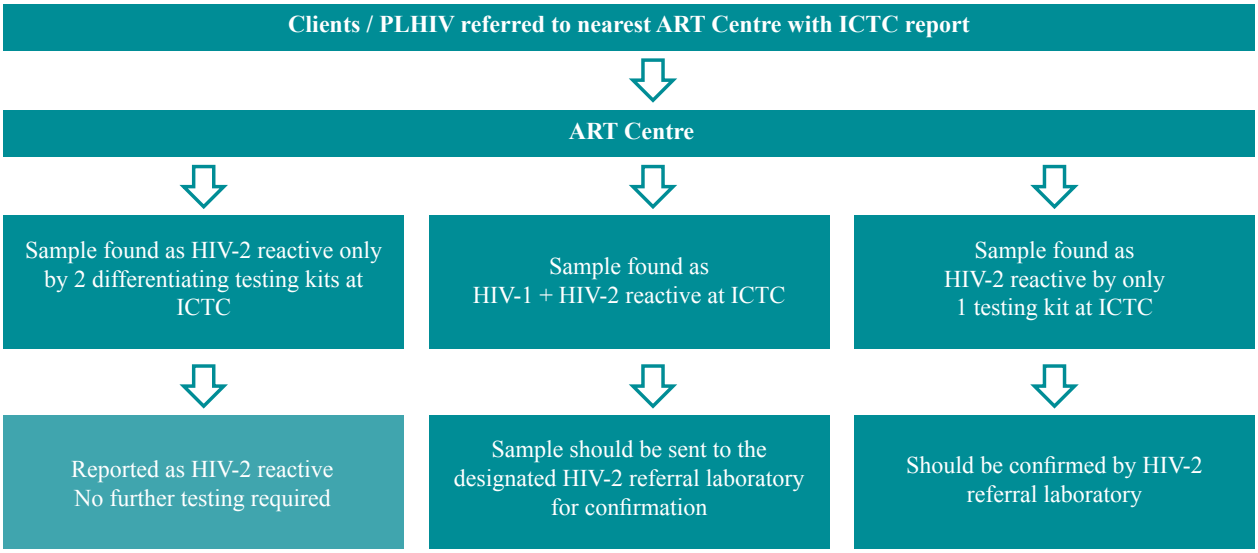
Test as per the national algorithm for HIV-2 sero-diagnosis

↓

Reporting to referring ART centre (both hard & soft copy)

↓

Retain a copy of report at ART and hand over original report to patient



Section 2

Adults and Adolescents

3. Assessment of Adults and Adolescents with HIV Infection

All persons diagnosed with HIV at the ICTC should be enrolled in the ART centres for HIV care.

'Adolescents' are defined as persons between 10-19 years of age.

This section deals with the assessment of adults and adolescents with HIV infection

3.1 Clinical Assessment

As soon as an individual is enrolled in HIV care, a comprehensive clinical assessment should be done to obtain a baseline status and to rule out opportunistic infections etc. This helps to:

- Determine the clinical stage of the HIV infection
- Identify the current HIV-related illnesses that may require treatment
- Identify any prior exposure to ARVs in the past
- Determine the need for OI prophylaxis
- Identify coexisting medical conditions like Diabetes, Hypertension, Hepatitis and any other treatment that may influence the choice of ARV drugs
- Determine the nutritional status and needs
- Elicit the history of past illnesses (especially TB, STIs)
- Assess the need for psycho-social support

The recognition of HIV-related clinical events helps to determine the WHO clinical stage of a patient and to decide when to initiate OI prophylaxis and ART. (Please refer to the Table 3 below for WHO clinical staging).

3.2 Medical History

Many individuals with HIV infection may have concurrent risk behaviour. It is important to elicit those risk factors, which may influence how a person will be counselled and supported. The risk factors for HIV include:

- Past or present use of injecting drugs (PWID)
- Past or present unprotected sexual intercourse (especially with a sex worker)
- Past or present sexually transmitted infections (STI)
- Past or present recipient of blood or blood products
- Risk factors like MSM, FSW, etc. as this may require special counselling and ART delivery mechanisms
- Injections, tattoos, ear piercing or body piercing using non-sterile instruments

Medical officers of the ART centres must obtain the detailed medical history as per the check- list provided in Table 1.

Table 1 : Medical History Checklist

HIV Testing	HIV risks (can be multiple)
• Ever tested for HIV in the past • Date and place of the first HIV test • Reason for the test • Documentation of the result • Date of the last negative HIV test result • Previous CD4 cell counts (if available) • Previous viral load (if available)	• Unprotected sexual contact • Injecting drug use • Commercial sex work • Men having sex with men • Occupational exposure (HCW) • Perinatal transmission • Recipient of blood products • Sero-discordant couple • Unknown
Review of Clinical symptoms	**Past History of HIV related illness**
• Unexplained weight loss • Swollen lymph nodes • Night sweats and fever • Unusual headaches or poor concentration • Changes in appetite • Skin rashes • Sores or white spots in mouth • Painful swallowing • Chest pain, cough or shortness of breath • Stomach pain, vomiting or diarrhoea • Numbness or tingling in hand or feet • Muscular weakness and changes in vision	• Oral candidiasis or candida oesophagitis • Persistent diarrhoea • Tuberculosis • Varicella zoster (Shingles) • Oral hairy leucoplakia (OHL) • Pneumocystis jiroveci pneumonia (PCP) • Recurrent bacterial pneumonia • Cryptococcal meningitis • Toxoplasmosis • Kaposi sarcoma • Disseminated Mycobacterium avium complex • Cytomegalovirus (CMV) infection • Invasive cervical cancer
Tuberculosis history	**ART history**
• Latest chest X-ray • History of past TB • Treatment given (drugs and duration) • History of exposure to TB in the family/close contacts • Ask the four TB screening questions “4 S screening “(any cough, fever or weight loss and night sweat)	• Current and past exposure to ARVs • ARV use during pregnancy of PMTCT • Use of PEP in the past • Drugs taken and for how long • An understanding of the treatment and readiness to commence ART • Partner’s ART history (if HIV-positive)
Sexually transmitted infections (STIs)	**Substance use**
• Genital ulcer or other lesions • Genital discharge (abnormal vaginal discharge in women) • Lower abdominal pain	• Alcohol, stimulant, opiate and use of other drugs • Smoking history

General medical history	Allergies
• Any other past medical condition such as Diabetes, Hypertension, Coronary Artery Disease, Hepatitis B, Hepatitis C, Hyperlipidaemia o Mental health issues, e.g. Depression	• Known allergies to drugs or other substances or materials
Medication	**Vaccination History**
• Past use of drugs and reasons for taking those drugs • Current use of drugs and reasons • Current use of traditional/herbal remedies • Opioid Substitution Therapy (OST)	• BCG • Hepatitis A vaccine • Hepatitis B vaccine
Gynaecological history	**Pregnancy and contraception history**
• Last PAP smear • Menstrual irregularities o Pelvic pain or discharge	• Previous pregnancies and MTP (years) • Children and HIV status of the children (living and dead) • Exposure to ARVs during pregnancy • Drugs and duration of ART • Contraception used • Last menstrual period
Psychosocial history	**Functional Status**
• Family history, e.g. other immediate family members with known HIV infection • Social history e.g. marital status, education, occupation, source of income. • Financial and family support status • Disclosure status, readiness to disclose • Availability of care and treatment supporter	• Able to work, go to school, do housework • Ambulatory but not able to work • Bed ridden • Amount of day-to-day care needed

3.3 Physical Examination

It is essential to have a thorough physical examination for clinical staging and screening. Table 2 details the specific physical signs related to HIV/AIDS that should be screened.

Table 2: Checklist for physical examination

General	Record vital signs, body weight, height and body mass index (BMI), temperature, blood pressure, pulse rate, respiratory rate, pallor & icterus
Appearance	• Unexplained moderate or severe weight loss, HIV wasting • Rapid weight loss is suggestive of active Opportunistic Infections, especially if associated with fever • Gradual weight loss (not caused by malnutrition or other obvious illness) is suggestive of HIV infection • "Track marks" and soft tissue infections which are common among IDUs

Consider conditions other than HIV	• Malaria, Tuberculosis, Syphilis, Gastrointestinal Infections, Bacterial Pneumonia, Pelvic Inflammatory Disease, Viral Hepatitis other than HIV
Skin	• Look for signs of HIV-related and other skin problems. These include diffuse dry skin, typical lesions of PPE, especially on the legs, Seborrhoeic Dermatitis on the face and scalp • Look for Herpes Simplex and Herpes Zoster or scarring of previous Herpes Zoster (especially multi-dermatome)
Lymph nodes	• Start with posterior cervical nodes • PGL (Persistent Glandular Lymphadenopathy) typically presents as o Multiple bilateral, soft, non-tender, mobile cervical nodes, other than axillary or inguinal nodes • Tuberculous lymph nodes typically present with constitutional symptoms such as fever, night sweats and weight loss
Mouth	• Look for signs suggestive of HIV infection including white plaques on tongue, cheeks and roof of mouth (oral candida), white striped lesions on the side of the tongue (OHL) and cracks at the corners of the mouth (Angular Cheilitis) • Difficulty in swallowing is commonly caused by oesophageal candida
Chest	• The most common problems are TB, CAP and PCP • Signs and symptoms are cough, shortness of breath, haemoptysis, weight loss / poor weight gain in children, fever, night sweats, congestion or consolidation • Perform a chest X-ray PA view
Abdomen	• Hepatosplenomegaly, masses and local tenderness
Neurological	• Perform comprehensive neurological examination. • Fundus examination if CD4 less than 100
Ano-genital	• Herpes Simplex and other genital sores / lesions, vaginal or urethral discharge; perform PAP smear
Note: During each consultation, the patient must be clinically screened for TB (history, 4-symptom screening and physical examination)	

All PLHIV must be assessed for WHO clinical staging on the first and all the subsequent visits by the medical officer. (Please refer Table 3 below)

Table 3: WHO Clinical Staging in Adults, Adolescents and Children

Adults and adolescents	Children
Clinical stage 1	
• Asymptomatic • Persistent generalized lymphadenopathy	• Asymptomatic • Persistent generalized lymphadenopathy
Clinical stage 2	
• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections (Sinusitis, Tonsillitis, Otitis Media, Pharyngitis) • Herpes Zoster • Angular Cheilitis • Recurrent oral ulceration • Papular Pruritic Eruption • Fungal nail infections • Seborrhoeic Dermatitis	• Unexplained persistent hepatosplenomegaly • Recurrent or chronic upper respiratory tract infections (Otitis Media, Otorrhoea, Sinusitis, Tonsillitis) • Herpes Zoster • Lineal gingival erythema • Recurrent oral ulceration • Papular Pruritic Eruption • Fungal nail infections • Extensive wart virus infection • Extensive Molluscum Contagiosum • Unexplained persistent parotid enlargement
Clinical stage 3	
• Unexplained severe weight loss (>10% of the presumed or measured body weight) • Unexplained chronic diarrhoea for more than 1 month • Unexplained persistent fever (intermittent or constant for longer than 1 month) • Persistent Oral Candidiasis • Oral Hairy Leucoplakia (OHL) • Pulmonary Tuberculosis • Severe bacterial infections (such as Pneumonia, Empyema, Pyomyositis, bone or joint infection, Meningitis, bacteraemia) • Acute necrotizing ulcerative stomatitis, Gingivitis or Periodontitis • Unexplained anaemia (<8 g/dl), neutropenia (<0.5 x 109/l) and/or chronic thrombocytopaenia (<50 x 109/l)	• Unexplained moderate malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month) • Persistent Oral Candidiasis (after the first 6 weeks of life) • Oral Hairy Leucoplakia (OHL) • Lymph node Tuberculosis • Pulmonary tuberculosis • Severe recurrent bacterial Pneumonia • Acute necrotizing ulcerative gingivitis or Periodontitis • Unexplained anaemia (<8 g/dL), neutropenia (<0.5 x 109/l) or chronic thrombocytopaenia (<50 x 109/l) • Symptomatic Lymphoid Interstitial Pneumonitis • Chronic HIV-associated lung disease, including Bronchiectasis

Clinical stage 4	
• HIV wasting syndrome • Pneumocystis (jiroveci) Pneumonia • Recurrent severe bacterial Pneumonia • Chronic Herpes Simplex infection (orolabial, genital or anorectal of more than 1 month duration or visceral at any site) • Oesophageal Candidiasis (or Candidiasis of trachea, bronchi or lungs) • Extra pulmonary Tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system Toxoplasmosis • HIV encephalopathy • Extra pulmonary Cryptococcosis, including Meningitis • Disseminated non-tuberculous mycobacterial infection (NTM) • Progressive Multifocal Leukoencephalopathy (PML) • Chronic Cryptosporidiosis • Chronic Isosporiasis • Disseminated mycosis (extra pulmonary Histoplasmosis, Coccidioidomycosis) • Lymphoma (cerebral or B-cell non-Hodgkin) • Symptomatic HIV-associated nephropathy or cardiomyopathy • Recurrent septicaemia (including non-typhoidal Salmonella) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis	• Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy • Pneumocystis (jiroveci) Pneumonia • Recurrent severe bacterial infections (such as Empyema, Pyomyositis, bone or joint infection, Meningitis, but excluding Pneumonia) • Chronic Herpes Simplex infection (orolabial or cutaneous of more than 1 month duration or visceral at any site) • Oesophageal Candidiasis (or Candidiasis of trachea, bronchi or lungs) • Extra pulmonary Tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month) • Central nervous system Toxoplasmosis (after the neonatal period) • HIV encephalopathy • Extra pulmonary Cryptococcosis, including Meningitis • Disseminated nontuberculous mycobacterial infection (NTM) • Progressive Multifocal Leukoencephalopathy (PML) • Chronic Cryptosporidiosis (with diarrhoea) • Chronic Isosporiasis • Disseminated endemic mycosis (extra pulmonary Histoplasmosis, Coccidioidomycosis, Penicilliosis) • Cerebral or B-cell non-Hodgkin Lymphoma • HIV-associated nephropathy or cardiomyopathy
a) In the development of this table, adolescents were defined as 15 years or older. For those aged less than 15 years, the clinical staging for children should be used. b) For children younger than 5 years, moderate malnutrition is defined as weight-for-height <–2 z-score or mid-upper arm circumference ≥ 115 mm to < 125 mm. c) Some additional specific conditions can be included in regional classifications, such as penicilliosis in Asia, HIV-associated rectovaginal fistula in southern Africa and reactivation of trypanosomiasis in Latin America. d) For children younger than 5 years of age, severe wasting is defined as weight-for-height <–3 z-score; stunting is defined as length-for-age/height-for-age <–2 z-score; and severe acute malnutrition is either weight for height <–3 z-score or mid-upper arm circumference <115 mm or the presence of oedema.	

Source: Adapted from WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva, World Health Organization, 2007 (www.who.int/ HIV/pub/guidelines/ HIVstaging150307.pdf).

3.4 Nutritional Requirements and Assessment

Good nutrition is a key factor for maintenance of good health and quality of life for all people while poor nutrition reduces a person's ability to work and be active. In PLHIV, poor nutrition worsens the effects of HIV by weakening the immune system further. This leads to frequent illnesses and an inability to replace and repair body cells and tissues, resulting in severe weight loss. It may lead to a more rapid progression of the disease.

Food and nutritional intake can influence the adherence to antiretroviral drugs (ARVs) as well as the effectiveness of ARVs. HIV and associated infections increase the need for energy, proteins, and micronutrients like iron, zinc, vitamin C, etc. Opportunistic infections like TB, Pneumonia and diarrhoea etc. further increase the nutritional demands of the body, accelerating the decline in the nutritional status. Thus, a vicious cycle exists between HIV infection and malnutrition.

Appropriate nutritional support from the early stages of HIV infection can prevent the onset of malnutrition and other nutritional deficiencies. It will also help maintain the performance of the immune system. Nutritional care and support, which includes counselling, education, information-sharing and linkage to social welfare schemes like AAY and ICDS etc., is an important component of the comprehensive package of care and support services for all people living with HIV, both adults (PLHIV) and children (CLHIV).

Causes of Under Nutrition In Patients With HIV/AIDS:

- **Reduced food intake**
  - Inability to eat because of oral lesions such as painful oral ulcers/candidiasis in the mouth and throat
  - Loss of appetite due to HIV infection or associated fatigue, depression and changes in the mental state
  - Food insecurity and poverty leading to poor access to food
  - Physical handicap leading to difficulty in accessing and preparing food – e.g. disease related visual or other neurological handicaps
  - Opportunistic Infections (e.g. TB) adding to the loss of appetite, diarrhoea causing malabsorption, etc.
  - Side-effects of the medications: nausea, loss of appetite, altered taste in the mouth, diarrhoea, vomiting
- **Reduced nutrient absorption**
  - HIV and other infections reduce the absorption of nutrients from the gastrointestinal tract
  - Diarrhoea results in malabsorption leading to water and nutrient losses from the body
  - Medications also affect nutrient absorption
- **Changes in metabolism:**
  - Due to increased breakdown of tissues, there is an increased energy requirement in PLHIV
  - In the asymptomatic phase, the energy requirements increase by 10%
  - In the symptomatic phase, energy requirements increase by 20-30%

- Deranged metabolism in HIV infection causes weight loss
- There is an imbalance between pro-oxidants and antioxidants leading to oxidative stress on the body
- Oxidative stress contributes to HIV wasting syndrome

- **Changes in body composition**

In the case of PLHIV, proteins are used rather than fats to meet the energy demands. Hence proteins are broken down while fat continues to accumulate.

Nutritional Requirements of Adult and Adolescent PLHIV:

- Energy Requirements
  - During the asymptomatic stage, energy needs are increased by 10% over the requirements in healthy people
  - An increased energy intake of 20 to 30% above the daily requirements is recommended for adults during periods of symptomatic disease or Opportunistic Infections
  - The recommended energy intake for HIV infected adults also apply to HIV infected pregnant and lactating women
- **Protein Requirements:** Average protein requirements: 1 g / kg / day
- **Fat Requirements:**
  - About 20-30% of the total energy should be provided by fat
  - At least 50% of the fat intake should consist of vegetable oils rich in Essential Fatty Acids (EFA)
  - The amount of saturated, mono-saturated and polyunsaturated fat in the diet should be ≤7%, ≥10% and ≤10% respectively, of the total caloric intake
- **Micronutrient requirements:**
  - A daily dose of micronutrients providing "Recommended Daily Allowance" of vitamins and minerals may be supplemented if the available diet is not balanced or does not contain a variety of animal sourced foods, fruits and vegetables
  - Multiple micronutrient supplements may be given to those with vitamin or mineral deficiency, or those who are vulnerable to micronutrient deficiency

Nutritional needs of HIV infected children are detailed in the chapter on paediatric HIV

3.6 Comprehensive Laboratory Evaluation in HIV/AIDS

The purpose of the baseline laboratory evaluation is to

- Rule out other concomitant infections, Opportunistic Infections
- Determine baseline safety parameters

The following investigations are recommended for monitoring of PLHIV at the ART centres

Table 4: Laboratory monitoring for patients at ART centre

Baseline Investigations: Essential tests for all patients registering in HIV care at ART centre
• Haemogram/CBC • Urine for routine and microscopic examination • Fasting blood sugar • Blood urea, Serum creatinine • Serum Bilirubin, ALT (SGPT) • VDRL • CD4 count • Lipid profile (if available) • HBsAg and Anti- HCV IgG (if available) • X-ray Chest PA view • Pregnancy test (if required) • rk 39 strip test to confirm or rule out leishmaniasis (especially in patients with HIV infection who live in or travel to endemic areas i.e. Bihar, Eastern Uttar Pradesh, Jharkhand and West Bengal) • For women, cervical PAP smear or other method of cervical cancer screening (if available) • For MSM, anal PAP smear (if available)
Additional tests in the baseline as per the physician's decision
• Symptoms and signs directed investigations for ruling out Opportunistic Infections, including M. Tuberculosis by testing sputum/appropriate specimen by CBNAAT (Cartridge Based Nucleic Acid Amplification Test) and/or other required investigations • Complete LFT (Liver function test) for those being initiated on ATT and for patients with Hepatitis B or C co-infection • Lipid profile (if available) • USG whole abdomen
NON-AVAILABILITY / NON-FEASIBILITY OF ANY OF THESE TESTS SHOULD NOT DELAY THE INTIATION OF ART Note: All above investigations other than CD4 estimation shall be done from the health facility where the centre is located, with support from the state Health Department.

3.7 Assessment and management of the patient at first and at follow-up visits

Table 5: Assessment and management of the patient during the first and follow-up visits at the ART centre

General	Activities
Visit 1	• Registration in HIV care • Medical history • Symptom checklist • 4-symptom TB screening • Physical examination • Behavioural/psycho-social assessment • Educational level, employment history, financial resources • Social support, family/household structure • Disclosure status, readiness to disclose • Understanding of HIV/AIDS, transmission, risk reduction, treatment options • Nutritional assessment • Family/household assessment to determine if there are other HIV-infected family members who may need care • Recommend condom use during every visit • Preparedness counselling • Baseline investigation: Essential tests including CD4 count and additional tests as per requirement. • Initiate Co-trimoxazole Prophylaxis Therapy (CPT) if eligible
Visit 2	• History • Symptom checklist • 4-symptom TB screening • Physical examination • Review lab reports • Co-trimoxazole Prophylaxis Therapy (if required) • Psycho-social support • Preparedness counselling (Adherence counselling on at least 2 occasions & assessment of client preparedness for life-long ART) • Commence ART if the patient is adequately prepared
Visit 3	• 4-symptom TB screening • Review lab reports • Psycho-social support • Preparedness counselling • Commence ART if patient is adequately prepared

Subsequent follow-up visits (after initiating ART)	• History (new problems) • Symptom check list • Clinical examination • 4-symptom TB screening • Note any side-effects (anaemia, rash, fever, signs of hepatotoxicity / nephrotoxicity) • Investigations as per monitoring & follow up related to ARV • Counselling • Adherence assessment/support

4. Prophylaxis for Opportunistic Infections

HIV-infected individuals become susceptible to a multitude of opportunistic micro-organisms including protozoa, fungi, viruses and bacteria, which are generally innocuous in healthy individuals. HIV-infected subjects tend to contract OI during the course of the disease, which roughly corroborates with the CD4 cell counts. Although no definitive relationship between OIs and CD4 cell count has yet been established, cumulative information points towards a relationship. Also, since opportunistic events tend to recur, prophylaxis needs to be continually given regardless of any previous successful treatment. Alongwith Anti-retroviral therapy, measures are taken by Government for providing diagnostic facilities for Opportunictic Infection Management to people living with HIV or AIDS.

Co-trimoxazole (Sulfamethoxazole/ Trimethoprim [SMX–TMP]) 800 mg/160 mg PO once daily is effective in preventing Pneumocystis Jiroveci Pneumonia (Pneumocystis Pneumonia- PCP) and Toxoplasmosis. It could help in the prevention of certain bacterial Pneumonias, Nocardiosis and enteric pathogens (Isosporiasis). In case of allergy to Co-trimoxazole, an alternative for primary prophylaxis against PCP and Toxoplasmosis is Dapsone 100 mg once daily. Desensitization may be suggested for sulpha allergy.

Primary prophylaxis for Cryptococcus is not routinely recommended due to the relatively low incidence of the disease, lack of definite survival benefit, drug interactions, and development of resistance to the azole class of antifungals, cost of the treatment, and absence of mortality benefit.

Prophylaxis for PCP:

Co-trimoxazole preventive therapy (CPT) must be initiated in all HIV-infected patients (PLHIV) with any of the following-

- CD4 count < 350cells/cmm
- WHO clinical stage 3 and 4

One double-strength tablet of Co-trimoxazole (Sulfamethoxazole/Trimethoprim [SMX–TMP]) 800 mg/ 160 mg PO once daily is used for prophylaxis. Alternative regimens include Dapsone 100 mg once a day.

NACO's recommendation on Co-trimoxazole Preventive Therapy (CPT) is given in Table 1.

Table 1: Co-trimoxazole Preventive Therapy for Adults and Adolescents:

Prophylaxis	Recommendations
Commencing primary CPT	Co-trimoxazole Prophylaxis must be initiated in PLHIV with CD4 count < 350/cmm or with WHO clinical stage 3 and 4
Commencing secondary CPT	For all patients who have completed successful treatment for PCP until CD4 is > 350cells/cmm (at least on two occasions, done 6 months apart)

Timing the initiation of Co-trimoxazole in relation to initiating ART	• Start co-trimoxazole prophylaxis first • Start ART after starting co-trimoxazole or as soon as CPT is tolerated, and the patient has completed the "preparedness phase "of counselling
Dosage of Co-trimoxazole in adults and adolescents	One double-strength tablet or two single-strength tablets once daily– total daily dose of 960 mg (800 mg SMZ + 160 mg TMP)
Co-trimoxazole for pregnant and breastfeeding women	• Women, who fulfil the criteria for CPT, should continue on it throughout pregnancy. • If a woman requires CPT during pregnancy, it should be started regardless of the stage of pregnancy • Breastfeeding women should continue CPT where indicated
Patients allergic to sulpha-based medications	• Dapsone 100 mg per day. • Co-trimoxazole desensitization may be attempted but not in patients with a previous severe reaction to co-trimoxazole or other sulpha- containing drugs
Monitoring	No specific laboratory monitoring is required in patients receiving co-trimoxazole
Discontinuation of co-trimoxazole prophylaxis	When CD4 count > 350/cmm on two different occasions 6 months apart with an ascending trend and devoid of any WHO clinical stage 3 and 4 conditions

Co-trimoxazole desensitization:

If the patient reports a history of hypersensitivity to sulpha-containing drugs, start him/her on a desensitization regimen as an in-patient. Desensitization can be attempted two weeks after a non-severe (grade 3 or less) Co-trimoxazole reaction that has resulted in temporary interruption in the use of the drug. Co-trimoxazole desensitization has been shown to be successful and safe in approximately 70% of the patients with previous mild to moderate hypersensitivity (Table 2).

Table 2: Protocol for Co-trimoxazole desensitization

Step	Dosage	
Day 1	80 mg SMX + 16 mg TMP	2 ml oral suspension
Day 2	160 mg SMX + 32 mg TMP	4 ml oral suspension
Day 3	240 mg SMX + 48 mg TMP	6 ml oral suspension
Day 4	320 mg SMX + 64 mg TMP	8 ml oral suspension
Day 5	400 mg SMX + 80 mg TMP	(One single – strength SMX-TMP tablet
Day 6	800 mg SMZ + 160 mg TMP	Two single-strength SMX-TMP tablets or one double-strength tablet)
Note: Co-trimoxazole oral suspension contains 40 mg TMP + 200 mg SMX per 5 ml		

Desensitization should not be attempted in individuals with a history of severe Co-trimoxazole or any other Sulphonamide reaction. If a reaction occurs, the desensitization regimen should be stopped. Once the patient recovers fully, Dapsone at a dosage of 100 mg per day may be tried.

Prophylaxis for Cryptococcosis:

Primary Prophylaxis: There is no role for primary prophylaxis against Cryptococcal Meningitis .

Secondary Prophylaxis or Maintenance Therapy:

- **Indications:** Previous cryptococcal disease, such as Meningitis

After 2-3 weeks of Induction Therapy and 8 weeks of Consolidation Therapy, secondary prophylaxis is started.

- **Regimen:** Fluconazole 200 mg/day (Itraconazole is associated with significantly higher relapse rate)

Discontinuation: Secondary prophylaxis or Maintenance Therapy with Fluconazole 200 mg daily must be continued until the CD4 cell count remains at > 200 cells/cmm for a period of 6 months in a person on ART.

Isoniazid Preventive Therapy (IPT):

About 50% of the adults in the community have Latent TB Infection (LTBI). Isoniazid is one of the most effective bactericidal anti-TB drugs available currently. Isoniazid protects against progression of latent TB infection to active disease (against endogenous reactivation). It also prevents TB re-infection after exposure to an open case of TB (against exogenous re-infection / super infection / nosocomial transmission)

The duration of effectiveness of IPT in PLHIV in the absence of ART (not receiving concomitant ART) is limited because of the ongoing progressive immunodeficiency. With the concomitant administration of both ART and IPT, there is a likelihood of restoration of tuberculosis-specific immunity by ART and prolongation of the beneficial effect of IPT .

(For details on IPT, please refer to the chapter 8 on HIV-TB)

Table no. 3 Summary of OI prophylaxis:

Name of OI	Type of prophylaxis	What to start (preferred)*	Adult Dose	When to start	When to Stop
PCP	Primary	Co-trimoxazole	One double strength tablet (Sulfamethoxazole 800 mg + Trimethoprim 160 mg)	CD4 < 350 cells/cmm or WHO Clinical stage 3 or 4 condition	CD4 > 350cells/cmm (at least on two occasions, done 6 months apart) and devoid of any WHO clinical stage 3 and 4 conditions
	Secondary	Co-trimoxazole	One double strength tablet (Sulfamethoxazole 800 mg + Trimethoprim 160 mg)	After successful treatment for PCP (21 days)	CD4 > 350cells/cmm (at least on two occasions, done 6 months apart) and devoid of any WHO clinical stage 3 and 4 conditions

Cryptococcal Meningitis	Primary	Not recommended			
	Secondary	Fluconazole	Tab Fluconazole 200 mg	After successful treatment of Cryptococcal Meningitis (induction phase of 2-3 weeks and consolidation phase of 8 weeks)	CD4 > 200 cells/ cmm (at least on two occasions, done 6 months apart)
*The clinicians should check if there is/are any contraindications to the drugs being prescribed for prophylaxis. In that case, alternate drugs are to be considered.					

5. ART in Adults and Adolescents

There has been a rapid decline in the HIV related mortality and morbidity due to the wider availability of affordable, more efficacious and less toxic Antiretroviral (ARV) drugs over the last two decades. Antiretroviral Therapy (ART) consists of the use of a combination of at least three antiretroviral drugs from different classes to inhibit the replication of HIV and reduce viremia to undetectable levels. Continued suppression of viral replication leads to the restoration of immune response, reflected by an increase in the CD4 count. This increase leads to slowing of the disease progression, reduced frequency of Opportunistic Infections, improvement in the quality of life and increased longevity. Successes achieved by Antiretroviral Therapy (ART) have now transformed the perception about HIV infection from being a 'virtual death sentence' to a 'chronic manageable illness'. ART was earlier known as Highly Active ART (HAART) and as combination ART (cART).

Goals of Antiretroviral Therapy (ART)

ART cannot cure HIV infection, as the currently available ARV drugs cannot eradicate the virus from the human body. This is because a pool of latently infected CD4 cells is established during the earliest stages of acute HIV infection. It persists within the organs/cells and fluids (e.g. brain, liver and lymphoid tissue) despite prolonged suppression of plasma viraemia by ART to <50 copies/ml. The primary goals of ART are maximal and sustained reduction of plasma viral levels and restoration of immunological functions. The reduction in the viral load also leads to reduced transmissibility and reduction in new infections. The defined goals of ART are depicted in Table 1.

Table 1: Goals of ART

Goals of ART	
Clinical goals	Increased survival and improvement in quality of life
Virological goals	Greatest possible sustained reduction in viral load
Immunological goals	Immune reconstitution, that is both quantitative and qualitative
Therapeutic goals	Rational sequencing of drugs in a manner that achieves clinical, virological and immunological goals while maintaining future treatment options, limiting drug toxicity and facilitating adherence
Preventive goals	Reduction of HIV transmission by suppression of viral load

Due to the continued viral suppression, the destruction of CD4 lymphocyte cells is reduced and over time there is an increase in the CD4 count, which is accompanied by partial restoration of pathogen-specific immune function. This leads to a reduction in Opportunistic Infections, reduced morbidity and mortality.

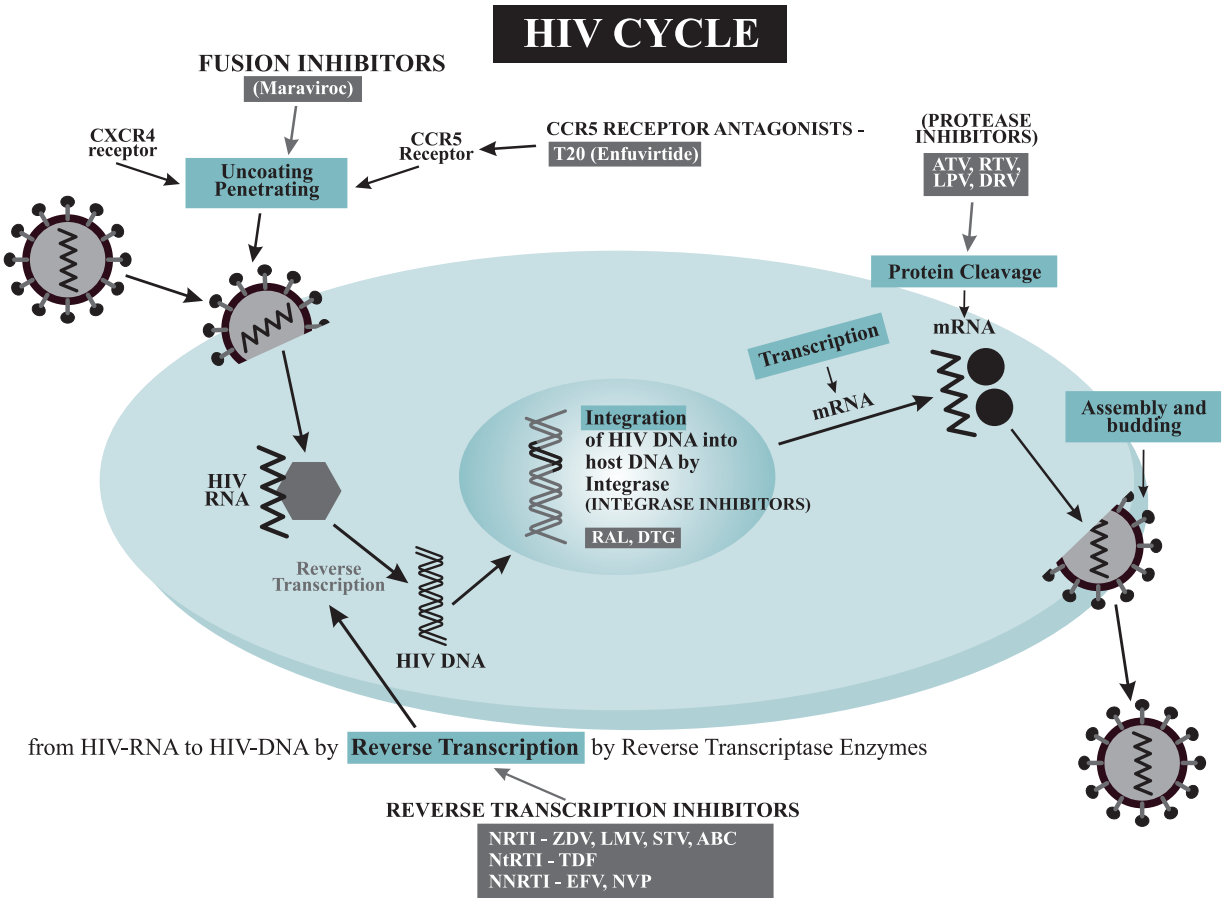
Principles of Antiretroviral Therapy

A continuous high level of replication of HIV takes place in the body right from the early stages of the infection. At least one billion viral particles are produced during the active stage of replication. The antiretroviral drugs act on various stages of the replication of the virus in the body and interrupt the process of viral replication. The Figure 1 depicts the various enzymes involved in viral

replication and the points where ARVs target the virus. The ARV drugs act on the viral replication in the following steps and are labelled according to site of their action:

1. Block binding of HIV to the target cell **(Fusion Inhibitors and CCR 5 co-receptor blockers)**
2. Block the viral RNA cleavage and one that inhibits reverse transcriptase **(Reverse Transcriptase Inhibitors)**
3. Block the enzyme integrase, which helps in the proviral DNA being incorporated into the host cell chromosome **(Integrase Inhibitors)**
4. Block the RNA to prevent viral protein production
5. Block enzyme protease **(Protease Inhibitors)**
6. Inhibit the budding of virus from host cells

Fig 1: Targets of Antiretroviral Drugs



The most commonly used drugs target the virus mainly by inhibiting the enzymes reverse transcriptase (RT) and protease. They are depicted in Table 2

Table 2: Classes of ARV Drugs

Nucleoside reverse transcriptase inhibitors (NsRTI)	Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Protease inhibitors (PI)
Zidovudine (AZT/ZDV)*	Nevirapine* (NVP)	Saquinavir (SQV)
Stavudine (d4T)	Efavirenz*(EFV)	Ritonavir (RTV)*
Lamivudine (3TC)*	Delavirdine (DLV)	Nelfinavir (NFV)
Abacavir (ABC)*	Rilpivirine (RPV)	Amprenavir (APV)
Didanosine (ddl)	Etravirine (ETV)	Indinavir (INV)
Zalcitabine (ddC)	**Integrase Inhibitors**	Lopinavir (LPV)*
Emtricitabine (FTC)	Raltegravir (RGV)*	Fosamprenavir (FPV)
Nucleotide reverse Transcriptase inhibitors (NtRTI)	Elvitegravir (EVG)	Atazanavir (ATV)*
	Dolutegravir (DTG)	Tipranavir (TPV)
Tenofovir (TDF)*		Darunavir (DRV)*
Fusion inhibitors (FI)	**CCR5 Entry Inhibitor**	
Enfuvirtide (T-20)	Maraviroc	
*Available in the national programme		

Clinical Pharmacology of Commonly Used ARV Drugs

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

The first effective class of antiretroviral drugs discovered was the Nucleoside analogues, which act by incorporating themselves into the DNA of the virus, thereby stopping the building process. The resulting DNA is incomplete and cannot create new virus. Nucleotide analogues work in the same way as nucleosides, but they have a non-peptidic chemical structure. The details of individual ARV drugs of this class are shown in Table 3.

Table 3: Commonly used NRTIs

Generic Name	Dose	Adverse effects
Tenofovir (TDF)	300 mg once daily	Renal toxicity, bone demineralization
Zidovudine (ZDV, AZT)	300 mg twice daily	Anaemia, neutropenia, bone marrow suppression, gastrointestinal intolerance, headache, insomnia, myopathy, lactic acidosis, skin and nail hyperpigmentation
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily	Minimal toxicity, rash (though very rare)
Abacavir (ABC)	300 mg twice daily or 600 mg once daily	Hypersensitivity reaction in 3 to 5% (can be fatal), fever, rash, fatigue, nausea, vomiting, anorexia, respiratory symptoms (sore throat, cough, shortness of breath); Re-challenging after reaction can be fatal.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) stop HIV production by binding onto the reverse transcriptase and preventing the conversion of RNA to DNA. These drugs are called "non-nucleoside" inhibitors because, even though they work at the same stage as nucleoside analogues, as chain terminators, they inhibit the HIV reverse transcriptase enzyme by directly binding to it.

The details of individual ARV of this class are shown in Table 4.

Table 4: Commonly used NNRTIs

Generic Name	Dose	Food related advices	Adverse Effects
Efavirenz (EFV)	600 mg once daily (bed time administration is suggested to decrease CNS side-effects)	Avoid taking after high fat meals	CNS symptoms (dizziness, somnolence, insomnia, confusion, hallucinations, agitation) and personality change. Rash occurs, but less common than NVP.
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily	None	Hepatitis (usually within 12 weeks); sometime life-threatening hepatic toxicity. Skin rash occasionally progressing to severe conditions, including Stevens Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Patients who develop severe hepatic toxicity or grade 4 skin rashes should not be re-challenged.

Integrase Inhibitors

Integrase inhibitors are a class of antiretroviral drugs designed to block the action of Integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell.

Since integration is a vital step in retroviral replication, blocking it can halt further spread of the virus. Raltegravir was the Integrase inhibitor approved for use in 2007. It is metabolized primarily through uridine diphosphate glucuronosyltransferase 1A1 and has a single inactive glucuronide metabolite. Raltegravir is not a substrate, inhibitor or inducer of cytochrome P450 enzymes and it exhibits low potential for drug–drug interactions. It is well tolerated; most commonly reported adverse effects include nausea, headache, diarrhoea, fever, CPK elevation, muscle weakness and insomnia. The major toxicities are given in Table 5. Raltegravir has been approved for use in both treatment-naïve and treatment-experienced patients; it is being primarily used for third-line ART in the national ART programme. Raltegravir is given in the dose of 400 mg twice daily. Dolutegravir (DTG) and Elvitegravir (ELV) are the other approved drugs.

Table 5: Integrase Inhibitors

Generic Name	Dose	Adverse Effects
Raltegravir (RAL)	400mg twice daily	Rhabdomyolysis, Myopathy, Myalgia, diarrhoea, fever, Rash, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, Hepatitis and Hepatic failure,
Dolutegravir (DTG)	50mg once daily	Insomnia and headache. Dolutegravir can cause serious, life threatening side effects. These include hypersensitivity (allergic) reactions and liver problems. People with a history of Hepatitis B virus (HBV) or Hepatitis C virus (HCV) infection or who have elevated results on liver function tests may have an increased risk of developing new or worsening liver problems while taking dolutegravir.

Protease Inhibitors (PIs)

Protease Inhibitors work at the last stage of the viral reproduction cycle. They prevent HIV from being successfully assembled and released from the infected CD4 cell. All PIs can produce GI intolerance, altered taste, abnormal liver function test and bone disorder and all have been associated with metabolic abnormalities, such as hyperglycaemia, insulin resistance and increase in triglycerides, cholesterol and body fat distribution (lipodystrophy). The details of individual ARV of this class are shown in Table 6.

Generic Name	Dose	Adverse Effects
Atazanavir/ ritonavir (ATV/r)	300 mg Atazanavir + 100 mg Ritonavir once daily	Unconjugated hyperbilirubinaemia, lipid abnormality, hyperglycaemia, fat maldistribution, nephrolithiasis, cholelithiasis, PR prolongation
Lopinavir / ritonavir (LPV/r) Heat stable tablets	200 mg Lopinavir/50mg Ritonavir Fixed dose tablet 2 tablets twice daily	Diarrhoea, nausea, vomiting, abnormal lipid profiles, glucose intolerance.
Darunavir (DRV)	600 mg twice a day (when used with Ritonavir 100 mg twice daily)	Hepatotoxicity, skin rash (10%), diarrhoea, nausea, headache, hyperlipidaemia, serum transaminase elevation, hyperglycaemia
Ritonavir (RTV)	100 mg twice daily (used only to boost another PI)	Common-gastrointestinal (diarrhoea, nausea, vomiting, abdominal pain (upper and lower), rarely neurological disturbances (including paraesthesia)

Co-administration of antitubercular and antiretroviral agents, especially Protease Inhibitors, is associated with important drug-drug interactions. Combinations are limited by the alterations in the activity of the hepatic cytochrome P450 (CYP) enzyme system, which may produce sub-therapeutic plasma concentrations of antiretroviral drugs. For example, Protease Inhibitors must often be avoided if the potent CYP inducer Rifampicin is co-administered. Alternatively, Rifamycin, Rifabutin, which have similar efficacy to rifampicin, can be used with appropriate dose reduction. Available clinical data suggest that, for most individuals, Rifampicin-based regimens can be successfully combined with the non-nucleoside reverse transcriptase inhibitor, Efavirenz. Whenever Protease Inhibitor based ART regimens are used, the co-infected TB must be treated with anti-TB regimen containing Rifabutin instead of Rifampicin.

Considerations before Initiation of ART

All people with confirmed HIV infection should be referred to the ART centre for registration in HIV care, comprehensive clinical and laboratory evaluation to assess baseline status, treatment of pre-existing Opportunistic Infections, treatment preparedness, counselling and timely ART initiation.

The following principles need to be kept in mind:

- **The patient should be adequately prepared, and informed consent should be obtained from the patient or from the caregiver in-case the patient is a minor, before initiating HIV care and ART (refer annexure 03: Consent form)**

- Treatment should be started based on the person's informed decision and preparedness to initiate ART with information and understanding of the benefits of treatment, life long course of medication, issues related to adherence and positive prevention
- A caregiver should be identified for each person to provide adequate support. Caregivers must be counselled and trained to support treatment adherence, follow-up visits and shared decision-making
- All patients with clinical stage 3 and 4 and those with CD4 less than 350 cells/cmm need to be put on Co-trimoxazole Preventive Therapy (CPT). All patients need to be screened for TB, using the 4-symptom tool (current cough, fever, night sweats and weight loss) and those who do not have TB need to be started on Isoniazid Preventive Therapy (IPT) in addition to ART.
- **ART should not be started in the presence of an active OI.** In general, **OIs should be treated or stabilized before commencing ART.** Mycobacterium Avium Complex (MAC) and Progressive Multifocal Leukoencephalopathy (PML) are exceptions in which commencing ART may be the preferred treatment, especially when specific MAC therapy is not available. For details on starting ART in patients with HIV-TB co-infection, please refer to the section on the management of HIV-TB. Some conditions, which may regress following the commencement of ART, include Candidiasis and Cryptosporidiosis. The following OIs and HIV-related illnesses need treatment or stabilization before commencing ART.

Table 7: Opportunistic Infections and HIV related conditions and ART initiation

Clinical Picture	Action
Any undiagnosed active infection with fever	Diagnose and treat first; start ART when stable
TB	Start TB treatment first; start ART as soon as possible after 2 weeks and before 2 months. For those with CD4 less than 50/cmm, start ART within 2 weeks Caution is needed for PLHIV with TB Meningitis, since immediate ART is associated with more severe adverse events than initiating ART 2 months after the start of TB treatment
PCP	Treat PCP first; start ART when PCP treatment is completed
Invasive fungal diseases: Oesophageal Candidiasis, Penicilliosis, Histoplasmosis	Start treatment for Qesophageal Candidiasis first; start ART as soon as the patient can swallow comfortably. Treat Penicilliosis, and Histoplasmosis first; start ART when patient is stabilized or OI treatment is completed.
Cryptococcal Meningitis	Treat Cryptococcal Meningitis. ART initiation should be deferred until there is evidence of sustained clinical response to anti-fungal therapy and after 4 weeks of induction and consolidation treatment with Amphotericin B containing regimen
Bacterial Pneumonia	Treat Pneumonia first; start ART when treatment is completed
Malaria	Treat Malaria first; start ART when treatment is completed
Acute diarrhoea which may reduce absorption of ART	Diagnose the cause and treat diarrhoea first; start ART when diarrhoea is stabilized or controlled
Non-severe anaemia (Hb< 9 g/dl)	Start ART if no other causes for anaemia are found (HIV is often the cause of anaemia);

Skin conditions such as PPE and Seborrhoeic Dermatitis, Psoriasis, HIV-related Exfoliative Dermatitis	Start ART (ART may resolve these problems)
Suspected MAC, Cryptosporidiosis and Microsporidiosis	Start ART (ART may resolve these problems)
Cytomegalovirus Retinitis	Start treatment for CMV urgently and start ART after 2 weeks of CMV treatment
Toxoplasmosis	Treat Toxoplasmosis; start ART after 6 weeks of treatment and when patient is stabilized

Once the evaluation is completed, the key questions pertaining to ART are:

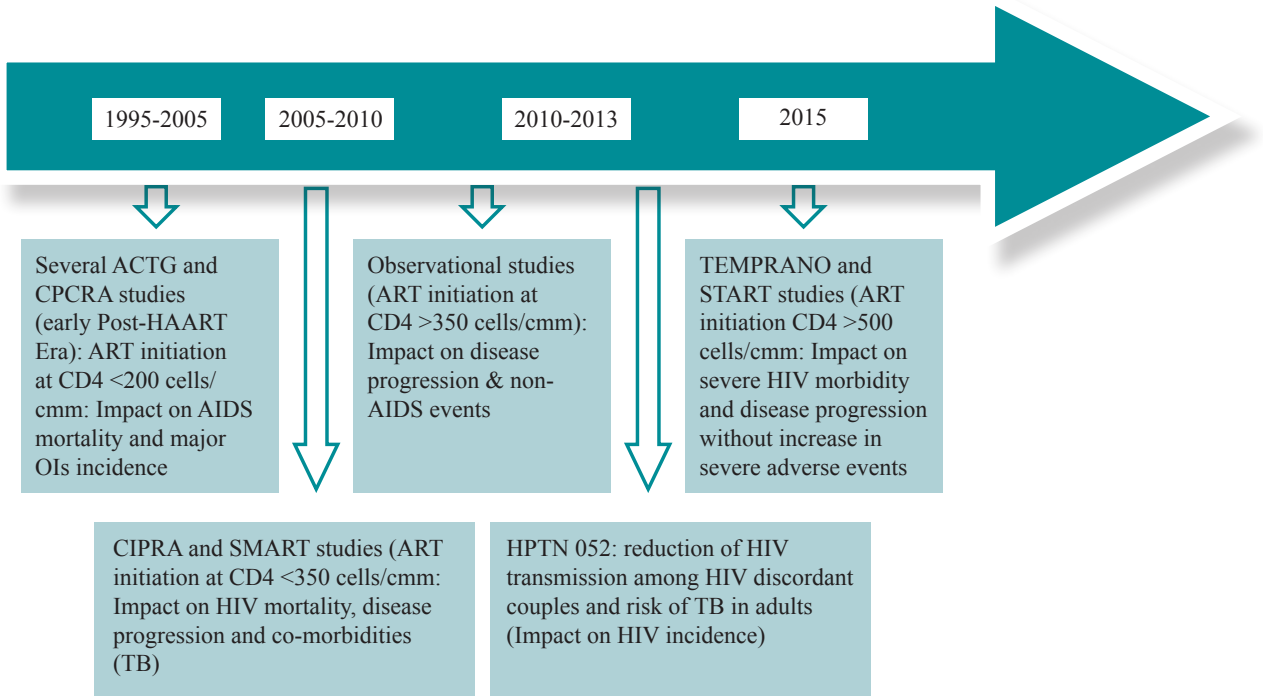
- When to start treatment?
- Which and how many agents to use? Choice of optimal regimen?
- How to monitor the therapy?
- How long to give therapy?
- When to change therapy and to what?
- Drug interactions involving antiretroviral therapy

When to start ART in Adults and Adolescents

In general, the clinical management of an HIV infected patient revolves around optimizing the treatment regimen, reducing drug toxicity, reducing the pill burden and increasing adherence to the treatment.

The guidelines on **When to start ART** have evolved over the years towards earlier initiation of ART; CD4 count cut-off point for ART initiation moving from less than 200 cells/cmm in 2004 to less than 350 cells/cmm in 2010 and then to less than 500 cells/cmm in 2013. The current recommendation is to **TREAT ALL**, regardless of the clinical stage or CD4 count. These changes have been based on the evidence from various randomized clinical trials (RCT) and large observational cohorts which have revealed that with earlier ART initiation, there is a significant delay in progression to AIDS and reduction in the incidence of TB. These studies are summarized in Figure 2 below:

Fig 2: Evolution of CD4 cut offs for ART initiation over time



The current NACO guidelines (2017) on when to start ART

All persons diagnosed with HIV infection should be initiated on ART regardless of the CD4 count or WHO Clinical Staging or age group or population sub-groups

Ensuring good adherence to treatment is imperative for the success of the treatment as well as for the prevention of drug resistance. To achieve this, counselling must start from the first contact of the patient with the clinical team. Counselling should include preparing the patient for treatment and providing psycho-social support through an identified caregiver / guardian / treatment buddy and support networks. All patients should undergo adequate counselling sessions (preparedness counselling) before the initiation of ART. The period of waiting for investigations and their results should be utilized for counselling, co-trimoxazole prophylaxis, Isoniazid Preventive Therapy (in eligible patients) and treatment preparation. All efforts should be made to trace the patients who have defaulted on their visits or are lost to follow-up, to initiate ART in all PLHIV registered at the ART centres. NGOs and positive network linkages should be established by each ART centre for their respective locality.

What to Start: Antiretroviral Therapy Regimens

Fixed-dose combinations (FDCs) of ARVs are preferred because they are easy to prescribe and easy for patients to take, thereby facilitating improved and desirable treatment adherence. This is essential for PLHIV as the treatment is life-long and we need to minimize the chances of developing drug resistant mutants in their body and the resultant treatment failure. Further, FDCs have distinct advantages in drug procurement and distribution, essentially the drug stock management itself. The national experience has shown that regimens with FDCs are more acceptable, well tolerated and adequately complied with.

Recommended Choice of First Line Regimen

The regimens described in this chapter are for HIV-1 infected individuals unless specified otherwise

The basic principle for **first-line ART** for treatment naïve adult and adolescent patients is to use a triple drug combination from two different classes of ARVs.

The first-line ART essentially comprises of a NRTI backbone, preferably Non-Thymidine (Tenofovir plus Lamivudine) and one NNRTI, preferably EFV. Based on the evidence supporting better efficacy and fewer side effects, it is now recommended that all PLHIV with HIV-1 infection be initiated on a regimen consisting of

TENOFOVIR (TDF 300 mg) + LAMIVUDINE (3TC 300 mg) + EFAVIRENZ (EFV 600 mg) (TLE) as Fixed Dose Combination (FDC) in a single pill once a day

This regimen has the advantage of harmonization in the treatment of all adults, adolescents, pregnant women and those with HIV-TB and HIV Hepatitis co-infections. It is a simple, potent and well-tolerated regimen that offers the advantage of a decentralized service delivery and monitoring. It also simplifies the supply chain and minimizes the monitoring requirements.

In cases where the preferred first-line ARV regimen of TDF +3TC +EFV cannot be used, the alternative regimen of AZT +3TC +EFV, TDF +3TC +NVP, ABC +3TC +EFV or ABC +3TC +NVP can be used.

Note: The patients with HIV-2 and both HIV-1 and HIV-2 co-infections need to be initiated on a PI containing regimen, as NNRTIs (EFV/ NVP) are not active against HIV-2 virus. **For patients with HIV-2 infection (HIV-2 alone or both HIV-1 and HIV-2 co-infections), the preferred first-line ART regimen shall be Tenofovir (300 mg) plus Lamivudine (300 mg) plus Lopinavir/ Ritonavir (800/200 mg)**

A summary of different ARV regimens with specific indications are given below in Table 8

Table 8: First-line ARV Regimen guidance

ART Regimen	Recommended For
Tenofovir + Lamivudine + Efavirenz	First-line ART regimen for: All ARV naive PLHIV patients with HIV-1 infection, age > 10 years and body weight > 30 kg
Abacavir + Lamivudine +Efavirenz	First-line ART regimen for all patients with abnormal serum creatinine values - Refer to ART guidance for special situations. All adults and adolescents with body weight less than 30 kg
Tenofovir + Lamivudine + Lopinavir/ritonavir	First-line ART regimen for: All women with single dose Nevirapine exposure in a past pregnancy; All confirmed HIV-2 or HIV- 1 & HIV-2 co-infection
Zidovudine + Lamivudine + Nevirapine Zidovudine + Lamivudine + Efavirenz	All patients who are on either of these first-line regimens initiated earlier in the programme need to be continued on the same regimen unless failing

General Guidance:

- A single pill of TLE should be taken at bed time, 2- 3 hours after dinner; fatty food should be avoided as far as possible
- Patients with severe Diabetes and Hypertension should be monitored more closely for TDF toxicity

Considerations for ART in Adolescents

According to WHO, adolescence is the period between 10-19 years of age. During this period, healthy HIV infected adolescents pass through well-described stages of physical, psychological and sexual maturation for which appropriate support and care are required.

An estimated 2.1 million adolescents (10–19 years old) were living with HIV globally in 2013. HIV-related deaths among adolescents are estimated to have tripled since 2000, making HIV the second leading cause of death among adolescents worldwide (WHO 2016).

Adolescence is marked by rapid physical, neuro-developmental, emotional and social changes. Adolescents have significantly lesser access to ART and coverage of ART than adults, high risk of loss to follow-up, suboptimal adherence and special requirements for comprehensive care, including psycho-social support and sexual and reproductive health care. Adolescents also face significant barriers to the access of essential health and support services, especially because of policy and legal barriers related to the age of consent.

Perinatally infected adolescents are more likely to experience chronic diseases and neuro-developmental growth and pubertal delays in comparison to their age-matched peers. Older adolescents who acquire HIV behaviourally do not present the same clinical features but face potentially greater challenges in dealing with stigma and lack of family and community support to access care.

Physicians giving care and treatment to such adolescents should consider the following issues:

- Disclosure
- Developmental delays
- Transition difficulties from childhood to adulthood which may influence choice of appropriate ART regimens
- Adherence issues
- Psychosocial support needs
- Physical and sexual issues

Monitoring of Patients on ART

Follow-up and monitoring is essential in patients initiated on ART to track clinical progress, monitor well-being and to identify adverse drug reactions and toxicities.

ART monitoring includes clinical monitoring and laboratory monitoring. Clinical monitoring includes monitoring of adherence to ART as well. The client should be monitored every month for clinical progress, side effects of the ARV/s and treatment adherence. Clinical and laboratory evaluations are carried out at specified intervals for patients who are on ART. The various monitoring indicators are listed below:

- **Clinical monitoring**

- o Monthly clinical evaluation
- o Body weight, overall well-being, any new symptoms / signs, four symptom screening for TB at every visit
- o Monthly Treatment Adherence-Evaluation--pill count, self-reported adherence
- **o Adherence to ART must be assessed at each visit and adherence must be reinforced through counselling at each visit**
- o Adverse reactions of ART / OI drugs
- o Drug-drug interactions, look for all concomitant drug use (prescribed and over the counter)
- o IRIS (Immune Reconstitution Inflammatory Syndrome)

- **Immunological monitoring**

  CD4 testing should be done every 6 months.

  As and when routine virological monitoring becomes available, CD4 testing should be done every 6 months till CD4 count reaches to greater than 350 cells/cmm and viral load is less than 1000 copies/ml (when both tests are conducted at the same time).

- Virological monitoring: At 6 months and 12 months after ART initiation and then every 12 months

The laboratory monitoring of PLHIV on ART is also very important. Regular monitoring of the patient's laboratory parameters is crucial to identify ARV related toxicities, inter-current illnesses and drug-drug interactions and other metabolic abnormalities. The frequency of monitoring and the parameters to be monitored depend upon the components of the regimen. This is important to remember as quite a significant number of PLHIV are still continuing their older first-line regimens (ZLN/ ZLE). The summary of the laboratory monitoring recommended under the programme is presented below in the Table 9. Additional laboratory tests outside this schedule may be performed as clinically indicated by the ART medical officer.

Table 9: Laboratory Monitoring of individual ARV drugs

For all patients on ART, we need to do CD4, Hb, TLC, DLC, ALT (SGPT), serum creatinine once in every six months								
Tests for monitoring patients on ART (Follow-up tests)- Drug specific tests frequency as below								
Monitoring ARV Drug in regimen	**Monitoring Test**	**Baseline**	**15th Day**	**First Month**	**Third Month**	**Sixth Month**	**Then every 6 months**	**At 12 months**
On Zidovudine based ART	**CBC**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**--**
On Tenofovir based ART	**Serum creatinine**	**Yes**	**--**	**--**	**--**	**Yes**	**Yes**	**--**
Nevirapine containing ART	**ALT**							
(SGPT)	**Yes**	**Yes**	**--**	**--**	**Yes**	**Yes**	**--**	

Efavirenz containing ART	**Lipid profile**	**Yes**	**--**	**--**	**--**	**--**	**--**	**Yes**
Atazanavir containing ART	**LFT**							
Lipid profile	**Yes**	**--**	**--**	**--**	**Yes**	**Yes**	**--**	
Lopinavir containing ART	**Lipid profile & Blood sugar**	**Yes**	**--**	**--**	**--**	**Yes**	**Yes**	**--**

- The prevalence of lipid abnormalities is significantly frequent in patients on ART, particularly if they are on d4T, EFV or PIs. In case of these patients and those with significant risk factors for coronary artery disease, a fasting lipid profile should be done at six months or earlier as required. Otherwise, yearly evaluations suffice.

  Fasting blood sugar is recommended as part of the baseline screening of all patients to be started on ART, as currently one of the major causes of morbidity in India is Diabetes Mellitus.

  To summarize, a combination of clinical and laboratory monitoring is to be carried out in all PLHIV after initiation of ART. This is depicted in the Table 10 below.

Table 10: Monitoring and follow-up schedule for patients on ART

Monitoring Tool	When to Monitor?
Body weight	Every Visit
Treatment adherence	Every Visit
Clinical monitoring & T – staging	Every Visit
4 Symptoms TB screening	Every Visit
CD4 Count*	CD4 has to be done every 6 months*
Viral load	At 6 months, 12 months and then every 12 months
*CD4 Count: 1. As and when routine virological monitoring becomes available, CD4 testing should be done every 6 months till CD4 count reaches greater than 350 cells/cmm and viral load is less than 1000 copies/ml (when both tests are conducted at the same time). 2. CD4 monitoring should be re-started for any patient if (a) the patient has suspected treatment failure i.e. virological failure (VL >1000 copies/ml) or (b) if the patient has undergone a switch in regimen	

More frequent visits or additional laboratory monitoring may be required, if the patient develops any symptoms or side-effects of the ARVs or experiences difficulties in adherence to ARVs due to any reason, including clinically indicated reasons as per the discretion of the Medical Officer.

Once the patient has stabilized and CD4 starts improving, the patient does not have any OI or adverse events and has been adherent to ART for at least 1 year, the frequency of visits can be reduced to once in 3 months. **NACO has defined stable patients as those who are on ART for at least one year, have good treatment adherence, an increasing CD4 count and are devoid of any active OI. Such patients should be encouraged to get linked out to the nearest link ART centre or be given 3 months of drugs, subject to the availability of sufficient stocks.**

What to Expect in the First Six Months of Therapy

Taking ART is a lifelong commitment and the first six months of therapy are especially important. Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART. However, certain opportunistic infections and/or Immune Reconstitution Inflammatory Syndrome (IRIS) may develop, as may early adverse drug reactions, such as drug hypersensitivity, especially in the first three months of treatment. ART significantly decreases the overall mortality, but death rates are highest in the first three months of ART initiation. As the immune system recovers, there may be exacerbation of previously sub-clinical co-existing infections (e.g. TB), resulting in an apparent worsening of the disease. It is to be remembered that this is not due to the failure of therapy, but due to the success of the therapy and resulting immune reconstitution. Complications are commonest among the first few weeks of treatment, especially among people starting ART with advanced HIV disease, those with severe immunodeficiency and existing co-infections and/or co-morbidities, very low haemoglobin, low body mass index, very low CD4 counts or those who are severely malnourished. Poor adherence in this period is also associated with the risk of early treatment failure and rapid development of drug resistance.

CD4 recovery

In most adults and children, CD4 cell counts rise by 40- 60 cells per year when ART is initiated and immune recovery starts. Generally, this increase occurs during the first year of treatment, achieves a plateau and then continues to rise further during the second year. However, severe immunosuppression may persist in some individuals who do not experience a significant rise in CD4 cell count with treatment, especially those with a very low CD4 cell count at the time of initiating ART. Failure to achieve some CD4 recovery should alert the health care provider to potential adherence problems or primary non-response to ART and consideration should be given to continue prophylaxis for opportunistic infections such as co-trimoxazole preventive therapy.

Several other factors can influence CD4 T cell counts apart from laboratory-related variables. These include:

- Concurrent infections, specifically Hepatitis
- Leucopenia of varying aetiology especially caused by ARV itself and steroids or other immunosuppressive therapies
- Pregnancy can also lead to lower values
- Diurnal variation occurs; CD4 T cells are lower at noon, and highest in the evening around 8 pm
- Psychological stress seems to play a negligible role, even though patients often assume the contrary

Several factors can influence the extent of immune reconstitution during ART. The degree of viral suppression is crucial – the lower the viral load, the more pronounced the effect. The absolute increase in CD4 count is higher if CD4 counts were high at the start of ART. Presence of naive T- cells the time of ART initiation is particularly an important factor for long-term immune reconstitution/ recovery. Hence CD4 response may vary widely and we need to focus on viral suppression.

Patients with declining CD4 but undetectable VL should be evaluated for recent viral infection, immunization and CD4 variability; if all these have been ruled out, one may consider the possibility of HIV-2 or HIV-1 and HIV-2 co-infection.

Viral Load

Within the first few weeks of therapy the viral load should start decreasing and after 6 months viral load test should be done to evaluate the response to ARVs. Viral load testing should be done at 6 months after initiation of ART, again at 12 months and once the viral load is suppressed, every 12 months. Most people will achieve viral suppression at 24 weeks of initiation of treatment.

Virological suppression in context of national programme means a viral load of less than 1000 copies/ ml after at least six months on ART.

Early ARV toxicity

First-line drug toxicities fall into two categories. Early toxicity usually presents in the first few weeks to months of ART. Early and potentially severe toxicities such as skin rashes, neuro-psychiatric side effects to NNRTIs (EFV and NVP) normally occur within the first few weeks of therapy. AZT-related anaemia and gastrointestinal side effects like severe vomiting and occasional diarrhoea typically present in the first few months of therapy while some toxicities may occur years after initiation of treatment like TDF induced toxicities. More details about toxicity are described in a separate chapter on toxicities. The guidelines for substitution of ARV drugs in such cases are also described in the same chapter.

Mortality on ART

While ART significantly decreases mortality, the risk of death is higher in the first six months than during the subsequent period on therapy, particularly when patients start ART with clinical stage 4 events, such as diagnosed with TB meningitis at baseline, low BMI during follow up, severe immunosuppression and/ or very low CD4 counts.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Definition:

"The worsening of signs and symptoms due to known infections" or "the development of disease due to occult infections that results from an inflammatory response by a re-invigorated immune system following the initiation of anti-retroviral therapy."

This is a condition that can occur shortly after a person starts ART for the first time. It is a spectrum of clinical signs and symptoms resulting from the body's ability to mount an inflammatory response associated with immune recovery. The suppression of CD4 T cells by HIV causes a decrease in the body's normal response to certain infections. Antiretroviral therapy partially restores the immune defects caused by chronic HIV infection, including the restoration of protective pathogen-specific immune responses. If the CD4 count rapidly increases (due to effective treatment of HIV), a sudden increase in the inflammatory response produces nonspecific symptoms such as fever and in some cases a paradoxical worsening of pre-existing symptoms of infective or non-infective conditions, e.g. TB, MAC or CMV. In general, people with profound immunosuppression before starting HIV therapy are most at risk for IRIS. It occurs in 10-30% of patients initiating ART, usually within first 4-8 weeks. However, late IRIS can be observed upto 6 months of initiating ART. Some risk factors for IRIS are as below:

- People with CD4 counts below 100 cells/cmm before starting therapy (lower CD4 counts at ART initiation) or lower CD4: CD8 ratio at ART initiation
- People with rapid initial fall in HIV viral load due to therapy

- People with diagnosis of another infection before starting therapy; the closer the appearance or diagnosis is to starting therapy, the higher the risk (Shorter interval between OI therapy initiation and ART initiation)
- Severity of TB disease, especially high pathogen burden, and short interval between initiation of ATT and ART
- Male sex
- Younger age
- Higher HIV RNA at ART initiation
- Genetic susceptibility

Working definition of IRIS in Programme Conditions:

"The worsening of signs and symptoms due to known infections, or the development of disease due to occult infections within 6 weeks to 6 months after initiating ART, with an increase in CD4 count."

The various categories of IRIS along with the possible antigen are mentioned in the table below.

Table 11: Categories of IRIS

Categories	Antigen Target
Infection-unmasking	Viable replicating infective antigen
Infection-paradoxical	Dead or dying organisms
Auto immune	Host
Malignancies	Possible tumour or associated pathogen

Source: Devesh J. Dhasmana, Keertan Dheda, PernilleRavn, Robert J. Wilkinson and Graeme Meintjes. IRIS in HIV-Infected Patients Receiving Antiretroviral Therapy Pathogenesis, Clinical Manifestations & Management. Drugs, 2008; 68 (2):191-208

Unmasking IRIS refers to, for e.g., the initial clinical expression of active TB occurring soon after ART is started. **Paradoxical IRIS** refers to, for e.g., the worsening of TB clinical manifestations after the initiation of ART in patients, who are receiving anti-TB treatment. IRIS should be considered only when the presentation cannot be explained by a new infection, expected course of a known infection or drug toxicity. IRIS should be diagnosed by excluding:

- Active OI
- Treatment failure
- Side effect from ARV
- Failure to Antimicrobial Therapy

The clinical spectrum of IRIS is diverse in terms of early or delayed onset, atypical symptoms, generalized or localized infection, variation in severity and it may be infectious or non- infectious.

The following can help in the diagnosis of IRIS:

- Temporal association between the initiation of ART and the development of new clinical event (mostly within 3 months).

1. Typically, IRIS occurs within 2–12 weeks of the initiation of ART, although it may present later (usually between 6 weeks to 6 months)

2. The incidence of IRIS is estimated to be 10% among all patients in whom ART has been initiated and upto 25% among those initiated on ART having CD4 cell count of below 50 cells/cmm

- Unusual clinical manifestations in patients responding to ART include:

1. Unexpected localized disease, e.g. lymph nodes (appearance or enlargement and/or suppuration) or involving liver or spleen or development of pleural effusion
2. Exaggerated inflammatory reaction, e.g. severe fever, with exclusion of other causes
3. Painful lesions
4. Atypical inflammatory response in affected tissues, e.g. granulomas, suppuration, necrosis
5. Perivascular lymphocytic inflammatory cell infiltrate
6. Progression of organ dysfunction or enlargement of pre-existing lesions
7. Development or enlargement of cerebral space-occupying lesions after treatment, for e.g., cerebral cryptococcosis or toxoplasmosis
8. Progressive pneumonitis or the development of organizing pneumonia after treatment for pulmonary TB or PCP
9. Onset or worsening of uveitis / vitritis after the resolution of CMV retinitis
10. Fever and cytopenia after treatment for disseminated MAC

The most serious and life-threatening forms of paradoxical IRIS are TB and Cryptococcosis. BCG vaccine–associated IRIS (localized and systemic) may occur in infants infected with HIV in settings where BCG immunization is a routine. A low CD4 cell count (< 50 cells/cmm) at ART initiation, disseminated Opportunistic Infections or tumours, a shorter duration of therapy for opportunistic infections before ART starts and rapid increase in the CD4 and a rapid decrease in the viral load after ART initiation are the main risk factors.

The most important steps to reduce the development of IRIS include: earlier HIV diagnosis and initiation of ART before decline of CD4 below 200 cells/cmm; improved screening for opportunistic infections before ART, especially TB, Cryptococcus, CMV and optimal management of opportunistic infections before initiating ART. Timing of ART in people with opportunistic infections requires balancing a greater risk of IRIS after early initiation against continuing high mortality if ART is delayed.

IRIS Management

IRIS is generally self-limiting, and interruption of ART is rarely indicated, but people may need to be reassured in the face of protracted symptoms to prevent discontinuation of ART or poor adherence to ART.

- Mild form (with ongoing ART)
    - o Observation
- Localized IRIS (with ongoing ART)
    - o Local therapy such as minor surgical procedures for lymph node abscesses (Drainage)
    - o As per system involvement e.g. neurological, respiratory
- Most of the situations (with ongoing ART)

- Recognition and management of ongoing infections
- Antimicrobial therapy is required to reduce and to eliminate the triggering pathogen (antigenic load)

- Reconstituting immune reaction to non-replicating antigens
  - No antimicrobial therapy is required

Short term therapy with corticosteroids or non-steroidal anti- inflammatory drugs can be given to reduce the inflammation – Prednisolone in dose of 1.5 mg/ kg orally for two weeks followed by 0.75 mg/ kg orally for two weeks and then tapered off.

Temporary cessation of ART must be considered only if potentially life-threatening forms of IRIS develop.

6. Adherence to ART

Adherence: "Extent to which a person's behaviour - the taking of medication and the following of a healthy lifestyle including a healthy diet and other activities – corresponds with the agreed recommendations of the health care providers" (WHO, 2003).

Though the terms adherence and compliance are synonymously used, adherence differs from compliance. Compliance is the extent to which a patient's behaviour matches the prescriber's advice. Compliance implies patient obedience to the physician's authority, whereas adherence signifies that the patient and physician collaborate to improve the patient's health by integrating the physician's medical opinion and the patient's lifestyle, values and preferences for care.

A high degree of adherence to ARV drugs is necessary for optimal virological suppression. Adherence should be assessed and routinely reinforced by everyone in the HIV care team (Treating physicians, counsellors, nurses, pharmacists, peer educators, care coordinator, CSC staff and others) at each of the patient's visits to the ART centre. Studies indicate that > 95% of adherence is required for optimal viral load suppression. Lesser degrees of adherence are often associated with Virological failure.

Factors associated with poor adherence include a poor patient-clinician relationship, high pill burden, lack of caregiver, distance of ART centre from home, financial problems, home or job work responsibilities, frequent travelling, forgetfulness, mental illness, psychological factors, lack of patient education, inability of patients to identify their medications, substance abuse, drug toxicity, cultural factors (e.g. religious fasting), beliefs about treatment, faith in traditional faith healers, false perception of good health and the impression of being too ill for treatment.

At least two to three preparatory adherence counselling visits should be made before the start of ART. After the final preparatory visit, the treating physician and counsellor should jointly consider the patient's readiness to start treatment. The steps of preparatory counselling are provided in Table 1.

Table 1: Counselling for Treatment Preparation and Adherence

Step 1	• Establish rapport and relationship of trust with the patient • Provide necessary information and guidance • Encourage peer participation and help to identify treatment support persons • Encourage disclosure to an identified family member • Encourage positive living and positive prevention • Provide information about cough Hygiene and for TB prevention • Perform 4S screening • Develop an individual treatment plan, fitting ART into the patient's lifestyle/daily events and identifying treatment reminders

Step 1	• Assess patient's readiness for and commitment to ART; readiness to commence ART may be assessed by: o Assess the ability to attend ART centre regularly and not miss appointments o Assess the ability to take OI prophylaxis, e.g., co-trimoxazole o Assess the ability to complete full course of TB therapy, if patient co-infected with TB **List barriers to adherence and develop strategies to overcome these barriers** • Adequate understanding of ARV adverse drug effects • There should be strict adherence to treatment. Adherence to recommended regimens should be > 95 % to avoid development of ARV drug resistance. • If patients have difficulty in adhering to regular doses, reinforce adherence counselling • Enlist community outreach teams and peer support groups of PLHIV, as appropriate • Inform that treatment is lifelong • The timing of drug intake is critical (e.g. drugs taken twice daily must be taken every 12 hours, while drugs to be taken once daily, must be taken at 24-hour interval). Missed doses can be taken up to 6 hours later in a twice-daily regimen. If > 6 hours have elapsed, skip the dose and take next normal dose. If the pill of the once daily regimen of TLE is missed, then it should be taken as soon as patient remembers within 12 hours. • Dietary requirements with ARV drugs: Some drugs are taken with food, some on an empty stomach. Fatty food needs to be avoided before some drugs and some require an increased intake of water • The side-effects of the drugs have to be explained to and understood by the patient before commencing ART. Give an information sheet to patients about the ART regimen they are taking • People on ART need to continue to use condoms regularly and practice safe injecting drug use • Other medications, including herbal/traditional products, may interact with ART • Patients need careful counselling about which medications are allowed and which are not with their ART • Regular clinic attendance for monitoring of efficacy, side-effects and adherence is essential • Help the patient explore his/her feelings. Many patients are preoccupied with problems related to family, job, relationships, etc. and cannot focus on strict adherence until negative feelings about these problems are sorted out

Step 2	**Counselling - in one or more individual sessions:** • Help the patient explore his/her feelings. Many patients are preoccupied with problems related to family, job, relationships, etc. and cannot focus on strict adherence until negative feelings about these problems are sorted out • Many have no private place to store their medicines and are not able to take them in privacy. Not wanting others to know their HIV status is by far the commonest reason for poor adherence by patients. Patients must be realistic about whom to confide their HIV status and how to tell them **Check for any financial difficulties the patient may be experiencing:** • Some patients may not follow up if they do not have money to travel to the centre, or their health maybe affected by a poor diet • Help patients develop secondary support systems for themselves
Step 3	**Solving practical problems and creating a treatment plan** • Where will the ARV drugs be stored? • At what time will they be taken? • How will the patient remember or who will remind him/her to take the medication if he/she forgets? • What will the patient do if his/her normal routine is interrupted? • A time should be agreed upon to meet or telephone the patient within a few days of starting ART to discuss any problems • If patients cannot keep the appointment, counsellors should make phone calls and or arrange home visits through CSC

The counsellors shall follow the following check-lists as given in Table 2

Table 2: Check-lists to be used for identifying treatment adherence*:

No.	Check-lists for treatment adherence
1	On time pill pick up
2	Number of doses missed since the last visit
3	Whether doses are taken at correct time interval (if not, ask about delay in hours)
4	Reasons for missing / incorrect dosing / non-adherence
*For more details, refer to Annexure 4 (Checklist for Adherence Counselling)	

The key to successful adherence is educating the patient before the initiation of therapy, supporting ARV initiation as the patient first starts taking medications, and continuously monitoring and supporting adherence. The reinforcement of the principles of adherence by treatment supporters (guardian), relatives, friends and community support personnel are of great help. Providing PLHIV with an information sheet on the ART regimen they are taking will facilitate adherence and education.

Calculating Adherence:

There are number of ways of measuring adherence like self- reporting by patient, pill count, home visit, patient diary etc. Pill count is the most commonly used method to assess the adherence. In each follow up visit, patient should be asked to bring the pill box with the unconsumed remaining pills. For more than one type of pill, adherence needs to be calculated for all drug combination

separately and reasons for different adherence patterns to different drugs should be explored. Following formula is used to calculate the adherence.

$$\text{Adherence (in \%)} = \frac{\text{Total number of pills the patient has actually taken}}{\text{Total number of pills should have taken in that time period}} \times 100$$

This is equal to

$$\frac{\text{Number of pills given to the client} - \text{Number of pills balance in the bottle}}{\text{Number of pills the client should have taken}} \times 100$$

Examples:

1) Tab TLE (Single pill daily) = Number of pill balance- 9, patient returns on 28th Day. Adherence Calculation-

   (30-9) / 28 X 100 = 75%

2) Tab ZLN (One Pill Twice daily dose) = Number of pill balance- 23, patient returns on 25th Day. Adherence Calculation-

   (60-23) / (25x2) x 100 = 37 / 50 x 100 = 74%

3) Tab TL +ATV/r (TL and ATV/r Two pill once daily dose) = Number of pill balance- 9 TL and 11 ATV/r, patient returns on 25th Day.

   Adherence Calculation- individual drug combination adherence needs to be calculated and whichever is lower, can be considered for reporting purpose

   TL Adherence = (30- 9) / 25 x 100 = 21 / 25 x 100 = 84%

   ATV/r adherence = (30- 11) / 25 x 100 = 19 /25 x 100 = 76%

   Hence overall adherence = 76%

4) Tab ZL +LPV/r (ZL-One Pill twice daily and LPV/r Two pill twice daily dose) = Number of pill balance- 11 ZL and 25 LPV/r, patient returns on 25th Day. Adherence Calculation- individual drug combination adherence needs to be calculated and whichever is lower, can be considered for reporting purpose

   ZL Adherence = (60- 11) / (25x2) x 100 = 49 / 50 x 100 = 98 %

   LPV/r adherence = (120- 25) / (25x4) x 100 = 95 /100 x 100 = 95 %

   Adherence Calculation- individual drug combination adherence needs to be calculated and whichever is lower, can be considered for reporting purpose

   Hence overall adherence = 95 %

Refer to consolidated HIV Counselling Training Modules for ICTC, PPTCT and ART Counsellors, NACO for more details.

Role of Care and Support Centre (CSC) in improving adherence of PLHIV:

The overall goal of CSC is to improve the survival and quality of life of PLHIV. To improve treatment adherence and education for PLHIV is one of the specific objectives of CSC, because adherence education and support by CSC can help the PLHIV sustain and manage their treatment regimes. The CSC serves as a comprehensive unit for treatment support, retention, adherence, positive living and referral linkages to need based services and strengthening enabling environment for PLHIV.

The day-to-day functioning of the CSC is supported by a team comprising of project coordinator, counsellor, peer counsellor and outreach workers, all of them have different roles in improving adherence of PLHIV by providing treatment education and adherence counselling at the CSC or during outreach activities. The CSC can arrange a support group meeting with a thematic area of ART adherence for a specific group of clients with compromised adherence. The main reasons for sub optimal or poor adherence need to be identified by counsellor / peer counsellor or outreach worker during home visit of the client or during their visit at CSC. An effective outreach should bridge these gaps by providing comprehensive information to enhance the knowledge and ultimately result in improved adherence and better quality of life.

Refer to operational section of NACO Guidelines for ART services for more details about role of CSC in improving adherence of PLHIV and also refer to NACO guidelines on Care and Support Centres.

7. PPTCT and ART in Pregnant Women

Parent-to-child transmission of HIV is a major route of new HIV infections in children. Children born to women living with HIV acquire HIV infection from their mother, either during pregnancy, labour/delivery or through breast feeding which is largely preventable with appropriate intervention, by providing Anti-retroviral therapy (ART) to mothers and Anti-Retroviral (ARV) prophylaxis to infants. A total of 61,000 lakh children (0 to 14 years) are estimated to be living with HIV in India . Out of 29 million pregnancies every year, an estimated 22000 occur in HIV infected women. All these HIV infected pregnant women have to be detected and provided with timely ART in order to reduce mother to child transmission and ultimately to eliminate paediatric HIV. Counselling and information regarding the outcome of pregnancy and HIV related treatment to the HIV infected women is provided under the programme.

Table 1: Risk of HIV transmission from Mother to Child with ARV interventions

ARV Intervention	Risk of HIV Transmission from mother to child
No ARV; breastfeeding	**30-45%**
No ARV; No breastfeeding	**20-25%**
Short course with one ARV; breastfeeding	**15-25%**
Short course with **one ARV;** No breastfeeding	**5-15%**
Short course with **two ARVs;** breastfeeding	**5%**
3 ARVs (ART) with breastfeeding	**2%**
3 ARVs (ART) with No breastfeeding	**1%**

Source: Anti retroviral drugs for treating pregnant women and preventing HIV infectionin infants: Towards universal access, Recommendations for public health approach – 2006 version – WHO

There has been a significant scale-up of HIV counselling and testing, prevention of parent to child transmission (PPTCT) and ART services across the country over the last few years. The number of pregnant women tested annually under the Prevention of Parent-to-Child Transmission (PPTCT) programme has significantly increased over the last decade. However, the HIV testing rates for ANC attendees is still far from universal coverage. The PPTCT services have a reach in a wide area, including sub district level.

Under the national programme, it is recommended to provide lifelong ART for all pregnant and breastfeeding women living with HIV, in which all pregnant women living with HIV receive a "single-pill" triple-drug ART regimen (TDF +3TC + EFV) regardless of CD4 count or clinical stage, both for their own health and to prevent vertical HIV transmission and for additional HIV prevention benefits.

ARV for Pregnant women and Exposed Infant

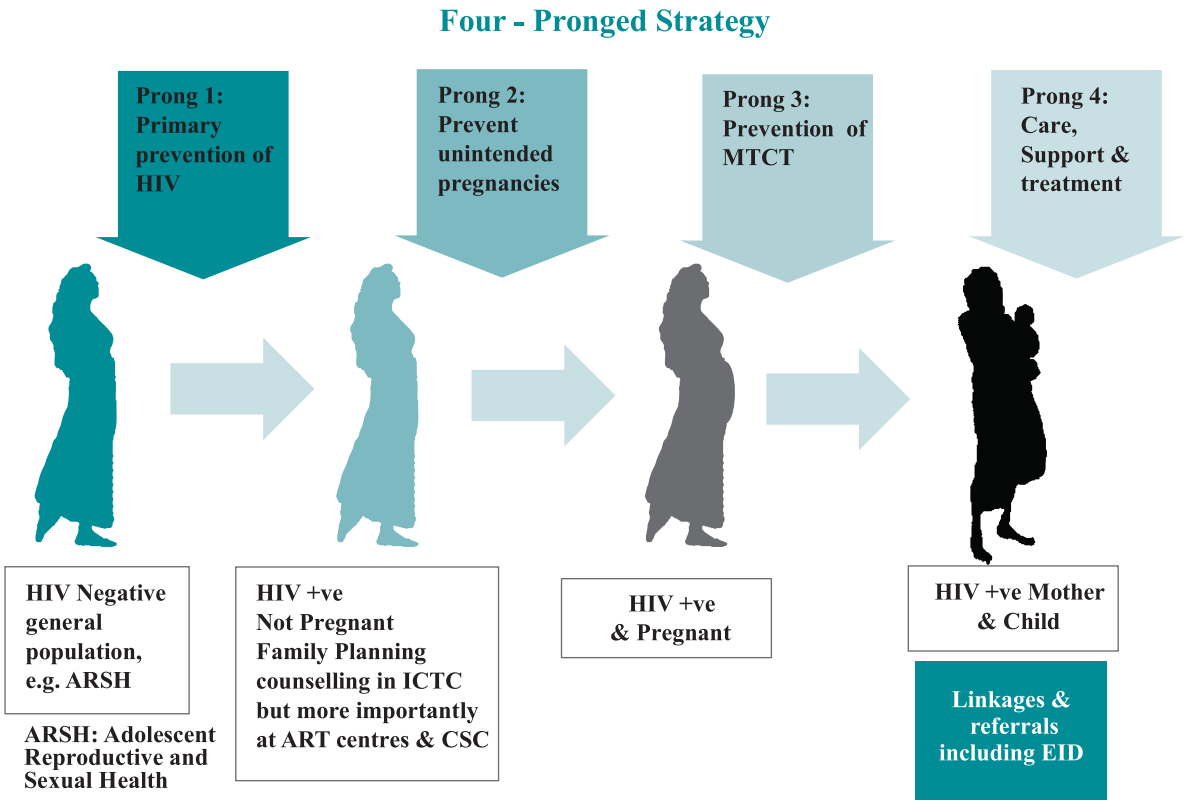
- All HIV positive pregnant women including those presenting in labour and breast feeding should be initiated on a triple drug ART regardless of CD4 count and clinical stage (Test and Treat), for preventing Mother-to-Child Transmission and continue lifelong ART.
- `The duration of Nevirapine prophylaxis to HIV exposed infant should be minimum of 6 weeks. However, this duration of Nevirapine prophylaxis should be extended to 12 weeks, if the duration of ART in pregnant mother falls short 4 weeks during pregnancy and before delivery or reporting at the time labour or after delivery, if not already on ART

- PPTCT Services:

The National PPTCT programme recognizes the 4 elements (Figure 1) integral to preventing HIV transmission among women and children. These include:

- Prong 1: Primary prevention of HIV, especially among women of childbearing age
- Prong 2: Prevention of unintended pregnancies among women living with HIV
- Prong 3: Prevention of HIV transmission from pregnant women infected with HIV to their children
- Prong 4: Provide care, support and treatment to women living with HIV and to their children and families

Figure 1: Four-Pronged strategy



The National PPTCT programme adopts a public health approach to provide these services to pregnant women and their children. Currently, the major activities focused under PPTCT services have been Prong- 3 and 4. However, Prong 1 and prong 2 are also emphasized, to achieve the overall results of the PPTCT Programme.

PPTCT: Interventions during pregnancy:

- Primary prevention of HIV in childbearing women
- Provide HIV information to ALL pregnant women
- Antenatal visits are opportunity for PPTCT
- Prevention of unwanted pregnancies in HIV-positive women
- Prevention of PTCT through ART
- Safe obstetric practices

PPTCT: Interventions during labour and delivery:

- Minimize vaginal examinations
- Avoid prolonged labour; consider oxytocin to shorten labour
- Avoid artificial rupture of membranes
- Early cord clamping after it stops pulsating and after giving the mother oxytocin
- Use non-invasive foetal monitoring
    - o Avoid invasive procedures
    - o Avoid routine episiotomy / support perineum
    - o Minimise the use of forceps or vacuum extractors

Considerations in Mode of Delivery:

1. In India, normal vaginal delivery is recommended unless the woman has obstetric indications (like foetal distress, obstructed labour) for a Caesarean section
2. Use of ART can reduce risk of PTCT better and with lesser risk than a C-section

Goal and Objectives of PPTCT Services in India

Vision: Women and children, alive and free from HIV

Goal: To work towards elimination of paediatric HIV and improve maternal, newborn and child health and survival in the context of HIV infection

Objectives:

1. To detect more than 90 % HIV infected pregnant women in India
2. To provide access to comprehensive PPTCT services to more than 90 % of the detected pregnant women
3. To provide access to early infant diagnosis to more than 90 % HIV exposed infants
4. To ensure access to anti-retroviral drug (ARVs) prophylaxis or Anti-Retroviral Therapy (ART) to 100 % HIV exposed infants
5. To ensure more than 95 % adherence with ART in HIV infected pregnant women and ARV/ ART in exposed children

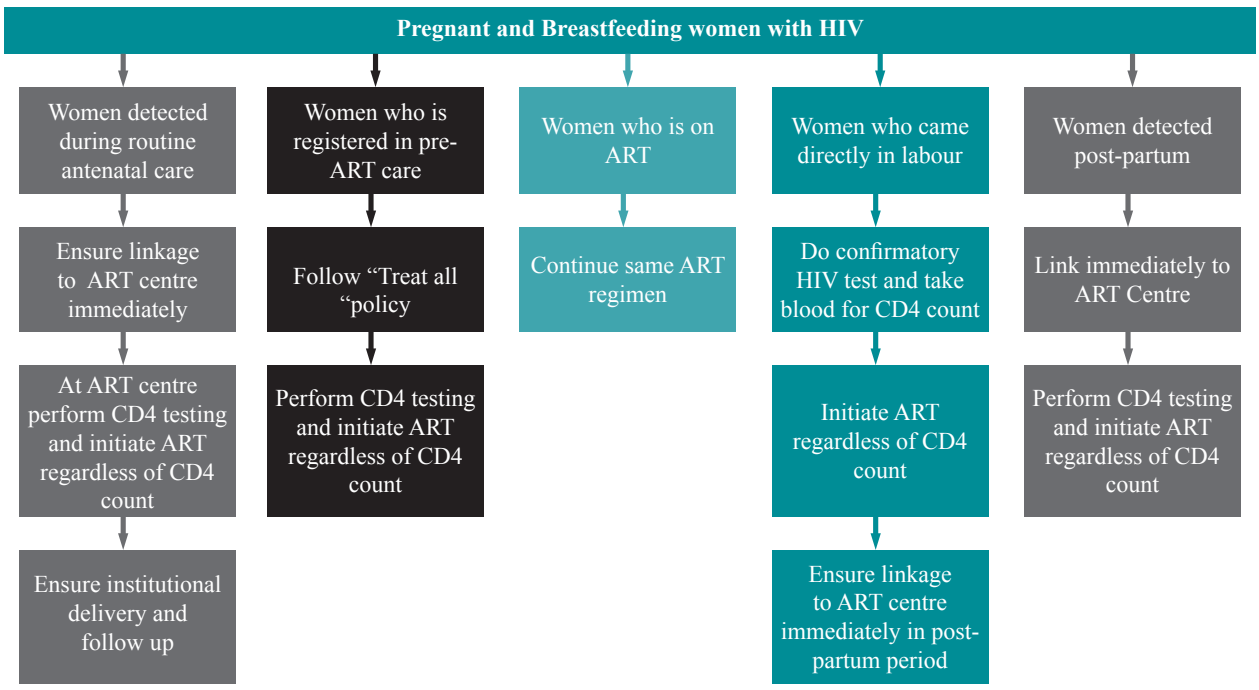
The PPTCT services provide access to all pregnant women for HIV diagnostic, prevention, care and treatment services. As such, the key goal is to ensure the integrated PPTCT services delivery with existing Reproductive & Child Health (RCH) programme.

The Essential Package of PPTCT Services in India includes:

1. Routine offer of HIV counselling and testing to all pregnant women enrolled into antenatal care (ANC) with 'opt out' option
2. Ensure involvement of spouse & other family members and move from an "ANC Centric" to a "Family Centric" approach
3. Provision of lifelong ART (TDF +3TC + EFV) to all pregnant and breastfeeding HIV infected women regardless of CD4 count and clinical stage
4. Promote institutional deliveries of all HIV infected pregnant women
5. Provision of care for associated conditions (STI/ RTI, TB & other Opportunistic Infections -OIs)
6. Provide nutrition counselling and psychosocial support to HIV-infected pregnant women
7. Provide counselling and support for initiation of exclusive breastfeeds within an hour of delivery as the preferred option; continue BF atleast for one year for those infants with negative HIV status (Early Infant Diagnosis Protocol) and 2 years for HIV positive children
8. Provide ARV prophylaxis to infants from birth upto minimum 6 weeks
9. Integrate follow-up of HIV-exposed infants into routine healthcare services including immunization
10. Ensure initiation of Co-trimoxazole Prophylactic Therapy (CPT) and Early Infant Diagnosis (EID) using HIV-DNA PCR at 6 weeks of age onwards as per the NACO EID guidelines.
11. Strengthen community follow-up and outreach through local community networks to support HIV-positive pregnant women and their families

Evaluating HIV Infected Pregnant Women under different case scenario

The decision tree below shows some of the steps taken as part of the evaluation process of HIV-infected and breastfeeding women at the ART Centre:



WHAT ART TO START?

ART in Pregnant / Breast feeding Women

The following table describes the specific groups to which the pregnant women belong and guides the medical officer in selecting the regimen

Table 2: ART regimens in pregnant and breastfeeding with HIV

Target Population	Drug Regimen	Remark
Pregnant and breastfeeding women with HIV (ART Naïve / "Not-already" receiving ART)	TDF + 3TC + EFV	FDC of TDF (300 mg) + 3TC (300 mg) + EFV (600 mg)- To be given 2 hours after low-fat or fat-free dinner
Pregnant and breastfeeding women with HIV already receiving ART	The same ART regimen must be continued	E.g. If they are already on AZT +3TC +NVP/ EFV, continue the same regimen
ART regimen for pregnant women having prior exposure to NNRTI for PPTCT	TDF + 3TC and LPV/r	FDC of TDF (300 mg) + 3TC (300 mg) -- 1-tab OD and FDC of LPV (200 mg)/r (50 mg) - 2-tab BD

- Abacavir + Lamivudine +Efavirenz: First line ART Regimen: for all patients with known renal disease or who develop toxicity to Tenofovir
- As per PPTCT guidelines, all positive pregnant women exposed to NVP/EFV in past should be initiated on Lopinavir/ritonavir (LPV/r) instead of Efavirenz (EFV).

Care and Assessment for Women presenting Directly-in-labour

- Labour room nurse will offer bed side counselling and HIV screening test
- If the woman consents, screen using the "Whole Blood Finger Prick test" in delivery room or labour ward
- If detected HIV positive, the medical Officer i/c will initiate TDF + 3TC + EFV and ensure immediate linkage to ART centre

Labour room nurse informs the ICTC counsellor and lab technician for further confirmation of HIV test as per guidelines

Table 3: Pregnant women presenting in active labour:

Maternal Status	Intra-partum	Post-partum
Presenting in active labour, no prior ART	Initiate TDF (300 mg) + 3TC (300 mg) + EFV (600 mg)	Continue TDF (300 mg) + 3TC (300 mg) + EFV (600 mg)
Nevirapine prophylaxis for breastfeeding infant should be for 12 weeks, as mother did not receive any ART during ante-natal period		

ARV Prophylaxis for Infant:

The infant should be started on Nevirapine. The duration of NVP prophylaxis will depend on the duration of ART that has been given to the mother during her ante-natal period.

- Infants should be started on daily NVP prophylaxis at their first encounter with the health services

- Daily infant NVP prophylaxis can be started even if more than 72 hours have passed since birth and should continue; during this period the mother should be linked to appropriate ART services

Duration of daily infant NVP prophylaxis will depend on "how long the mother was on life-long ART [for a minimum of 4 weeks or not]"

- The duration of NVP given to infant is a minimum of 6 weeks, regardless of whether the infant is exclusively breast fed or exclusive replacement fed
- 6 week-Nevirapine prophylaxis should be increased to 12 weeks, if ART to the mother has been started in late pregnancy, during or after delivery and she has not been on ART for an adequate period as to be effective to achieve optimal viral suppression (which is at least 4
- The recommendation on extended Nevirapine duration (12 weeks) applies to infants of breast-feeding women only and not to those on exclusive replacement feeding
- Infants of women with prior exposure to NVP should get syrup Zidovudine (AZT) in place of syrup Nevirapine

Table 4: Recommended ARV Prophylaxis for HIV Exposed Infants

Infants Birth Weight	NVP daily dose (in mg)	NVP daily dose (in ml) (10 mg Nevirapine in 1 ml suspension)	Duration
Infants with birth weight < 2000 g	2 mg/kg once daily	0.2 ml/kg once daily	Upto minimum of 6 weeks of age regardless of whether exclusively breast fed or exclusively replacement fed Extended to 12 weeks, if the duration of ART received by the mother is less than 24 weeks and she is breast feeding
Birth weight 2000 – 2500 g	10 mg once daily	1 ml once daily	
Birth weight > 2500 g	15 mg once daily	1.5 ml once daily	

Pregnant women with HIV-2 infection

Although the great majority of HIV infections in India are due to HIV-1, there are small foci of HIV-2 infection as well, primarily in western India. HIV-2 also progresses to AIDS, although the progression is generally much slower. HIV-2 has the same modes of transmission as HIV-1 but has been shown to be much less transmissible from mother to child (transmission risk 0-4%).

NNRTI drugs, such as NVP and EFV, are not effective against HIV-2. Follow 'Adult ART guidelines' in HIV-2 infection. If a pregnant woman is detected and confirmed to have HIV-2 alone or combined HIV-1 and HIV-2 infection, she should receive PPTCT treatment interventions recommended for women with HIV-2 infection. This maternal intervention should be coupled with daily Zidovudine (AZT) to the infant from birth for minimum 6 weeks of age.

HIV Exposed Infants of HIV-2 infected mother

Start syrup AZT in place of NVP syrup, immediately after birth till 6 weeks of age

The recommended dosages are:

- Birth weight > 2.5 Kg: 15 mg per dose twice daily
- Birth weight < 2.5 Kg: 10 mg per dose twice daily

Specific Interventions during Infancy:

- Observe for signs and symptoms of HIV infection
- All HIV exposed infants should receive co-trimoxazole at 6 weeks of age
- Follow standard immunization schedule
- Routine well baby visits
- Early Infant Diagnosis: DNA PCR test
    - 18-month visit for HIV antibody testing

Safer Infant Feeding:

Exclusive Breast feeding for first 6 months of life is recommended.

In a situation where the mother is practicing mixed feeding, Health-care workers and Counsellors should motivate her to exclusively breastfed.

When exclusive breast feeding is not possible for any reason (maternal sickness, twins), Mothers and health care workers can be reassured that maternal ART reduces the risk of postnatal HIV transmission in the context of mixed feeding as well.

Mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first six months of life, introducing appropriate complementary foods thereafter and continue breastfeeding.

Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided.

Mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or beyond (similar to the general population) while being fully supported for ART adherence.

Adequate and timely ART, safe methods of delivery and good care of the mother during the antenatal period will help to decrease risk of transmission.

ARVs require ongoing care and monitoring and reduce risk of PTCT in the following ways:

- Reduce viral replication and viral load
- Treat maternal infection
- Protect the HIV-exposed infant
- Improve overall health of mother

Choice of breastfeeding should be the decision of woman based on proper information; counselling on breastfeeding should begin during the ante-natal period itself

As India embarks on the goal of eliminating parent to child transmission of HIV, it is evident that good coverage with ANC, high rates of HIV testing, effective ART for pregnant and breastfeeding mothers with ARV prophylaxis to infants will remain key factors contributing to the success of preventing the vertical transmission.

For more programmatic details on PPTCT, please refer to the updated National Strategic Plan on Multi Drug ART for Parent to Child Transmission of HIV, 2013, NACO and the National HIV Counselling and Testing Services Guidelines (HCTS), 2016, NACO.

Table 5: PPTCT Case Scenarios

No.	Case Scenarios	Required actions
1.	Mrs. A was given single dose (sd) NVP prophylaxis during labour 2 years back. Now she is again pregnant and CD4 is 400. What regimen (ART) should be given now? What ARV prophylaxis to be given for infant and for what duration?	As per national guidelines, all HIV infected pregnant women should be initiated on ART regardless of the CD4 count; hence she is eligible for ART. She has received single dose NVP previously and hence there are chances of arcHIVed resistance to NNRTI (Nevirapine & Efavirenz). Considering this, she shall be initiated with the regimen TDF +3TC +LPV/r. Considering the chances of arcHIVed resistance to NNRTI in mother and subsequent transmission to infant, Nevirapine is not the ideal agent for prophylaxis. In such cases Zidovudine syrup is the preferred ARV prophylaxis*. If Zidovudine syrup is not available, Nevirapine syrup may be used
2.	Mrs. B was given sd NVP during labour 2 years back. Her latest CD4 is 200. She is not pregnant now. What regimen should be given now?	The patient is eligible for ART as per Test and Treat policy. She has received sd NVP previously and hence there are chances of arcHIVed resistance to NNRTIs. Considering this, the proposed regimen should be TDF +3TC +LPV/r.
3.	Mrs. C received option B (triple ARV) in 2013 during her first pregnancy. Now she reports to the ART centre in December 2016 presenting with second pregnancy (first trimester). Her latest CD4 count is 420. What regimen should be given to her now? What ARV prophylaxis should be given for infant and for what duration, if baby is on ERF?	The patient received option B (TDF +3TC +EFV) and it was stopped 7 days after discontinuation of breast feeding. As she was on triple drug ART, chances for arcHIVed resistance to NNRTIs are minimal. Hence it is recommended that life-long ART be initiated, with the same regimen that is TDF +3TC +EFV. For the infant, give syrup Nevirapine for 6 weeks
4.	Mrs. D received option B in 2013 during her first pregnancy. At present her CD4 count is 576. She is not pregnant. What regimen should be given now?	Initiate ART (TDF +3TC +EFV), as she is eligible for ART initiation
5.	Mrs. E presented directly – in labour in 2013. She was given sd NVP and ZL for 7 days. Now she is presenting with second pregnancy (third trimester) What regimen should be given now? What ARV prophylaxis should be given to infant and for what duration, if the baby is breastfed?	Initiate life-long TDF +3TC +LPV/r Syrup Zidovudine should be given to the baby for 12 weeks. If not available, then syrup Nevirapine may be given for 12 weeks.

6.	Mrs. F, an asymptomatic post-natal PLHIV presents 3 days after delivery at the ART Centre; her CD4 count is 550. She has opted for exclusive replacement feeding (ERF). What is the next step in the management of the mother? What is the next step in the management of the baby?	Even though the mother has opted for ERF, she needs to be started on ART, as she is eligible for ART initiation, as per "Test and Treat Guidelines" For the baby, give syrup Nevirapine for 6 weeks (baby is on ERF)
7.	Mrs. G, 21 years, HIV positive and pregnant, presented in the ANC clinic, and opted for MTP; her CD4 count is 580. Should we initiate her on ART? If yes, which regimen?	She needs to be started on ART, as she is eligible for ART initiation, as per "Test and Treat Guidelines. TDF +3TC +EFV will be the appropriate regimen.
8.	Mrs. H, 26 years, registered at the ART centre in 2010. She was initiated on ART in 2010 on AZT +3TC +EFV. She reported at the ANC clinic with 2 months pregnancy in December 2014. Her last visit to the ART Centre for ART was in December, 2014. She missed her ART due date in January 2015. She was followed up through ORW and linked back to the ART centre in February 2015. What regimen should be given now? What ARV prophylaxis should be given to the infant, if the mother is breastfeeding and for what duration?	Continue the same Regimen, AZT+3TC+EFV Syrup Nevirapine for 6 weeks
10.	Mrs. J, 28 years, last visited the ART centre in September 2015. She was followed up by the ORW and linked back to the ART centre in February 2016. She reported that she was pregnant (6 months). What regimen should be given now? What ARV prophylaxis should be given to the infant and for what duration, if the baby is ERF	Continue the same regimen, if she is already on ART. Start TDF +3TC +EFV regimen, if she is not already on ART Syrup Nevirapine for 6 weeks, as the baby is on ERF
11.	Mrs. K was diagnosed HIV +ve direct-in-labour. She was initiated on ART (TDF +3TC+EFV). On discharge, she was given 7 pills and was advised to visit ART centre. However, she visited the ART centre after 45 days. What regimen should be given now? What ARV prophylaxis should be given to the infant and for what duration, if the baby is breastfed?	Continue the same regimen (TDF +3TC +EFV) Syrup Nevirapine for 12 weeks to the baby

12.	Guidance is required for management of mother and baby in case of HIV 1 and 2 co-infections. As per national guidelines, HIV 2 and HIV 1 and 2 should be treated with PI based regimen.	Patients of HIV 1 and 2 co-infection shall be treated as HIV 2 Mother should get TDF +3TC +LPV/r For baby, syrup Zidovudine is the drug of choice.
13.	Guidance is required for babies born to HIV infected mother presenting 72 hours after delivery	Current guidelines – ARV prophylaxis is to be given to babies brought even after 72 hours of delivery
	Scenario A: Mother (not on ART) and breast-feeding baby presenting within 6 months of delivery	**Mother:** Initiate ART (TDF +3TC +EFV) **Infant:** Initiate syrup Nevirapine prophylaxis (duration 12 weeks) At 6 weeks (and after): Follow Early Infant Diagnosis (EID) algorithm; perform DNA PCR • If DNA PCR is positive, initiate ART (AZT/ ABC + 3TC + LPV/r) • If DNA PCR is negative, the child has to be followed up: At 6 months: Perform Rapid antibody test and subsequently DNA PCR (if necessary), as per EID algorithm
	Scenario B: Mother (not on ART) and baby presenting within 6 months of delivery; baby is on Exclusive Replacement Feeding	**Mother:** Initiate ART (TDF +3TC +EFV) **Infant:** Initiate syrup Nevirapine prophylaxis (duration 6 weeks) At 6 weeks (and after): Follow Early Infant Diagnosis (EID) algorithm; perform DNA PCR • If DNA PCR is positive, initiate ART (AZT/ ABC + 3TC + LPV/r) If DNA PCR is negative, the child has to be followed up: At 6 months: Perform Rapid antibody test and subsequently DNA PCR (if necessary), as per EID algorithm and take further decision accordingly
	Scenario C: Mother (on TDF +3TC +EFV from second month of pregnancy) and breast-feeding baby presenting after 6 months of delivery	**Mother:** Continue ART (TDF +3TC +EFV) **Infant:** Initiate syrup Nevirapine prophylaxis (duration 12 weeks) • Perform Rapid antibody test as per EID algorithm and subsequently DNA PCR (if necessary), as per EID algorithm and take further decision accordingly

8. Considerations for co-infection of Tuberculosis and HIV

Introduction

Available evidences show that PLHIV are nearly 29 times (26- 31 times) more likely to develop TB as compared to people without HIV in the same country[1]. TB accelerates HIV disease progression and AIDS and paves the way for clinical TB and mycobacteremia. It is also well recognized that HIV and TB make a fatal combination with extremely high death rates (15– 18%) reported among HIV- infected TB cases, notified under the Revised National Tuberculosis Control Programme (RNTCP). The management of patients with HIV and TB co-infection poses many challenges, including patient's acceptance of both diagnoses, relapses after stopping anti-TB treatment and re-infection with new exogenous infection. Early detection of TB, effective TB treatment, prompt linkage to HIV care and early initiation of treatment can mitigate the impact of TB on the health and survival of PLHIV. Patients with TB merit special consideration because the co-management of HIV and TB is complicated by drug interactions between Rifampicin and NNRTIs (e.g. Nevirapine) and Protease Inhibitors, IRIS, pill burden, adherence and drug toxicity. Active TB is the commonest OI among HIV-infected individuals and is also the leading cause of death amongst PLHIV.

NACO and Central TB Division (CTD) are now providing single window services for prevention and management of HIV-TB co-infection at ART centres so as to ensure seamless services to PLHIV.

This chapter has been broadly divided into two sections:

1. General principles for management of HIV-TB co-infected patients
2. General principles for prevention of TB in PLHIV

1. General Principles for Management of HIV-TB Co-infected Patients:

- Intensified Case Finding using 4-symptom complex for TB screening; fast-tracking and referral of symptomatic patients for CBNAAT test and other appropriate investigations, as required, for TB diagnosis
- If a patient with active TB is diagnosed with HIV, the first priority is to start TB treatment in accordance with the RNTCP guidelines
- All HIV-TB co-infected persons are to be initiated on ART regardless of the CD4 count. ART reduces the incidence and recurrence of TB, as well as case fatality rates.
- Co-trimoxazole prophylaxis should be given to all HIV-TB patients

Intensified Case Finding Using 4-Symptom Complex, Fast tracking and Referral for TB Diagnosis

Intensified case finding (ICF) involves systematic screening for active TB among high-risk

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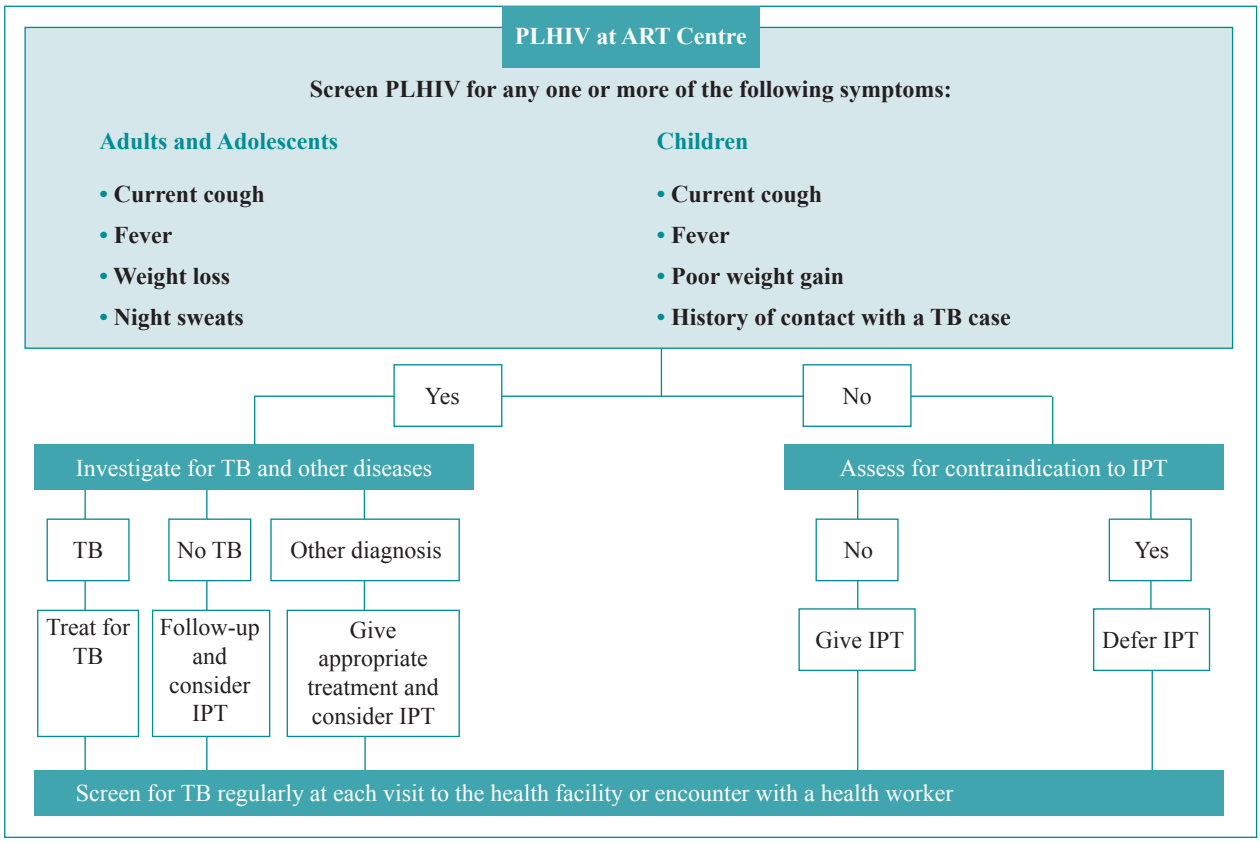
Tuberculosis prevalence surveys: a handbook. Geneva: World Health Organization; 2011

populations at each visit to a health facility. ICF is one of the critical interventions for increased TB case detection. It is an important step towards earlier diagnosis and treatment of TB to reduce mortality, prevention of ongoing TB transmission and also an initial step to rule out TB disease so that TB preventive therapy can be initiated

All PLHIV should be regularly screened for TB during every visit to the ART centres using the 4-symptom complex—current cough, fever, weight loss and night sweats among adults. In children, the 4-symptom complex includes current cough, fever, poor weight gain and history of contact with a TB case. PLHIV with all forms of TB showed that the sensitivity of 4S complex (current cough, fever, weight loss and night sweats) was 85%[2]. (Figure 1 presents the algorithm for ICF at ART centres). PLHIV found positive for any of the four symptoms (4S +) should be fast-tracked at the centre.

Figure 1: Algorithm for ICF at ART centres



Diagnosis of TB in PLHIV

PLHIV found positive for any of the four symptoms (4S +) should be referred for CBNAAT test/ other appropriate investigations for TB diagnosis. As per RNTCP guidelines, CBNAAT is the preferred diagnostic technique for TB testing in PLHIV as compared to smear microscopy. Sputum microscopy has poor sensitivity in detecting TB in PLHIV due to fewer organisms in sputum.[3] CBNAAT is a molecular test that detects the DNA of the TB bacteria in PLHIV. It uses sputum or any other biological specimen (except blood and blood-contaminated specimens) and can give

2 Getahun H.,etal. Development of a standardised screening rule for tuberculosis in people living with HIV in resource constrained settings: individual participant data meta-analysis of observational studies. PLoS Medicine, 2011, 8(1):e1000391.doi:10.1371/journal.pmed.1000391Meta-analysis of 12 studies and 8,148

WHO. 2014. Xpert MTB/RIF for people living with HIV

a result in less than two hours. It can also detect the genetic mutations associated with resistance to the drug Rifampicin. As per studies, the median sensitivity of smear microscopy was 52.8 % (range 22.2– 68.9), compared to 84 % (58.3– 91.7) with CBNAAT. Based on the clinical history and investigation reports, TB case need to be classified as:

- Microbiologically or clinically diagnosed TB case
- Pulmonary or extra pulmonary TB case
- Rifampicin sensitive or Rifampicin resistant or status not known
- New case or previously treated case

(Definitions for classification of TB case and type of TB case are provided as annexure-05)

Anti-TB treatment in HIV-TB co-infected patients:

Anti-TB drugs used under RNTCP are provided in table 1 below.

Table 1: Anti-TB drugs used under RNTCP

Regimen I	Regimen II	Regimen IV	Regimen V
Isoniazid	Isoniazid	Kanamycin	Capreomycin
Rifampicin	Rifampicin	Levofloxacin	PAS
Pyrazinamide	Pyrazinamide	Ethionamide	Moxifloxacin
Ethambutol	Ethambutol	Cycloserine	High dose-Isoniazid
	Streptomycin	Pyrazinamide	Clofazimine
		Ethambutol	Linezolid
		PAS*	Amoxyclav
		Capreomycin*	Clarithromycin*
		Moxifloxacin*	Thioacetazone**

Reserve drug* * Thioacetazone is contraindicated in PLHIV*

Studies showed that daily ATT is more efficacious than intermittent regimen (Odds of relapse relative to daily regimens was 2.8 (1.4– 5.7) for thrice-weekly intermittent regimen[4]). All PLHIV diagnosed with TB should be initiated on daily ATT at the ART centre itself, based on the classification of the type of TB patient and weight band. Table 2 describes the Anti-TB treatment and Tables 3 & 4 provide details of the daily dosage schedule for adult and paediatric patients respectively. The treatment dose remains the same (for both adult and paediatric patients) even if the weight band changes during the course of TB treatment. The details regarding management of MDR / XDR TB cases are given in Annexure 06. PLHIV diagnosed with MDR / XDR TB will be managed at DR-TB centres.

Table 2: Anti-TB treatment schedule

Type of TB Case	Treatment Regimen
New: A TB patient who has never had treatment with anti-TB drugs or has taken it for less than one month	2 H7 R7 Z7 E7 + 4 H7 R7 E7

4 Kwok Chiu Chang et al. American Journal of Respiratory Critical Care Medicine, 2011,17,1153-8

Previously Treated: A TB patient who has received one month or more of anti-TB drugs in the past	2 H7 R7 Z7 E7 S7 + 1 H7 R7 Z7 E7 + 5 H7 R7 E7
H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol, S: Streptomycin	

Table 3: Daily dose schedule for adults (as per weight band)

Weight Band	Number of Tablets		Inj. Streptomycin mg (Intensive Phase Only)
	Intensive Phase (IP)	Continuation Phase CP)	
	HRZE (4FDC)	HRE (3FDC)	
	75/150/400/275 mg	75/150/275 mg	
25– 39 kg	2	2	500mg
40– 54 kg	3	3	750 mg
55– 69 kg	4	4	1000 mg
>70 kg	5	5	1000 mg

Table 4. Daily dose schedule for paediatric patients (as per weight band)

Weight Band	Number of Tablets (Dispersible FDC)				Injection Streptomycin mg (Intensive Phase Only)
	Intensive Phase (IP)		Continuation Phase (CP)		
	HRZ 50/75/150 mg	E 100 mg	HR 50/75 mg	E 100 mg	
4– 7 kg	1	1	1	1	100 mg
8– 11 kg	2	2	2	2	150 mg
12– 15 kg	3	3	3	3	200 mg
16– 24 kg	4	4	4	4	300 mg
25– 29 kg	3 +1A	3	3 +1A	3	400 mg
30– 39 kg	2+2A	2	2+2A	2	500 mg
A=Adult 4FDC in IP and 3FDC in CP					

ART initiation in PLHIV with TB co-infection

In the absence of ART, TB therapy alone does not significantly increase the CD4 cell count. Nor does it significantly decrease the HIV viral load. Thus, CD4 counts measured during active TB are likely to reflect the actual level of immunosuppression. The use of ART in patients with TB can lead to a sustained reduction in the HIV viral load. It can also facilitate immunological reconstitution and decrease AIDS-defining illness and mortality. This benefit is seen across different ranges of CD4 counts.

All PLHIV diagnosed with active TB are to be initiated ART regardless of CD4 count, after initiation of TB treatment in accordance with the RNTCP guidelines discussed above. ART may need to be started later, keeping in mind the pill burden, time needed for acceptance of the diagnosis, counselling needs, drug interactions, toxicity and IRIS.

Table 5. ART in relation to initiation of TB treatment

Patient's details	Timing of ART in relation to initiation of TB treatment	ART recommendations
HIV-TB co-infected patients	• Start ART regardless of the CD4 count • Start ATT first, initiate ART as soon as TB treatment is tolerated (between 2 weeks and 2 months)	Appropriate ART Regimen*
Rifampicin	• HIV-TB co-infected patients with CD4 count < 50 cells/cmm, need to be started on ATT first and then ART within 2 weeks with strict clinical monitoring	Appropriate ART Regimen*

*The use of the standard 600 mg/day dose of Efavirenz is recommended for patients receiving Efavirenz and Rifampicin

IRIS may occur in upto one-third of patients who have been diagnosed with TB and who have been started on ART. It typically presents within three months of the initiation of ART but can occur as early as five days. Patients with TB-associated IRIS most commonly present with fever and with worsening of pre-existing lymphadenopathy or respiratory disease. The symptoms are similar to the paradoxical reactions seen in immuno-competent patients on ATT, but occur more frequently. Most cases resolve without any intervention and ART can be safely continued. Serious reactions, such as tracheal compression caused by massive adenopathy or respiratory difficulty, may occur. Therapy may require the use of anti-inflammatory drugs, including corticosteroids.

Recommendations if TB is diagnosed in patients already receiving ART:

There following points to be considered in PLHIV if TB is diagnosed in patients already receiving ART:

- **Modification of ART:** In PLHIV who are already on ART at the time of TB diagnosis, modification of ART needs to be done to maintain optimal efficacy of ATT as well as ART.

Table 6: Recommendations if TB is diagnosed in patients already receiving ART

ART regimen at the time when TB is diagnosed	Management options
(AZT or TDF or ABC) + 3TC + EFV	Continue with two NRTIs + EFV
(AZT or TDF or ABC) + 3TC + NVP	Substitute NVP with EFV and continue of EFV thereafter even after TB treatment is completed
Two NRTIs + PI	Substitute Rifampicin with Rifabutin* in the ATT
Raltegravir (RAL) (Integrase Inhibitor) containing regimen	Drug interaction between Rifampicin and Raltegravir- 1. Substitute Rifampicin with Rifabutin (or) 2. Dosage of Raltegravir has to be increased from 400 mg twice daily to 800 mg twice daily, in case Rifampicin is prescribed or continued
** If an HIV-TB co-infected patient on first line ART is to be initiated on PI based second line ART (Treatment failure based on viral load), then initially Rifampicin should be substituted with Rifabutin and PI based second line ART should be initiated after 15 days.*	

- When a patient on ART presents with active TB, there is a possibility of suspecting treatment (ART) failure. NACO recommends the following guiding principles in this context:
  - If an episode of TB occurs within the first six months of the initiation of ART, it should

not be considered as failure of the treatment. The ART regimen should be adjusted for co-administration with Rifampicin-containing regimens.

- If an episode of TB develops more than six months after the initiation of ART, and data on the CD4 count (and viral load), are available, the decision on whether the diagnosis of TB represents ART failure should be based on the CD4 count (and viral load, if available) data. The development of an episode of pulmonary TB after six months of ART, without other clinical and immunological evidence of disease progression, should NOT be regarded as representing ART failure. Extra pulmonary TB should be considered as indicative of ART failure, although simple lymph node TB or uncomplicated pleural disease may be less significant than disseminated TB. Close monitoring is needed, and adherence support should be reinforced.

Anti TB drugs – Adverse drug reactions and drug-drug interaction with ART

Anti TB drugs – Adverse drug reactions

It is difficult to determine and measure the efficacy or toxicity of a particular drug, since anti-TB drugs are almost invariably administered in combination regimens of several drugs. However, if two or more drugs are taken simultaneously, synergistic as well as antagonistic interactions may occur between the drugs and the host. Table 7 describes the common and rare side effects of anti-TB drugs.

Table 7: Common and rare side effects of anti-TB drugs

Common (1- 10%)	Rare (Less than 1%)
Nausea and vomiting Gastritis Hepatitis Hypersensitivity reactions Cutaneous reactions	Flu- like syndrome Peripheral neuropathy Ocular toxicity Joint related side effects Myelosuppression Anaemia Thrombocytopenia Psychosis Seizures

Adverse drug reactions of anti-TB drugs of regimens I and II in RNTCP are described below:

Isoniazid

- Peripheral neuropathy is the most common toxic manifestation. Tuberculosis patients infected with HIV are at higher risk of peripheral neuropathy. Isoniazid neurotoxicity can be prevented by pyridoxine. The recommended dosage of pyridoxine is 50 mg daily for adults, 25 mg daily for children between 14- 25 kg and 12.5 mg for children between 1- 13.9 kg.
- Some patients complain of light-headedness, lethargy and fatigue, particularly with the higher intermittent doses
- Isoniazid- induced hepatotoxicity is reversible, if the drug is stopped early
- Toxic psychosis and generalised epileptic convulsions (infrequent)

Rifampicin

- Rarely, serious hepatotoxicity, generally with a cholestatic pattern, may occur

- Rifampicin causes orange-red discoloration of body secretions such as urine, faeces, tears, and sweat, and may result in permanent discolouration of soft contact lenses

Pyrazinamide

- Joint pain is a common adverse effect in daily regimen. Management of Arthralgia: acetylsalicylic acid or other analgesic, anti-inflammatory agents; does not require withdrawal of the drug. Classic gout is rare (Elevated serum uric acid). Asymptomatic increase in serum uric acid does not require any treatment
- Severe hepatotoxicity has been observed when regimens containing Rifampicin and Pyrazinamide are used
- Hypersensitivity reaction (including fever, rash and other cutaneous reactions) may occur occasionally

Ethambutol

- Ethambutol may produce retro bulbar neuritis
    - An impairment of vision, with reduction in visual acuity, red– green blindness, blurring, central scotomas, and peripheral field defects
    - Ocular toxicity seems to be dose- dependent and occurs only rarely if no more than 15 mg/kg is given daily
    - Patients receiving Ethambutol should be warned that an ocular examination should be undertaken if visual symptoms occur
    - Vision usually returns to normal within a few weeks if the drug is stopped; the optic nerve may be permanently damaged if Ethambutol is continued

Streptomycin

- Hypersensitivity reactions such as fever and rash
- Toxicity is manifested as vertigo and ataxia, tinnitus and loss of hearing
- Transient and minor adverse effects, such as circum-oral numbness and tingling, may occur soon after injection
- Streptomycin is contraindicated in pregnant women because of the risk of impairing development of the eighth cranial nerve of the foetus
- Streptomycin also potentiates neuromuscular blocking agents used during anaesthesia and should be avoided in patients with myasthenia gravis

Please refer to section 1 of Annexure 07 for adverse drug reactions of Anti-TB drugs in general

Reintroduction of anti-TB drugs:

Algorithm for reintroduction of anti-tubercular drugs is described in Section 2 of Annexure 07 (Anti-TB drugs – Adverse Drug reactions and Drug- drug interactions). Re-introduction, even if warranted, must be done by experts and must be closely supervised. Details about management of drug- induced Hepatitis are given in section 3 of Annexure 07.

Anti TB drugs – Drug- drug interactions

Rifampicin Drug Interactions

Rifampicin is an inducer of many enzymes of the cytochrome P 450 super family, including

CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP3A5 and CYP3A7. It will speed up the metabolism of any drug metabolised by any of these enzymes in the body. Possible interactions listed include antiretroviral agents, atorvastatin, rosiglitazone/pioglitazone, celecoxib, clarithromycin, caspofungin and lorazepam.

Rifabutin Drug Interactions

Rifabutin is an anti-mycobacterial agent similar to Rifampicin however Rifabutin has significantly less effect on drugs metabolised by cytochrome P 450 3a enzymes; this may reduce the magnitude of drug- drug interactions. Drugs that induce or inhibit CYP3A metabolizing enzymes can influence Rifabutin concentrations leading to the need for Rifabutin dose adjustment, which adds to the complexity of co-treatment. If a patient whose Rifabutin dose was decreased to avoid drug interactions related to co-treatment with antiretroviral therapy, subsequently stops taking the interacting antiretroviral drug (e.g., ritonavir), the resulting Rifabutin concentrations can become sub-therapeutic, putting the patient at risk of tuberculosis treatment failure or emergence of "Rifamycin" resistance.

Please refer to annexure 08 for details on TB drug interactions with different ARVs

Management of HIV –TB co-infection Specific Situations

The table below provides information on the ATT regimen and ART for specific situations.

Table 8. TB treatment in specific situations

SCENARIO	ACTION
TB treatment in PLHIV on Protease Inhibitor (PI) based ART	• Rifampicin suppresses bioavailability of boosted PIs (Atazanavir/ritonavir, Lopinavir/ritonavir, Darunavir/ritonavir). However, Rifabutin, an effective anti-TB derivative of Rifamycin group, does not inhibit effectiveness of these drugs • Rifabutin is not available in FDC and hence should be provided as a loose drug. Substitute Rifampicin with Rifabutin (150 mg daily) for the entire duration of Anti-TB treatment in such cases • Anti-TB treatment initiation should be done as soon as TB is diagnosed even in patients on PI based ART. If substitution of Rifampicin with Rifabutin can not be done immediately, then try to replace Rifampicin with Rifabutin later, whenever Rifabutin is available. If Rifampicin is continued for longer duration, thiswill make the boosted PI based regimen ineffective and will fasten the emergence of drug resistance mutants and eventual treatment failure for ART
TB treatment in children living with HIV (CLHIV) on Protease Inhibitor (PI) based ART	• Super boosting of Lopinavir (LPV) with Ritonavir is recommended in children in proportion of 1:1 • If super boosting of LPV is contraindicated, triple NRTI is to be considered as next choice • Higher dose of Nevirapine (NVP) is to be considered as the last choice
Pregnant women	• Streptomycin is ototoxic to the foetus and should not be used during pregnancy • Injection Streptomycin should not be used in pregnant women
Use of Integrase Inhibitor (Raltegravir)	Drug interaction between Rifampicin and Raltegravir- dosage of RAL – 800 mg twice daily

<table>
<tr><td>Use of Injection Streptomycin for active TB, in patients over 50 years of age and/ or < 50 kg of weight</td><td colspan="2">• Patients aged over 50 years may not tolerate the daily dose of Streptomycin more than 750 mg
• Similarly, patients weighing less than 50 kg may not tolerate doses above 500-750 mg daily
• Extend Continuation Phase (CP) by 3 to 6 months</td></tr>
<tr><td rowspan="6">Renal Impairment (Creatinine clearance < 30 ml/min or for patients receiving haemodialysis)</td><td colspan="2">• Modification in dose and frequency*</td></tr>
<tr><td>Isoniazid</td><td>No adjustment necessary</td></tr>
<tr><td>Rifampicin</td><td>No adjustment necessary</td></tr>
<tr><td>Pyrazinamide</td><td>25- 35 mg/kg per dose three times per week (not daily)</td></tr>
<tr><td>Ethambutol</td><td>15- 25 mg/kg per dose three times per week (not daily)</td></tr>
<tr><td>Streptomycin</td><td>12- 15 mg/kg per dose two or three times per week (not daily)</td></tr>
</table>

2 General Principles for prevention of TB in PLHIV at ART Centres:

- Intensified Case Finding using 4-symptom complex
- Isoniazid Preventive Therapy
- Airborne Infection Control

Intensified Case Finding using 4-Symptom Complex

As discussed under Section 7.1, Intensified Case Finding (ICF) is one of the critical interventions for prevention of ongoing TB transmission and also the initial step to exclude the TB disease and initiate TB preventive therapy.

Isoniazid Preventive Therapy

Isoniazid Preventive Therapy (IPT) entails the administration of Isoniazid (INH) to individuals with latent TB infection so as to prevent progression to active TB disease. Isoniazid is one of the most effective bactericidal anti-TB drugs that protect against progression of latent TB infection to active disease (against endogenous reactivation). It also prevents TB re-infection post exposure to an open case of TB (against exogenous re-infection/ super infection/ nosocomial transmission). Several studies have shown that IPT administration in PLHIV prevents incidence and relapse of TB and is, therefore, a key public health intervention for TB prevention in PLHIV. The effects of IPT augment the effects of ART on reducing the incidence of TB. With the concomitant administration of both ART and IPT, there is a likelihood of restoration of TB-specific immunity by ART and the beneficial effect of IPT may be prolonged. IPT does not promote Isoniazid resistance when used to treat latent TB infection. In latent TB, the *Mycobacterium tuberculosis* bacilli are fewer in number and are dividing slowly, resulting in an extremely low risk of selecting drug-resistant mutants. A study[5] conducted in 2010 reflected that the prevalence of INH resistance among IPT-exposed persons was similar to the background population.

Ruling out Active TB

Adults and adolescents living with HIV should be screened for TB with a clinical algorithm. The absence of all the four symptoms of current cough, night sweats, fever and weight loss (4S–ve) can identify a subset of adolescents and adults living with HIV who have a very low probability

of having TB disease and who can be reliably initiated on IPT. This screening has a negative predictive value of 97.7 % (95 % CI [confidence interval] 97.4– 98.0) at 5 % TB prevalence in PLHIV. Children living with HIV (more than 12 months of age) who do not report current cough, fever, poor weight gain and history of contact with a TB case (4S-ve), are unlikely to have active TB. Additional investigations (chest X-ray and Tuberculin Skin Test) can help in ruling out active TB but are not mandatory.

Eligibility for IPT

All adults and adolescents living with HIV should be screened for TB with a clinical algorithm. Those who do not report any one of the four symptoms of current cough, fever, weight loss and night sweats are unlikely to have active TB and should, therefore, be assessed for IPT initiation. All children living with HIV (more than 12 months of age), who do not report with current cough, fever, poor weight gain and history of contact with a TB case, are unlikely to have active TB and should, therefore, be assessed for IPT initiation. IPT is not an emergency intervention. If there is any doubt about the TB status of a patient, IPT should be delayed.

Contraindications to IPT

IPT should not be provided to patients in the following conditions:

- Active TB disease
- Active hepatitis
- Signs and symptoms of peripheral neuropathy- Persistent tingling, numbness and burning sensation in the limbs
- Poor adherence to Co-trimoxazole Preventive Therapy (CPT)
- Poor understanding of IPT by the guardian
- Contact with MDR-TB case
- PLHIV who have completed DR-TB treatment

IPT Work Up

The patient should be evaluated for signs of liver disease (yellowness of eyes) and neuropathy (persistent numbness and burning sensation in feet and hands) and examined for jaundice and tenderness in the right upper quadrant of the abdomen. Wherever available, routine liver function tests/ ALT should be performed, but lack of LFT/ ALT results should not delay the initiation of IPT in asymptomatic patients. If the patient does not have any abnormality based on the assessment above, assess for adherence using the criteria on the backside of the ICF/IPT card.

IPT Regimen Plan

The regimen plan and dosing chart are provided below:

Adults and Adolescents: Isoniazid 300 mg + Pyridoxine 50 mg (Vitamin B6) per day for 6 months

5 Van Halsema et al. 2010. Tuberculosis outcomes and drug susceptibility in individuals exposed to isoniazid preventive therapy in a high HIV prevalence setting. AIDS. 2010 Apr 24;24(7):1051-5.

Table 9. Paediatric dosage chart for IPT

Weight Range (kg)	Number of 100 mg tablets of INH to be administered per dose (Total dose 10 mg/kg/day)	Dose (mg)
< 5	½ tablet	50
5.1– 9.9	1 tablet	100
10– 13.9	1 ½ tablet	150
14– 19.9	2 tablets	200
20– 24.9	2 ½ tablets	250
> 25	3 tablets or one adult tablet	300

IPT Initiation and Follow-up

All the 4S–ve patients should be assessed by SMO/MO to determine eligibility for IPT. IPT should be considered for both on-ART and pre-ART patients (if found 4S–ve). IPT should be initiated, if not contraindicated. IPT drugs must be provided on a monthly basis (30 days) to all eligible patients. If IPT must be used in conjunction with antiretroviral therapy, a rational approach would be to start IPT after completion of about 3 months of antiretroviral therapy (delayed IPT).

4S screening should be done for all the patients (on-ART and pre-ART) on IPT during every visit to exclude active TB. In case a patient becomes 4S+ve during the IPT course, he/ she should be investigated for TB and if found positive, IPT should be stopped and ATT should be initiated.

IPT in Specific Situations

IPT provision in special circumstances, such as patients who are previously treated for TB, patients with ART, pregnancy, and MDR-TB, is summarized in Table 10.

Table 10. IPT provision in specific situations

Scenario	Action
Patients previously treated for TB (Secondary prophylaxis)	• All CLHIV/ PLHIV who had successfully completed treatment for TB disease earlier should receive INH for six months • All CLHIV/ PLHIV who have just completed successful treatment for TB disease should receive INH for an additional six months
IPT with ART (Secondary prophylaxis)	• Combined use of IPT with ART is recommended for all CLHIV/ PLHIV regardless of: o Degree of immunosuppression o Previous treatment for TB o Pregnancy • ART should not be delayed while starting or completing a course of IPT
IPT and pregnancy	• Pregnant woman living with HIV should not be excluded from symptom-based TB screening and receiving IPT • Isoniazid is safe in pregnancy. Start IPT in all HIV positive pregnant women regardless of their gestation period • Advise women to complete IPT if a woman becomes pregnant while taking IPT • Assure patient that IPT is safe while breastfeeding

IPT in children born to microbiologically confirmed TB mothers	• If a baby is born to a microbiologically confirmed TB mother, assess the new born for active TB • Non-specific features suggestive of neonatal TB include: Fever, low birth weight, hepato-splenomegaly, irritability, feeding intolerance • If the child has none of the above, give IPT for 6 months
IPT and MDR-TB	• Contacts of MDR-TB and PLHIV who have completed DR-TB treatment are not eligible for IPT
Patient on IPT develops TB during IPT treatment	• If a patient develops TB symptoms during IPT treatment, evaluate the patient for TB and conduct DST. Based on DST results, the appropriate treatment should be provided • If the patient is sensitive to all the drugs, then based on history of ATT and duration of IPT decide on the following: o If the patient has not received anti-TB treatment in the past and has taken IPT for less than 1 month, then provide the patient with treatment for new case (CAT I) o If the patient has received anti-TB treatment in the past OR if the patient has taken IPT for more than 1 month, then provide the patient with re-treatment (CAT II) regimen • If the patient is found to have DR-TB, refer the patient to the DR-TB centre
Patients develop TB after IPT treatment	Treat the TB episode as new or previously treated case, based on previous TB treatment history and Rifampicin resistance pattern (whenever available). *IPT is not to be considered as past history of TB in such cases*
If a patient had taken IPT for less than one month in total and discontinued for any reason (like toxicity or loss to follow up)	• Conduct adherence counselling, address reasons for discontinuation, conduct ICF, and, if asymptomatic, restart INH afresh • Ensure they have completed a 6- month course
After taking IPT for more than one month: If the patient had discontinued IPT for less than three months	• Conduct adherence counselling, conduct ICF, and, if asymptomatic, restart INH • Ensure they complete a 6- month course within a 9- month period
After taking IPT for more than one month: If the patient discontinued for more than three months or had discontinued more than once	Do not re-initiate IPT

Airborne Infection Control Activities at ART Centres

Presence of immuno-compromised patients in health care and congregate settings lacking effective infection control measures creates a favourable environment for TB transmission. The national *Guidelines on Airborne Infection Control in Health care and Other Settings* have identified ART centres as one of the high-risk settings for TB transmission. Presence of robust systems and policies is vital to control airborne transmission of TB infection in PLHIV at ART centres. Effective implementation of AIC measures involves four recognized controls in a hierarchy:

1. Managerial controls

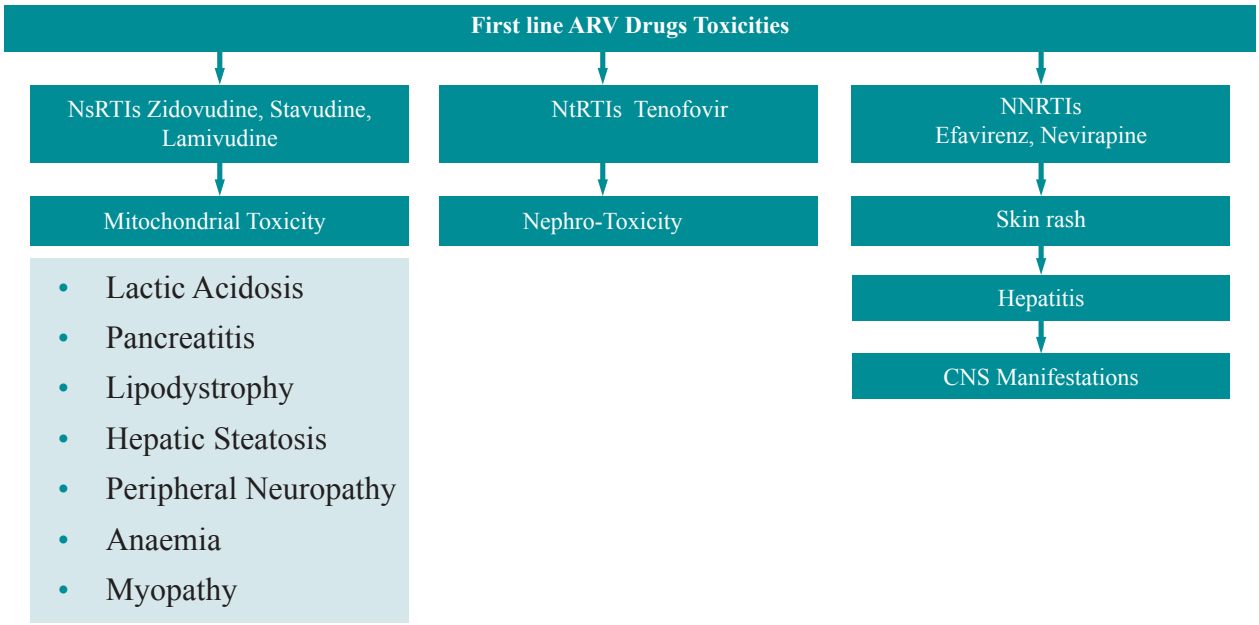
2. Administrative control strategies for health-care facilities
3. Environmental controls
4. Personal respiratory protection (PPE)

Note: For details, refer to "Guidelines on Prevention and Management of TB in PLHIV at ART Centres" Dec 2016

9. First line ART in adults & adolescents: Management of ARV Toxicities

ARV drugs used in first line ART regimens for adults and adolescents in the national ART programme in India are Zidovudine, Tenofovir, Abacavir, Lamivudine, Efavirenz and Nevirapine. These drugs are associated with toxicities, which may be class specific and/or drug specific. The class specific drug toxicities to Nucleoside Reverse Transcriptase Inhibitors (NsRTIs and NtRTIs) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are depicted in figure 1.

Fig 1: First line ARV Toxicities in adults and adolescents



ARV drugs are associated with a broad range of toxicities, ranging from low-grade intolerance, which may be self-limiting, to life-threatening adverse reactions. Differentiating between complications of HIV disease and ART toxicity is sometimes difficult. The toxicities of ARVs need to be differentiated from manifestations of a new opportunistic infection and Immune Reconstitution Inflammatory Syndrome (IRIS). Alternative explanations should be considered before it is concluded that the manifestations are related to ART toxicity. The factors to be considered include inter current illness (e.g. hepatitis A and malaria) and reactions to medications other than ARV drugs (e.g. Isoniazid-induced hepatitis or co-trimoxazole-induced rash). Most of the toxicities/side-effects can be adequately co-managed with efficient clinical monitoring at all levels of the health care system.

The management of ARV toxicities is based on clinical and laboratory monitoring. The frequently encountered Adverse Drug Effects for the first line anti-retroviral drugs are provided in table 1.

Table 1: Adverse Drug Effects of commonly used First line ARVs in adults and adolescents

Class of ARV Drugs	Drugs	Adverse Effects
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Tenofovir (TDF)	Renal toxicity, Bone demineralization
	Zidovudine (ZDV, AZT)	Anaemia, neutropenia, bone marrow suppression, gastrointestinal intolerance, headache, insomnia, myopathy, lactic acidosis, skin and nail hyperpigmentation
	Lamivudine (3TC)	Minimal toxicity, rash, though very rare
	Abacavir (ABC)	Hypersensitivity reaction* in 3 to 5 % (can be fatal), fever, rash, fatigue, nausea, vomiting, anorexia, respiratory symptoms (sore throat, cough, shortness of breath); re-challenging after reaction can be fatal.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Efavirenz (EFV)	CNS symptoms (dizziness, somnolence, insomnia, confusion, hallucinations, agitation) and personality change. Rash occurs, but less common than NVP. Avoid taking EFV after heavy fatty meals
	Nevirapine (NVP)	Hepatitis (usually within 12 weeks); sometime life-threatening hepatic toxicity. Skin rash occasionally progressing to severe conditions, including Stevens Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Patients who develop severe hepatic toxicity or grade 4 skin rashes while being treated with Nevirapine should not be re-challenged.
Protease Inhibitors (PIs)	Atazanavir/ ritonavir (ATV/r)	Hyper bilirubinaemia. Less lipid problems than LPV/r. Hyperglycaemia, fat maldistribution, nephrolithiasis
	Lopinavir /ritonavir (LPV/r) Heat stable tablets	Diarrhoea, nausea, vomiting, abnormal lipid profiles, glucose intolerance. PI should not be prescribed with Simvastatin as they significantly increase the level of Simvastatin leading tp rhabdomyolysis, resulting in severe kidney failure
* Abacavir hypersensitivity is linked to the presence of the HLA-B 5701 gene. It is associated with < 5% of adults and children in India. Hypersensitivity usually occurs during first 6 weeks of therapy, but may occur at any time; it can potentially be fatal. Whenever hypersensitivity reaction is noticed, abacavir has to be discontinued immediately; never re-challenge or use it again.		

The clinicians approach the commonly observed ARV drug toxicities in relation to the time of their occurrence after initiating first line ART. The toxicities can be termed as “short-term”, “medium term” and “long-term” and they are classified according to the class of ARV drugs in table 2.

Table 2: Common ARV drug toxicities

Class of ARV drugs	Drugs	Short term toxicities	Medium term toxicities	Long term toxicities
NRTIs	**Zidovudine**	Headache, nausea vomiting, malaise Diarrhoea Bone Marrow suppression Anaemia (Macrocytic)	Bone Marrow suppression Anaemia (Macrocytic) Hyper pigmentation Lactic Acidosis Proximal myopathy	None
	Lamivudine	Skin rash (rare)	None	None
	Stavudine	None	Lactic Acidosis Pancreatitis Peripheral Neuritis	Lipodystrophy Dyslipidaemia
	Abacavir	Hypersensitivity reaction in 3 to 5 % (can be fatal), fever, rash, fatigue, nausea, vomiting, anorexia, respiratory symptoms (sore throat, cough, shortness of breath)		
	Tenofovir	Nephrotoxicity (low incidence) Fanconi syndrome and rarely Acute Renal Failure Can reduce bone mineral density		
NNRTIs	**Efavirenz**	Drowsiness, dizziness Confusion, Vivid dreams Skin Rashes; Hepato toxicity (very rare)	none	None
	Nevirapine	Skin Rashes Hepato toxicity	None	None

Clinicians and other supporting staff of ART centres (counsellors, nurses and pharmacists) should be well versed with overlapping toxicities exhibited by ARVs and other co-administered drugs used for other co-existing conditions or for prophylaxis for certain opportunistic infections. Some conditions are provided in table 3.

Table 3: Overlapping Toxicities:

Overlapping Toxicities	Drugs
Bone marrow suppression	Zidovudine, Co-trimoxazole, Dapsone, Pyrimethamine, Ganciclovir, Amphotericin B, Ribavirin
Hepatotoxicity	Nevirapine, Atazanavir, Lopinavir, Ritonavir, Isoniazid, Rifampicin, Pyrazinamide, Fluconazole, Co-trimoxazole
Peripheral neuropathy	Stavudine, Isoniazid
Pancreatitis	Stavudine, Co-trimoxazole

Regardless of severity, toxicities may affect adherence to therapy. A proactive approach is required to manage them.

- Discuss potential side-effects of the ART regimen with the patient before initiation and during the early stages of treatment. This has to be part of preparedness counselling of the patient and the caregiver.
- Differentiate any new clinical event after the initiation of ART from Immune Reconstitution Inflammatory Syndrome (IRIS)
- Always assess the toxicity and grade its severity
- Offer support during minor and major adverse events
- Ensure that the patient is familiar with the signs and symptoms of toxicities that are serious and require immediate contact with the clinical team, especially in the case of EFV-associated Stevens-Johnson syndrome, hepatitis, NRTIs led lactic acidosis or Abacavir-associated hypersensitivity reaction
- The clinicians shall be able to recognize drug toxicities during the scheduled or unscheduled visits of PLHIV at the ART centres and shall be able to manage them as described in table 4.

Table 4: Clinical signs and Symptoms and Management of Adverse Effects of Antiretroviral Drugs

Adverse Effect	Possible Offending Drug(s)	Clinical Signs / Symptoms	Management
Acute hepatitis	Nevirapine (NVP) and Pl/r; Efavirenz (EFV) less common; Uncommon with Zidovudine (AZT), Stavudine (d4T) (< 1%)	Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia, NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia)	If possible, monitor serum transaminases and bilirubin. If ALT > 5 times the baseline level, stop ARVs until symptoms resolve. NVP should be permanently discontinued. Substitute the most likely offending ARV drug

Acute pancreatitis	Stavudine (d4T); Lamivudine (3TC) - infrequent	Nausea, vomiting and abdominal pain	If possible, monitor serum pancreatic amylase, lipase. All ARVs should be stopped until symptoms resolve. Restart ART with change to different NRTI, preferably one without pancreatic toxicity (e.g. AZT, TDF, ABC)
Lactic acidosis	All Nucleoside reverse transcriptase inhibitors, particularly Stavudine (d4T)	Initial symptoms are variable: a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhoea. abdominal pain, hepatomegaly, anorexia, and/or sudden unexplained weight loss, respiratory symptoms (tachypnoea and dyspnoea) or neurological symptoms (including motor weakness)	Discontinue all ART; symptoms may continue or worsen after discontinuation of ART. Give appropriate therapy. Resume ART with replacing offending ART with either ABC or TDF
Hypersensitivity Reaction	Abacavir (ABC) Nevirapine (NVP)	ABC: Constellation of acute onset of symptoms including: fever, fatigue, myalgia, nausea / vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea (with or without rash). While these symptoms overlap those of common infectious illnesses, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hypersensitivity reaction NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, eosinophilia with or without rash	Discontinue all ART until symptoms resolve. The reaction progressively worsens with drug administration and can be fatal. Administer supportive therapy. Do not re-challenge with ABC (or NVP), as anaphylactic reactions and death have been reported. Once symptoms resolve, restart ART with a change to different NRTI if ABC-associated or to PI- or NNRTI –based regimen if NVP-associated

Rash/drug eruptions- including Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis (TEN)	Nevirapine (NVP); Efavirenz (EFV)- rarely	Rash usually occurs during the first two to four weeks of treatment. The rash is usually erythematous, maculopapular, confluent; most prominent on the body and arms may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson syndrome or Toxic Epidermal Necrolysis has been reported in ~0.3 % of infected individuals receiving Nevirapine	In mild cases, give anti-histamines. If rash is moderate, non-progressing and without mucosal or systemic symptoms, consider substituting NVP to EFV after rash resolves. In moderate and severe cases, discontinue all ARVs until symptoms resolve and give supportive treatment. Permanently discontinue NVP for rash with systemic symptoms such as fever, severe rash with mucosal lesions or urticaria, or Stevens-Johnson syndrome or toxic epidermal necrolysis. Once resolved, switch ART regimen to different ARV class (e.g. two NRTIs and PI)
Peripheral Neuropathy	Stavudine / (d4T)	Pain, tingling, numbness of hands or feet, distal sensory loss, mild muscle weakness and areflexia can occur	Stop suspect NRTI early and switch to different NRTI that does not have neurotoxicity (e.g. AZT, ABC). Symptoms usually resolve in two to three weeks
Diarrhoea	Lopinavir/ritonavir (LPV/r)	Loose or watery diarrhoea	Usually self-limited. No need to discontinue ART. Offer symptomatic treatment; if diarrhoea is not controlled, switch to ATV/r, as dose of RTV is less in ATV/r (mostly Ritonavir is responsible for diarrhoea)
Dyslipidaemia, Insulin resistance and hyperglycaemia	PIs, EFV		Consider replacing the suspected PI by drugs with less risk of metabolic toxicity
Gastrointestinal intolerance	All ARVs	Gastritis, indigestion, etc.	Usually self-limited. No need to discontinue ARVs. Offer symptomatic treatment
Haematological toxicities e.g. anaemia, leucopoenia	Zidovudine (AZT)	Fatigue Breathlessness Palpitation	If severe (Hb < 6.5 g/dL and/or absolute neutrophil count < 500 cells/cmm) - substitute with an NRTI which has less effect on bone marrow e.g. d4T, ABC or TDF. Consider blood transfusion

Lipoatrophy **Lipodystrophy**	All NRTIs; particularly Stavudine (d4T)	Lipodystrophy syndrome: dyslipidaemia consisting of elevated total cholesterol, low high-density lipoprotein (HDL) cholesterol and elevated triglycerides; Insulin resistance with hyperglycaemia; Central fat accumulation (visceral, breast, neck) and local fat accumulation (lipomas, buffalo-hump); Generalized diminution of sub cutaneous fat mass (lipoatrophy). Lipoatrophy includes loss of sub cutaneous fat in the face, extremities and buttocks	Early replacement of suspected ARV drugs (e.g. d4T) with TDF or ABC. Consider aesthetic treatment and physical exercises
Neuro psychiatric changes	Efavirenz (EFV)	High rates of CNS effects in the first 2- weeks e.g. Confusion, abnormal thinking, nightmares, impaired concentration, depersonalization, abnormal dreams, dizziness, insomnia, euphoria, hallucinations, suicidal ideation. Severe depression has been reported in 2.4 %	Usually self-limited. No need to discontinue unless severe psychosis. Counsel to take EFV at night before bedtime
Renal Toxicity (Renal Tubular Dysfunction)	TDF	Features of Fanconi syndrome i.e. Hypophosphatemia, hypouricemia, proteinuria, normoglycemic glycosuria. Acute renal failure has been reported. Risk factors—low body weight and pre-existing renal disease	Discontinue TDF and give supportive treatment, after resolution, replace with another ARV
Note: Discontinuing the offending agent would mean substituting with an alternative drug to ensure efficacy of ART regimen			

Tenofovir Toxicity:

Tenofovir (TDF) is now preferred first line ART for all new patients to be enrolled in national ART programme. It has a good overall safety profile, with fewer metabolic side-effects & mitochondrial toxicities. TDF has a relatively long half-life, allowing once daily dosing and making compliance easier for patients. The major side effects of TDF are:

- Renal toxicity
- Decrease in bone marrow density

However, out of these, the most significant is TDF related renal toxicity, though overall incidence may by only 3- 5 %. The renal proximal tubule (PT) is the main target of TDF toxicity. For more details on Tenofovir toxicity, readers can refer to annexure 09 (Additional Guidance on Tenofovir

related renal toxicity).

Whenever Rash/ drug eruptions-including Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis (TEN) occur during first line ART in adults and adolescents, it is usual to condemn an NNRTI drug (Efavirenz/Nevirapine) as the causative agent. To hold Efavirenz/ Nevirapine as the offending agent may not be always right. Clinicians always need to be alert to suspect other offending agents as well.

- Co-trimoxazole can be an offending agent
- Many ART centres have identified Lamivudine to be the offending drug in limited number of patients
- There are sporadic reports on Zidovudine / Lopinavir / Atazanavir / Ritonavir / Darunavir / Raltegravir induced skin rashes

Therefore, in this situation, it is essential to identify the offending drug before appropriate action initiated. The clinicians are advised to follow the two guiding algorithms given hereunder (Figures 2 & 3).

Figure 2: For Patients starting ART (AZT/ TDF +3TC +NVP/ EFV) without co-trimoxazole or starting ART > 2 weeks after CPT initiation

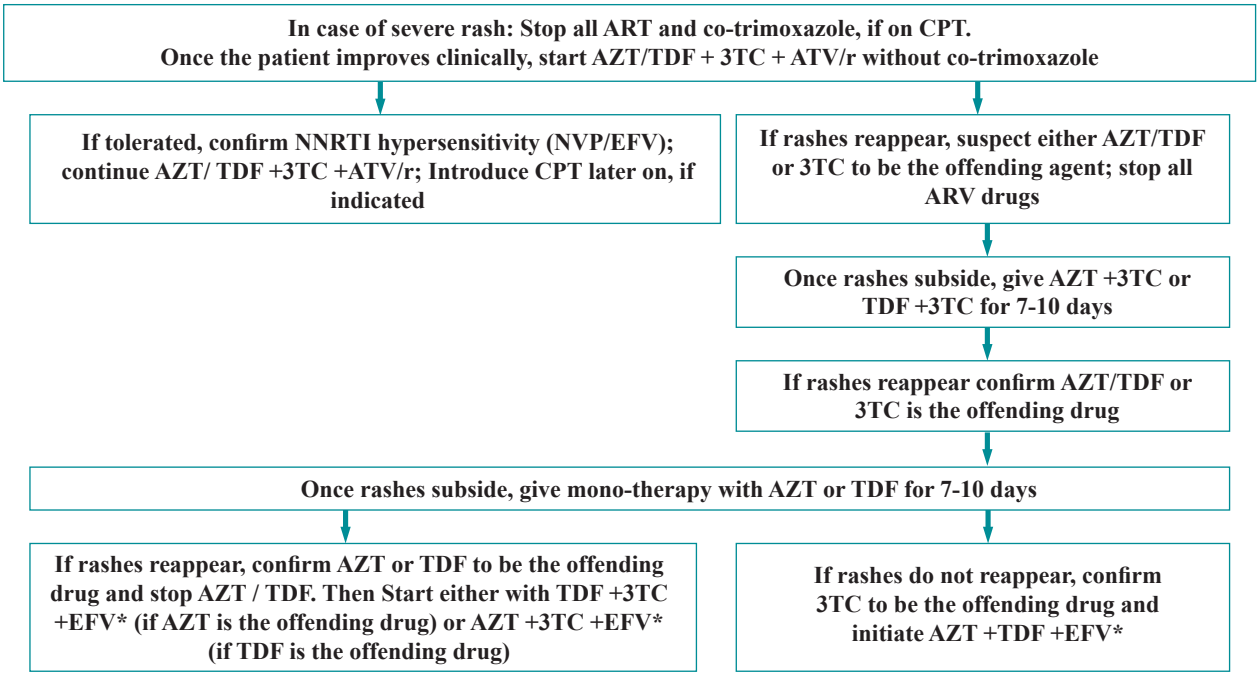
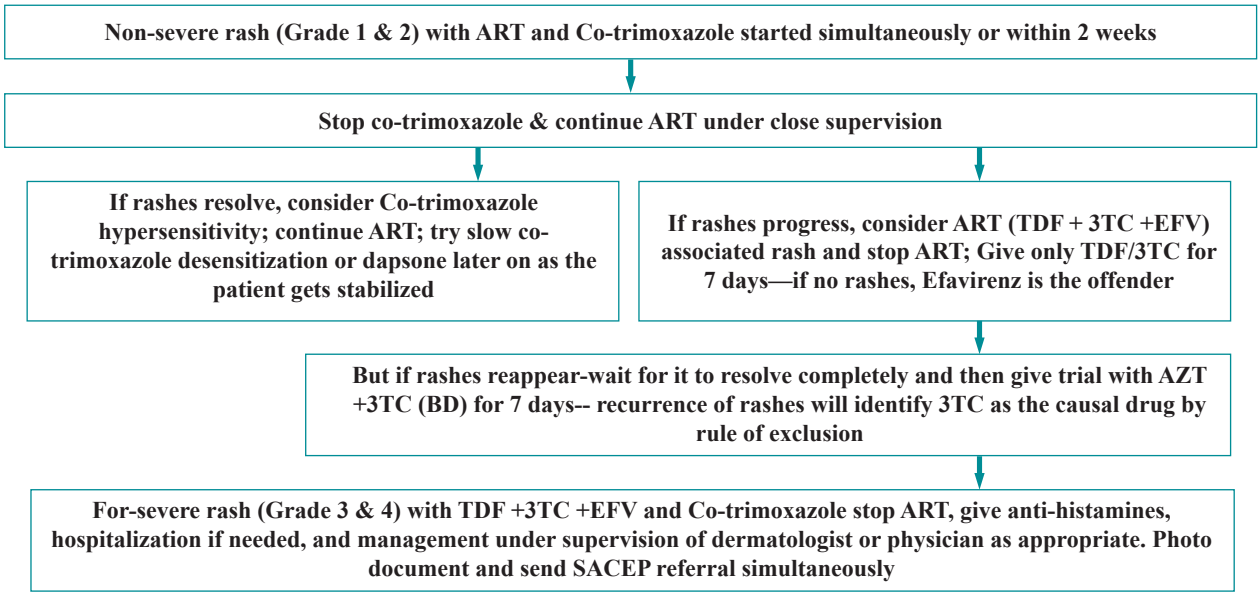


Figure 3: Algorithm for patients starting ART (TDF + 3TC +EFV) and CPT simultaneously or within 2 weeks



As a general principle, mild toxicities do not require the discontinuation of ART or drug substitution. Symptomatic treatment may be given. Moderate or severe toxicities may require substitution of the drug with another, of the same ARV class, but with a different toxicity profile. Severe life-threatening toxicity requires discontinuation of all ARV drugs until the patient is stabilized and the toxicity is resolved.

Grading of Toxicities:

Toxicity to ARV drugs can be identified by clinical manifestations (symptoms, signs) and or by abnormal laboratory parameters. Division of AIDS, National Institute of Allergy and Infectious Diseases (Version 1.0 December 2004) had categorized ARV drug toxicities into four grades:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Potentially life-threatening

Grading of selected clinical and laboratory toxicities are given in table 5.

Table 5: Grading of selected clinical and laboratory toxicities (Refer to annexure 10 for more details)

Estimating severity of grade	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life-threatening Grade 4
Clinical adverse events NOT identified elsewhere in the table	Symptoms causing minimal or no interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care OR medical or operative intervention indicated to prevent permanent impairment, permanent disability or death

Source: Division of AIDS, National Institute of Allergy and Infectious Diseases. Version 1.0 December 2004 clarification August 2009
Note: This clarification includes addition of Grade 5 toxicity, which is death

According to grading of toxicities, as reflected by severity of clinical adverse events, patients' have to be managed as guided with advisories given in the table 6.

Table 6: Grading of toxicities and Management advisories

ARV Drug Toxicity	Grading of ARV Drug Toxicities			
	Grade 1	Grade 2	Grade 3	Grade 4
Severity	**Mild**	**Moderate**	**Severe**	**Potentially life-threatening**
Clinical adverse events	Symptoms causing minimal or no interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care OR medical or operative intervention indicated to prevent permanent impairment, permanent disability or death
Advice	Changes of ART should be avoided; Observe	Changes of ART should be avoided; Observe	It will usually be necessary to discontinue the suspected drug until the condition resolves. Subsequently, it may be possible to cautiously re-administer the drug (under close monitoring)	Discontinue all the drugs and hospitalise the patient. The offending drug should not be re-administered. After improvement, institute the alternate ART regimen, comprising of a drug substituted for the offending drug

Drug Substitution:

Definition: Single drug replacement of individual ARV (usually within the same class) for toxicity, drug-drug interactions, or intolerance refers to SUBSTITUTION of individual (offending) drug and this does not indicate that a second line regimen is being used even if second line drugs like boosted PIs are used for substitution.

It is different from "Switch", which indicates "Treatment Failure", refers to the loss of antiviral efficacy to current regimen and it triggers the switch of the entire regimen from First to Second line. It is identified by clinical and/or immunological criteria and confirmed by the virological criteria.

Drug substitution: General Guidance:

1. The general principle is that single-drug substitution for toxicity should be made within the same ARV class.
2. If a life-threatening toxicity occurs, all ART should be stopped until the toxicity has resolved and a revised regimen commenced when the patient has recovered.
3. Whenever an ARV toxicity is suspected, rule out other OIs or other conditions that may be responsible. Always grade the toxicity according to their severity: refer to table 5

4. Patients with Dual Toxicity to Nevirapine and Efavirenz, needing substitution of protease inhibitors. These (PI based) regimens have to be started at CoE / ART plus centre after the review and approval of SACEP

Table 7 below provides guidance on what to change (drug substitution) in case of toxic manifestation.

Table 7: Drug Toxicity and Drug Substitution

ARV	Most Frequent Significant toxicity for the ARV drug	Suggested first line ARV substitution drug
Zidovudine (AZT)	Patients on older regimens (ZLN / ZLE) Severe anaemia or neutropenia Lactic acidosis Severe gastrointestinal intolerance	TDF
Abacavir (ABC)	Hypersensitivity reaction	TDF
Tenofovir (TDF)	Renal tubular Dysfunction (Fanconi's syndrome) Bone mineral density loss	ABC
Efavirenz (EFV)	Persistent and severe central nervous system toxicity Acute symptomatic hepatitis Severe or life-threatening rash (Stevens-Johnson Syndrome)	NVP in case of CNS side effects: ATV/r in case of Grade 4 rashes with EFV
	Severe neuropsychiatric manifestations	ATV/r
Both Efavirenz and Nevirapine	Persistent and severe central nervous system toxicity Acute symptomatic hepatitis Severe or life-threatening rash (Stevens-Johnson Syndrome) Severe neuropsychiatric manifestations	ATV/r
Atazanavir/ritonavir ATV/r	Intolerance	ATV/r
Lopinavir/ritonavir LPV/r	Intolerance	ATV/r
Multiple NRTIs (AZT, ABC, TDF)*	Toxicities / Intolerance	Raltegravir

*** Toxicity / Intolerance to multiple NRTIs:**

There are instances when PLHIV who are initiated on first line ART develop toxicities or intolerance to multiple NRTIs. For e.g., a patient develops nephropathy (contraindicating use of TDF), subsequently develops rash to ABC and develops anaemia subsequently on AZT. Such patients who develop or have documented toxicity / intolerance / contraindications to multiple NRTIs will need individualized drug regimen. Such regimen may include Integrase inhibitor (Raltegravir) in the first line ART itself. Only the CoE must take all these decisions. The ART centres have to send a referral request to the CoE with complete details of the toxicity (including its grading) and documentation of the same. The CoE will review individual situations and recommend the final regimen for the patient (in consultation with NACEP, if needed)

10. HIV and Hepatitis Co-infection

Note: This chapter is intended to provide information on various aspects of HIV and Hepatitis B and C co-infections as many co-infected patients are seen at ART facilities. However, these are not national hepatitis management guidelines and most of the diagnostic tests and drugs mentioned for Hepatitis B and C in this section are not available under national ART programme. The portion pertaining to ART in this section for these coinfected patients are part of national ART guidelines.

Introduction

Hepatitis is the inflammation of the liver caused by viruses A, B, C, D or E, which can be differentiated on the basis of the mode of transmission of the virus. An estimated 257 million people in the world have chronic hepatitis B and another 71 million chronic hepatitis C. Chronic hepatitis B and C claim almost 1.34 million lives each year globally. The South-East Asia region has almost 49 million people living with chronic hepatitis B and C. An estimated 0.35 million succumb to these infections and their complications each year. India has an estimated 39 million HBV carriers and around 6- 12 million people infected with HCV.

Chronic hepatitis B virus (HBV) infection affects 5– 20% of the 36 million people living with HIV worldwide, and hepatitis C virus (HCV) affects 5- 15%, rising to 90 % among people who inject drugs.

HBV, HIV and HCV share similar transmission routes. In general, concurrent or sequential infection with these viruses usually results in more severe and progressive liver disease, and a higher incidence of cirrhosis, hepato cellular carcinomas (HCC) and mortality.

Viral hepatitis is an increasing cause of morbidity and mortality among people living with HIV, including those on ART. A comprehensive approach includes prevention, HBV and HCV testing, hepatitis B vaccination and treatment and care for people with HIV, who are co-infected with hepatitis B and/or hepatitis C.

HIV and Hepatitis B co infection

Around 15- 25 % of PLHIV in South East Asia and Africa are co infected with Hepatitis B. In India, chronic hepatitis B affects around 2- 8 % of PLHIV, though there are wide variations in different parts of the country, with some studies indicating as high as 20 % in certain selected geographical areas. The major mode of transmission of hepatitis B in India is vertical. Around 90 % of children who acquire HIV vertically or perinatally will become chronic HBV carriers. This is as opposed to HIV negative adults, in whom, only 5% of those infected with hepatitis B, become chronic carriers.

The term **Acute HBV infection** refers to new-onset hepatitis B infection that may or may not be icteric or symptomatic. Diagnosis is based on detection of hepatitis B surface antigen (HBsAg) and IgM antibodies to hepatitis B core antigen (anti-HBc). Recovery is accompanied by clearance of HBsAg with seroconversion to anti-HBs (antibodies to hepatitis B surface antigen), usually within 3 months.

The term **Chronic HBV infection** is defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more after acute infection with HBV. Around 20- 40 % of PLHIV will fail to clear Hepatitis B virus beyond 6 months and will become chronically infected.

A. Natural History among HIV - Hepatitis B coinfected

The natural history of both diseases is affected when a person is co-infected with both HIV and Hepatitis B and this has implications on management of both diseases. HIV co-infection has a profound impact on almost every aspect of the natural history of HBV infection. The consequences include higher rates of chronicity after acute HBV infection, higher level of HBV DNA replication and rates of reactivation, reduction of the anti-HBe and anti-HBs sero-conversion, less spontaneous clearance, higher rates of occult HBV (i.e. detectable HBV DNA positivity in the absence of HBsAg seropositivity), increased fibrosis, more rapid progression to cirrhosis and HCC, higher liver-related mortality, and decreased treatment response compared with persons without HIV coinfection. In Western cohorts, liver disease has emerged as a leading cause of death in HIV-infected persons co-infected with either hepatitis B or C, as mortality due to other HIV-related conditions has declined following the introduction of antiretroviral therapy (ART).

Similarly, the Hepatitis B infection also negatively impacts the progression of HIV infection leading to faster immune deterioration and higher mortality. Some of the early cohort studies among co-infected population showed that there is 3- 6 times higher risk of progression to AIDS. Prospective observational cohort among those with primary HIV infection showed that HBV co-infection is an independent predictor of immunologic deterioration in such group of patients. In another large prospective multicentre cohort among PLHIV with sero-conversion window of less than 3 years, co infected persons with Hepatitis B were associated with two times higher risk of AIDS/death, higher among HBV co-infected patients compared to HBV mono-infected patients.

The HIV-Hepatitis co-infected persons show faster CD4 decline, slower CD4 recovery following ART, increased incidence of AIDS & non-AIDS events, increased rate of ARV toxicity and increased chances of immune reconstitution hepatitis. In one of the large cohort studies of more than 5000 co -infected persons, the relative risk of liver related deaths was found to be 19 times higher than those with HBV mono-infected patients.

Other challenges among coinfected include cross-resistance between HIV and HBV drugs, increased liver injury, either due to direct hepatotoxicity or to ART-related immune-reconstitution hepatitis, with elevation of ALT; if ART does not cover both HIV and HBV infections adequately, fulminant hepatitis is an eventuality.

Evaluation of HIV and Hep B coinfected persons

The risk of HBV infection may be higher in HIV-infected adults, and therefore all persons newly diagnosed with HIV should be screened for HBsAg. Those found positive for Hepatitis B surface antigen should be evaluated further following the guidelines for evaluation of those with Hepatitis B Infection. Besides routing clinical evaluation, one should look for sign of cirrhosis and hepatic decompensation like jaundice, conjunctival haemorrhages, anaemia, spider angioma, palmar erythema, petechiae, clubbing, gynaecomastia, testicular atrophy, parotid enlargement, asterixis (liver flaps, flapping tremors), caput medusa, ascites, oedema, longitudinal veins alongside of abdomen, hepatomegaly, hepatic bruit, venous hum and splenomegaly.

The lab investigations, besides routine haemogram and chemistry, should specifically include LFT, prothrombin time, alpha-fetoprotein (AFP), ultrasound and upper GI endoscopy. The virological

examination should include HBeAg – marker of HBV replication & infectivity, Anti-HBe antibody and HBV DNA quantitative (Real-Time PCR).

One important component in evaluation is the staging of cirrhosis. Earlier invasive techniques like liver biopsy were used and Metavir Score (F0 – F4) was done. But now, newer techniques like liver elastography (FibroScan) are used to measure liver stiffness and determine the stage of liver cirrhosis. In case on non-availability of FibroScan, APRI (AST to Platelet Ration Index) and FIB4 (Fibrosis 4) score are used. Also, it is important to do 'Child Pugh Scoring'. All these investigations need the opinion of a trained physician or a gastroenterologist. Hence, appropriate referral should be made by the ART MO.

APRI: Aspartate aminotransferase (AST)- to- platelet ratio index (APRI) is a simple index for estimating hepatic fibrosis based on a formula derived from AST and platelet concentrations. A formula for calculating the APRI is given: APRI = * (AST/ULN) x 100) / platelet count (109/L). An online calculator can be found at: http://www.hepatitisc. uw.edu/page/ clinical-calculators/apri

FIB-4: A simple index for estimating hepatic fibrosis based on a calculation derived from AST, ALT and platelet concentrations and age. Formula for calculating FIB-4: FIB-4 = (age (year) x AST (IU/L)) / (platelet count (109/L x [ALT (IU/L) x 1/2]). An online calculator can be found at http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4.

Treatment of HIV and Hepatitis B Co- infected patients

A detailed algorithm of WHO Recommendations on the management of persons with chronic Hepatitis B infection is given in Annexure 11.

The indications for anti-viral treatment in Chronic Hepatitis B (CHB) are as below:

- All adults, adolescent, children with CHB & clinical evidence of compensated / decompensated cirrhosis (or APRI score >2 in adults) should be treated, regardless of ALT, HBeAg status, HBV DNA levels
- Treatment is recommended for adults with CHB, who do not have clinical evidence of cirrhosis (or based on APRI score ≤ 2 in adults), but are aged > 30 years and have persistently elevated ALT levels and evidence of high-level HBV replication (HBV DNA > 20,000 IU/ ml) regardless of HBeAg status
- If HBV DNA testing is unavailable but patients have persistently elevated ALT, treat for Hepatitis B regardless of HBeAg status

The NACO guidelines on initiation of first line ART and ART regimens in HIV and HBV

co-infected patients are summarized in **Table 1** below:

Table 1: ART Guidelines for HIV and Hepatitis B co- infected persons

When to start ART	All persons diagnosed with HIV infection should be initiated on ART regardless of CD4 count or WHO clinical staging or age group or population sub-groups
Choice of regimen	Nucleoside analogues with dual activity against both the viruses such as 3TC and TDF should be included in the first-line ART regimen for HIV-infected patients who are HBsAg-positive (and HBeAg-positive, if known) In view of higher incidence of hepatotoxicity with NVP in co-infected patients, it is preferable to use EFV unless contraindicated
Preferred Regimen	TDF +3TC +EFV (TDF may be replaced by AZT* in case of TDF toxicity or contraindications)
Second Line Regimen	TDF and 3TC should be continued as part of the second-line ART following initial ART failure, even if it was used in the first-line regimen
HBV Resistance	Ideally, 3TC should be used either with TDF or not at all, because HBV resistance to 3TC develops quickly. HBV resistance to 3TC develops in 50 % of patients after two years and in 90 % after four years of treatment, if 3TC is the only active anti-HBV drug in the ART regimen
Therapy Outcomes	HBV seroconversion (loss of HBeAg and development of HBeAg) occurs in 11-22 % of HBeAg-positive HIV-infected patients who are treated with 3TC containing regimen for one year
Hepatic Flares	HBV flares on ART start soon after the initiation of ART as a manifestation of IRIS. Discontinuation of 3TC may also result in hepatic flares
FTC vs 3TC	The rate of suppression of HBV and the safety profile and resistance pattern with FTC are similar to those with 3TC. FTC is not provided in the national ART programme
***Whenever TDF is substituted with AZT, the treating physician shall recognize the fact that Lamivudine is the only active anti-HBV drug in the ART regimen and another agent active against hepatitis needs to be considered like entecavir- a gastro-enterologist may be consulted in such cases** **Notes:** Hepatic flares typically present as an unexpected increase in ALT / AST levels and symptoms of clinical hepatitis (fatigue, nausea, abdominal pain and jaundice) within 6-12 weeks of commencing ART. The flares may be difficult to distinguish from ART - induced hepatic toxicity. Drugs active against HBV should preferably be continued during a suspected flare. If it is not possible to distinguish serious hepatitis B flare from grade 4- drug toxicity, ART should be stopped until the patient stabilizes.	

This treatment strategy has achieved high rates of HBV DNA suppression (90 %), HBeAg loss (46 %) and HBsAg loss (12 %) in HBeAg-positive patients after 5 years of treatment, without evidence of resistance, and has reduced progression to cirrhosis with no significant differences in the response in those with or without HIV co-infection. Till date, no viral resistance to tenofovir in vivo has been described, although resistant strains have been identified in vitro. Although the risk of developing cirrhosis is negligible in HBV/HIV-co-infected persons on long-term tenofovir combined with lamivudine therapy, the risk of hepatocellular carcinomas (HCC) persists, but is low.

If ARVs need to be changed because of HIV drug resistance or some drug toxicity, then tenofovir and lamivudine should be continued together with the new ARV drugs unless TDF is specifically contraindicated due to its toxicity.

Prevention of Hepatitis B infection

The risk of HBV infection may be higher in HIV-infected adults, and therefore all persons newly

diagnosed with HIV should be screened for HBsAg and immunized if not infected. Those already infected with HBV (HBsAg positive) do not require HBV vaccine. PLHIV who have already suffered from HBV in the past and have developed protective titre of anti-HBs antibody (> 10 µIU/ml) also do not require HBV vaccine.

Those who are surface antigen negative need to be vaccinated against Hepatitis B besides following other precautions. Response to HBV vaccine is lower in persons with HIV or with a low CD4 count, and a meta-analysis has shown that a schedule of four double (40 µg) doses of the vaccine provides a higher protective anti-HBs titre than the regular three 20 µg dose schedule.

Besides this, all infants born to Hepatitis B positive women need to be immunized within 12 hours of birth (Dose - 0) followed by 1, 2 & 6 months (dose – 10 µg IM) and HBIG – 0.5 ml IM.

HIV and Hepatitis C co- infection

Viral hepatitis C infection is associated with significant morbidity and mortality. Chronic HCV infection can cause a wide spectrum of liver disease, potentially leading to severe liver damage, including cirrhosis, organ failure and hepatocellular carcinoma. It accounts for nearly 12– 32% of all cases of liver cancer and 10- 20% cases of cirrhosis of liver, both of which have high treatment costs and poor outcomes.

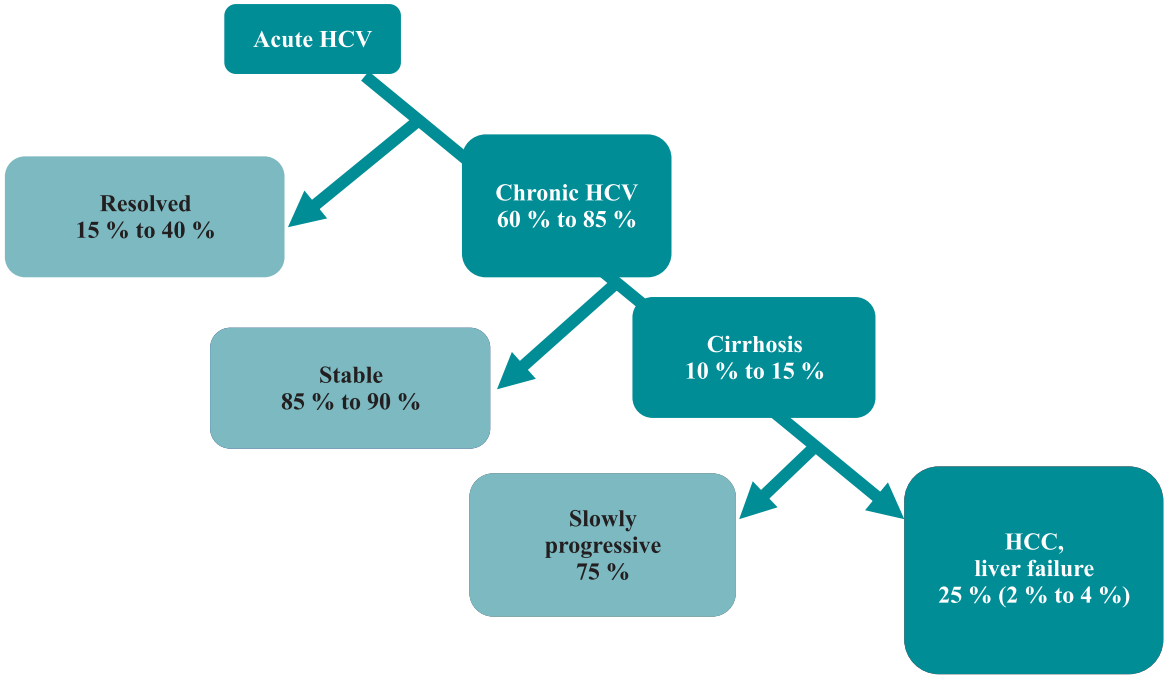
Globally, an estimated 71 million people may be chronically infected with Hepatitis C and nearly 7,00,000 persons die each year from HCV related complications. Around 2.3 million persons may be co-infected globally. An analysis from Africa estimated that 5.7% of persons with HIV were co-infected with HCV. Current HCV prevalence estimates in India are based on small studies that give estimates in a broad range of 6- 12 million people infected with hepatitis C. However, NACO and WHO are conducting studies for better estimation of the disease burden by analyzing around 5,00,000 samples collected for HSS and IBBS.

Because of shared routes of transmission, certain groups, in particular persons who inject drugs (PWID) have high rates of co-infection with HIV and HCV. Globally around 67 % of PWID are infected with HCV. Other high-risk groups are those who have a high frequency of injections and a low level of infection control, transmission from HCV infected mothers and people with HCV infected sexual partners. Persons with HIV infection, in particular MSM, are at increased risk of HCV infection through unprotected sex. Tattoo recipients have higher prevalence of HCV compared with persons without tattoos.

The distribution of HCV genotypes and sub genotypes varies substantially in different parts of the world. According to a recent review, genotype 1 is the most common, accounting for 46.2 % of all HCV infections, followed by genotype 3 (30.1 %). In India 54 % have genotype 3, 24 % had GT1, 6 % have GT 4 while 12 % have indeterminate genotype. This has implications on the drugs to be used for HCV treatment.

HCV causes both acute and chronic hepatitis. Infection with HCV is usually clinically silent, and is only very rarely associated with life-threatening disease. Spontaneous clearance of acute HCV infection occurs within six months of infection in 15–40 % of infected individuals in the absence of treatment. Almost all the remaining 60– 85 % of persons will harbour HCV for the rest of their lives (if not treated) and are considered to have chronic HCV infection (Figure 1). Anti-HCV antibodies develop as part of acute infection and persist throughout life. In persons who have anti-HCV antibodies, a nucleic acid test (NAT) for HCV RNA, which detects the presence of the virus, is needed to confirm the diagnosis of chronic HCV infection.

Fig 1: Natural Progression of HCV Infection



Natural history of HIV/HCV co-infection

The natural history of both diseases is affected when a person is co-infected with both HIV and Hepatitis C ; this has implications on the management of both diseases. Co-infection with HIV adversely affects the course of HCV infection, and co-infected persons, particularly those with advanced immunodeficiency (CD4 count < 200 cells/cmm), have significantly accelerated progression of liver disease to cirrhosis, decompensated liver cirrhosis and hepato cellular carcinomas (HCC) than HCV-mono infected persons. Furthermore, even among patients in whom ART leads to successful control of HIV infection (i.e. undetectable HIV viral load), the risk of hepatic decompensation among co-infected patients is higher than among patients with HCV mono-infection. In persons with HIV infection, HCC tends to occur at a younger age and within a shorter time period. For these reasons, all persons with HIV/HCV co-infection should be considered for HCV treatment.

The natural history of HIV is also affected by co infection with HCV. Two large European cohorts have shown that after ART initiation, CD4 recovery was impaired in HIV/HCV co-infected persons when compared to those infected with HIV alone. HIV/HCV co-infected persons also demonstrated more rapid HIV disease progression compared to those who were HIV-infected alone, and had impaired recovery of CD4 cells.

WHO guidelines recommend screening of all PLHIV for Hepatitis C infection. However, NACO guidelines recommend the screening of all PWID (IDUs), those with history of multiple blood/ blood product transfusion, or those with raised liver enzymes (ALT) more than two times the ULN or based on strong clinical suspicion. The test used detects anti- HCV antibodies. However, since anti-HCV antibodies developed as part of acute infection, they persist throughout life. Among those infected, 40 % may clear the virus but will still have persisting antibodies. Hence, in persons who have anti-HCV antibodies, a nucleic acid test (NAT) for HCV RNA, which detects the presence of the virus, is needed to confirm the diagnosis of chronic HCV infection. Another test which is useful is detection of HCV core antigen which can detect more than 1000 copies /ml of HCV.

Evaluation of HIV and HCV co-infected persons

The assessment of those with HCV/ HIV includes clinical evaluation – history, physical examination for jaundice, hepatosplenomegaly, ascites, cirrhosis/ decompensation and laboratory tests including LFT, prothrombin time, complete haemogram, AFP, etc. Other tests required are abdominal ultrasound, endoscopy, assessment of liver fibrosis (APRI/ FIB 4/ fibro-Scan), described earlier in the chapter, and HCV RNA quantitative assay.

Treatment of HIV and Hepatitis C co- infection

Treating HCV infected persons in the past with interferon and ribavirin combination therapy was very difficult, as many patients had to discontinue treatment due to side-effects such as depression or weight loss as well as severe anaemia, thrombocytopenia and neutropenia. Furthermore, Sustained Virological Response (SVR) rates in patients with co-infection were lower than among HCV mono- infected patients.

The advent of newer drugs, Directly Acting Antivirals (DAA), for HCV treatment has revolutionized the management of HCV. The results of treatment with DAAs in persons with HIV co-infection are comparable to those with HCV mono-infection. Thus, DAA therapy has substantially simplified the treatment of persons with HIV and HCV co-infection. There are fewer drug- drug interactions between DAAs and ARV medicines. SVR rates with DAA- based therapy among persons with HIV co-infection are higher than 95 %, even for those with prior HCV treatment failure or advanced fibrosis. However, the need to check for drug- drug interactions between HIV and HCV medications has to be emphasized. The reader is referred to the website "www.druginteraction.com" for more information.

The common DAAs are summarized in table 2 below:

Table 2: List of Directly Acting Antiviral (DAA) drugs

Group	Drugs	
NS 3 Protease Inhibitors	Telaprevir, Boceprevir, S**imeprevir, Paritaprevir**, Sovaprevir, Asunaprevir, Faldaprevir	
NS 5A Inhibitors	**Daclatasvir,** Samatasvir, **Ledipasvir, Ombitasvir, Velpatasvir,**	
Polymerase Inhibitors	***Nucleosides: Sofosbuvir***	Non-Nucleosides: Dasabuvir, Deleobuvir

Combination of **Sofosbuvir** 400 mg + **Daclatasvir** 60 mg for 12 weeks is recommended in non-cirrhotic patients and combination of **Sofosbuvir** 400 mg + **Velpatasavir** 100 mg for 12 weeks is recommended in cirrhotic patients .

Daclatasvir is associated with significant drug interactions with many NNRTIs and PIs, and its concomitant use requires caution, dose adjustments or consideration of alternative DAAs. The dose of daclatasvir dose will be 30 mg with ATV/r and 90 mg with EFV. Ledipasvir and sofosbuvir have shown reduced potential for drug interactions with ARV drugs due to their use of different metabolic pathways. A complete list of drug- drug interactions is available at www.hep-druginteractions.org. For more details on treatment guidelines refer to *National Guidelines for Diagnosis and Management of Viral Hepatitis* (http://clinicalestablishments.gov.in/WriteReadData/3591.pdf)

It is advisable to **first initiate treatment for HIV** and achieve HIV suppression before starting HCV treatment, although, there are some circumstances where it may make sense to treat HCV infection first and then initiate therapy for HIV. This could include persons with moderate-to-severe

fibrosis who at risk of rapid liver disease progression if the HIV infection is not associated with significant immunosuppression at the time of treatment. Also, in view of the short duration of HCV treatment, the risk of drug- drug interactions between HCV and HIV medicines and the increased risk of ART- related hepatotoxicity in the presence of HCV infection, treating HCV infection first can simplify subsequent ART depending on the regimen available locally.

The decision to start ART among people co-infected with HCV should follow the same principles as for HIV mono infection. The ARV regimen remains the same, Tenofovir, Lamivudine and Efavirenz in single pill FDC, for adults and adolescents. Potential harmful effects of ARV drugs include their hepatotoxic effects. However, the highest rates of hepatotoxicity have been observed with ARV drugs that are no longer commonly used or recommended, including stavudine, didanosine, nevirapine or full-dose ritonavir (600 mg twice a day). For most HIV/ HCV co-infected people, including those with cirrhosis, the benefits of ART outweigh the concerns regarding drug-induced liver injury.

Monitoring of therapy in persons with HIV/ HCV co-infection

Regular monitoring of liver and renal functions is required when using DAAs and ARV drugs together. Additional monitoring of liver function is recommended in persons with cirrhosis, including albumin, bilirubin and coagulation tests. Persons with evidence of neutropenia, thrombocytopenia and anaemia require 1- 2 weekly monitoring.

Prevention of HCV infection in HIV-positive

There is no effective HCV vaccine and PPTCT (PMTCT) protocol for prevention of Hepatitis C. The prevention of HCV infection among IDUs needs to be done by strict maintenance of disposal of needle, syringe, sharps etc. at the health care settings and safe sexual behaviours.

For further details on Hepatitis B and Hepatitis C, one may refer to the following documents

References:

- *Guidelines for the screening, care and treatment of persons with hepatitis C infection. Updated version, April 2016. Geneva: World Health Organization; 2016 (http://www. who. int/hepatitis/publications/hepatitis-c-guidelines-2016/en).*
- *Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015 (http://www.who.int/HIV/pub/ hepatitis/hepatitis-b-guidelines/en).*

11. ART Treatment Failure in adults and adolescents and when to switch

This chapter is applicable to all adults and adolescents (10- 19 Years) and children aged > 5 years. For management of treatment failure in children below 5 years please refer to the paediatric section

The most important goal of antiretroviral therapy is to ensure maximal and sustained suppression of viral replication while maintaining future therapeutic options for the PLHIV. Consistent high-level adherence to ART is the key to achieve this goal and to maintain patient on first line ART for as long as possible. However, on account of longer duration of therapy, prodigious replication rate and error-prone reverse transcriptase, varying amount of drug resistance is bound to occur even with high adherence levels. HIV drug resistance evolves naturally due to the selective pressure from drugs or from the immune system.

Poor adherence to ART can accelerate the development of drug resistance and the progression of disease. Hence continued adherence support with regular monitoring for response to therapy is crucial. The programme is planning to carry out pre-treatment resistance (PDR) and acquired drug resistance (ADR) surveillance studies. However, at patient level, there is a need to be well aware of the criteria for treatment failure so that these can be monitored regularly and appropriate intervention can be made early. The clinician must ensure that treatment adherence is checked, and the patient undergoes clinical monitoring besides monitoring of defined laboratory parameters, described in an earlier section, during each visit.

Prevention of the emergence of HIV drug resistance (HIV DR), is the key for success of national ART programme and prevention of transmission of resistant virus

Normal Response to Antiretroviral Therapy:

Virological response to ART: The viral load done 6 months after initiation of ART should be less than 1000 copies/ml.

Immunological response to ART: CD4 count of the patients should increase after initiation of ART. This increase is usually 50- 100 cells/cmm within 6- 12 months of the initiation of the ART in ARV naïve patients, who are adherent to their treatment.

Clinical response to ART:

With ART initiation, by 12 weeks most of the patients would be asymptomatic. Clinical monitoring should be done at every visit to the ART centre. Clinical monitoring should include evaluation of weight, general wellbeing (functional status), adverse reaction to drugs and drug- drug interaction keeping an eye out for IRIS (Immune Reconstitution Inflammatory Syndrome), especially in patients with low CD4 count. Each visit should be taken as an opportunity to evaluate adherence through pill count, to reinforce the treatment adherence and to provide nutritional counselling. Further, four-symptom screening for TB on each and every visit and provision of psycho-social support, as required have to be taken care of. Patient visits also provide the opportunity for spouse

testing, if not done already, and for emphasizing positive prevention methods. Various laboratory-monitoring parameters with in-built frequency of testing have been described in the earlier section.

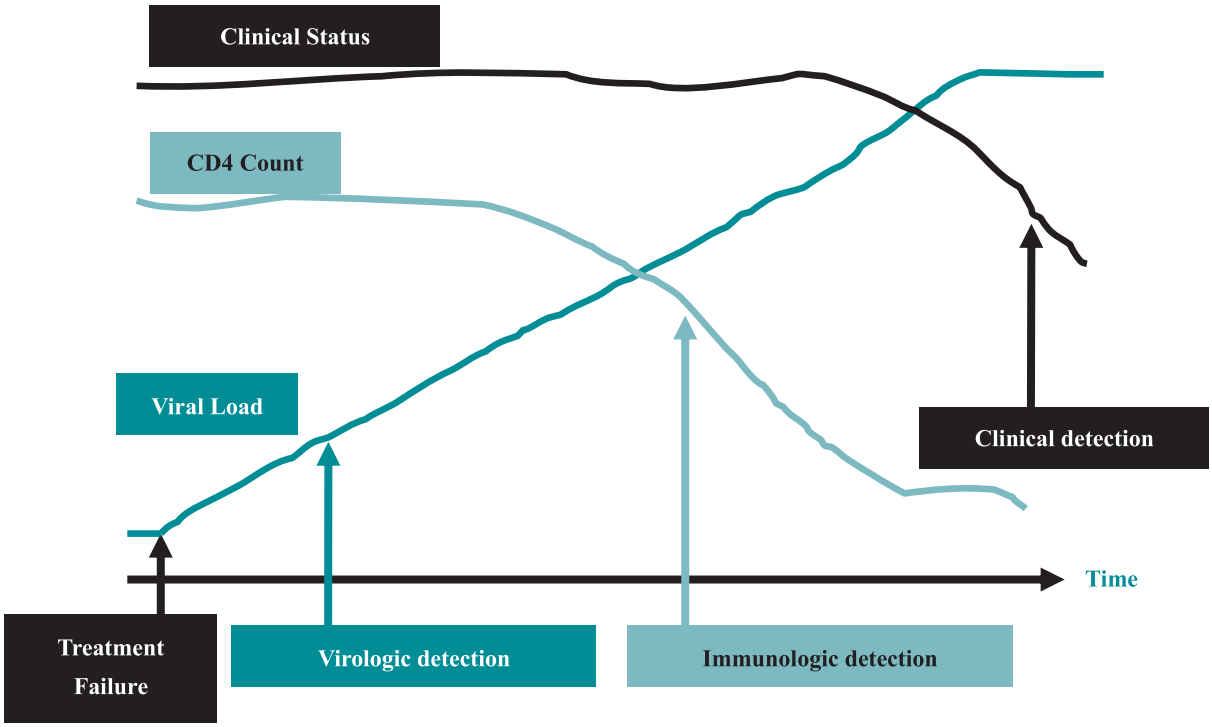
It is important to have a high index of suspicion for treatment failure. One should look for the following evidences of suspected treatment failure among patients who are on first line ART for at least 6 months:

- New OIs/ recurrence/ clinical events after 6 months on ART (after ruling out IRIS)
- Progressive decline in CD4 counts
- Slow/ no clinical improvement over 6- 12 months, associated with stationary CD4 count, despite good adherence. In cases of sub-optimal rise in CD4 count at 6 months, despite good adherence and absence of clinical symptoms, one may repeat CD4 count at 3 months. (Immunological response is defined as an increase of at least 50 CD4 cells/cmm at 6 months of ART).

Chronology and Identifying Treatment Failure

The sequence of treatment failure is virological failure followed by immunological and clinical failures, as depicted in figure 1. As a person fails on his current regimen, his viral load starts rising, which is followed by a decline in CD4 count. Then, after a few months, some clinical stage 4 manifestations may appear indicating clinical failure. Hence, a viral load test can give an indication of treatment failure much earlier than CD4 decline or appearance of clinical symptoms indicative of failure.

Figure 1: Chronology of Treatment Failure:



Hence, compared to clinical or immunological monitoring, viral load monitoring provides an early and more accurate indication of treatment failure and the need to switch from the first-line ART to second-line drugs, which can reduce the accumulation of drug-resistant mutants and improve clinical outcomes.

When to Switch

The decision regarding when to switch from first-line to second-line therapy is critical. If the decision is made too early, the months or years of any potential survival benefit from an effective first-line therapy may be lost. If the decision is made too late, the effectiveness of second-line therapy may be compromised and the patient may be placed at an additional risk of death.

The time of switching to second-line drugs is dictated by the failure of treatment, which can be measured in three ways: virologically, immunologically and clinically. The Table 1 below outlines the definition of treatment failure.

Table 1: Definitions of ART failure

Failure	Definition	Comments
Virological failure	Plasma viral load above 1000 copies/ ml.	An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed
Immunological failure	CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/cmm or 50% fall from "on treatment" peak level	Concomitant or recent infection may cause a transient decline in the CD4 cell count. Some experts consider persistent CD4 counts of below 50 cells/cmm after 12 months of ART to be more appropriate.
Clinical failure	New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment	The condition must be differentiated from IRIS. Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not indicate treatment failure. For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure.

Virological failure:

Virological failure means incomplete suppression of the viral replication. Under the national programme, it is defined as a Plasma Viral Load (PVL) value of 1,000 or more copies/ml at or after six months of ART, with patient being treatment adherent by > 95%. Viral rebound after being undetectable is also considered as virological failure. A low-level viral rebound (< 1000 copies/ml), termed blips, usually indicates a statistical variation in the determination of PVL and this does not require switch in therapy. Viral load remains the most sensitive indicator of ART failure. Recognizing early failure facilitates the decision to switch drugs before multiple resistance mutations develop to drugs of the first-line regimen.

In general, the clinical status and the serial CD4 cell counts should be used in an integrated fashion to suspect treatment failure, while the patient is on ART. However, the switch of a regimen from the first-line to second-line therapy should be made on basis of virological failure only.

It is important to note that the current clinical and immunological criteria have **low sensitivity**

and positive predictive value for identifying individuals with virological failure. Compared to clinical or immunological monitoring, viral load provides an early and more accurate indication of treatment failure and the need to switch from first-line to second-line drugs, reducing the accumulation of drug resistance mutations and improving clinical outcomes. Measuring viral load can also help to distinguish between treatment failure and non-adherence. Studies suggest that around 70 % of patients on first-line ART, who have a first high viral load, will be suppressed following an adherence intervention, indicating non-adherence as the reason for the initial high viral load in the majority of cases.

Immunological failure:

NACO definitions of immunological failure (any one of the following three):

- A return to or fall below the pre-therapy (baseline) CD4 atleast after 6-months of therapy
- A 50 % decline from the on-treatment peak value (if known)
- A persistent CD4 count of less than 100 cells/cmm after 12 months of therapy

One should keep in mind the phenomenon of virological- immunological discordance. Even though declining CD4 count helps in suspecting treatment failure, virological failure is essential for decision-making in switching over to second line ART.

Clinical failure:

There should be a reasonable trial of first-line therapy, lasting for at least 6 months before suspecting that the ARV regimen is failing on the basis of clinical criteria. Adherence should be assessed and optimized, inter-current OIs treated and resolved, and IRIS excluded before drawing such a conclusion.

The development of a new or recurrent WHO stage 3 or 4 condition, while on treatment (after the first six months), is considered as functional evidence of the progression of HIV disease. The assumption is that with immune restoration on ART, the subsequent progressive immunodeficiency means a failing ART regimen, the new clinical events signalling immune failure. This will be the same as those marking advanced and then severe immunodeficiency without ART, for e.g., WHO Clinical stage 3 and 4 conditions. TB can occur at any CD4 level and does not necessarily indicate ART failure. The response to TB therapy should be used to evaluate the need to switch ARV drugs. In the case of pulmonary TB and some types of extra-pulmonary TB (e.g. simple lymph node TB or uncomplicated pleural disease), the response to TB therapy is often good and the decision to switch ARV drugs can be postponed and monitoring can be stepped up. This also applies to severe and/ or recurrent bacterial infections (as stage 3 or 4 events) or oesophageal candidiasis; they respond well to therapy.

SOP for Determining Failure:

Identifying the cause of failure is important before deciding to modify the ART regimen. The following factors need to be assessed.

1. **Treatment Adherence:** A detailed assessment of adherence needs to be made. The reasons for non-adherence need to be explored. Unless these reasons are identified, a patient will find it difficult to adhere to the second-line regimen.
2. **Drug- drug interactions:** Assessing whether the patient is concomitantly taking medications that interfere with ARV activity is important. For example, many patients may not reveal that

they take herbal treatments along with the prescribed ART regimen.

3. Certain **Opportunistic infections** may lead to decline in the CD4 count, which may revert after treating those infections.

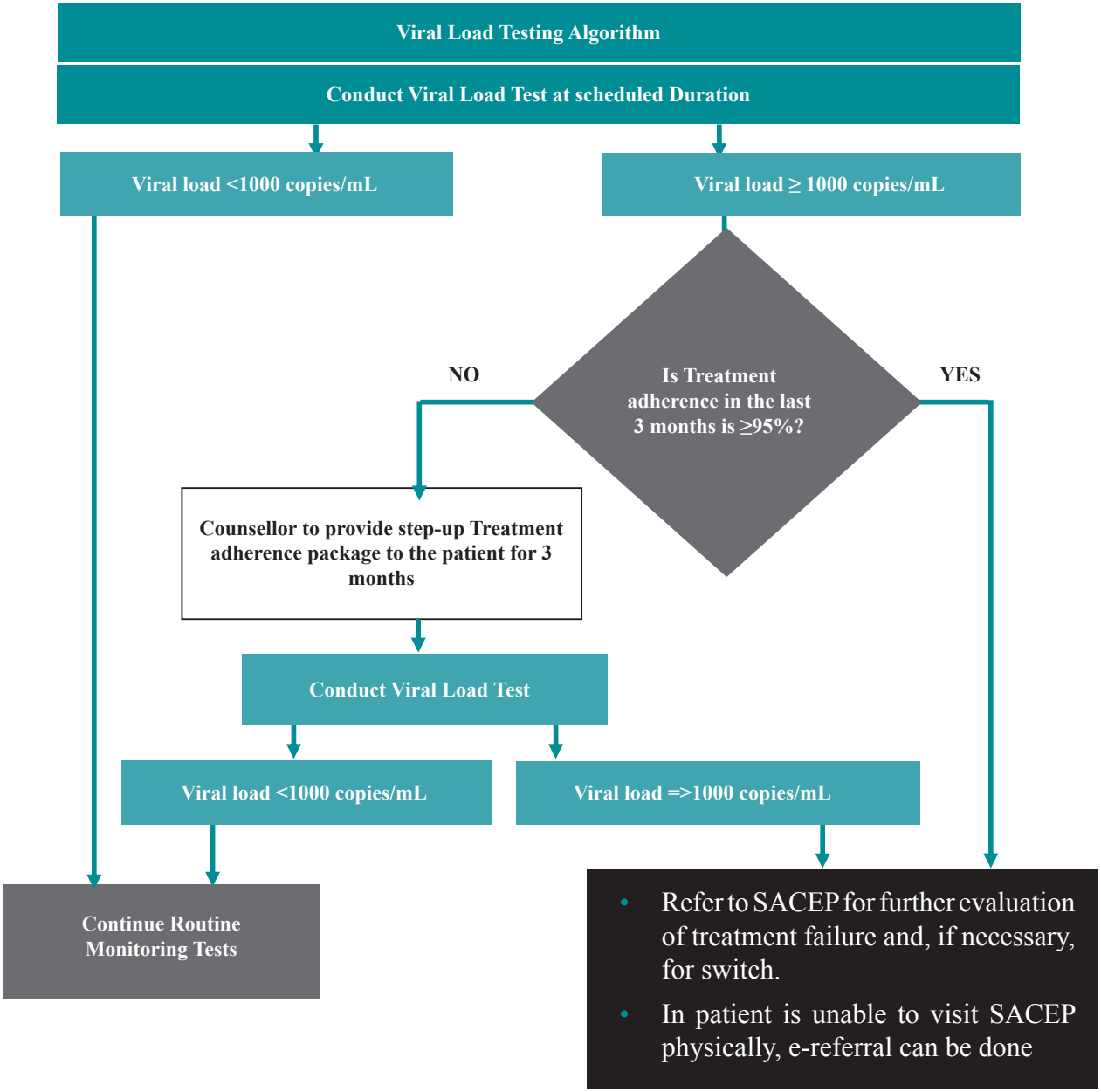
Confirming Treatment Failure:

The NACO recommendations in this regard are as below:

1. Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure.
2. **Timing for viral load test:**
    a. For all second/ third-line patients and key populations, viral load testing should be done every 6 months after initiation of second and third-line ART.
    b. For all other patients on first-line ART, viral load testing should be done at 6 months and 12 months after ART initiation and thereafter annually. For existing patients who have been on ART for more than 12 months, viral load testing should be done annually.

       For more details refer to National Operational Guidelines for Viral Load Testing *(http://naco.gov.in)*
    c. The treating doctor can request for a viral load test when deemed necessary for clinical management
3. Till the time viral load is routinely available for all, priority must be given to all patients with suspected treatment failure **(Targeted viral load approach).**
4. **Virological failure is identified by the detectable viral load count of 1000 or more copies/ml, in targeted or routine viral load monitoring, atleast 6 months after ART, with > 95% of treatment adherence for each of the last 3 months.**

Fig 1. Viral Load Testing Algorithm



* In case clinician feels discrepancy, a repeat Viral load, after three months step up adherence, may be done.

Treatment Failure to First line ART and Second line ART

Definitions

First-Line and Second-Line ART Regimen:

The working definitions of First and Second-line ART regimens are as follows:

First-line ART:

First-line ART is the initial regimen prescribed for an ART naïve patient.

Second-line ART:

Second-line ART is the subsequent regimen used in sequence immediately after First-line therapy has failed.

Third –Line ART

Third-line ART is the subsequent regimen used in sequence immediately after Second-line therapy has failed.

Substitution Vs Switch

Any change of ARVs prescribed should be carefully distinguished between substituting a drug within a given regimen and switching an entire ART regimen:

SUBSTITUTION: Single drug replacement of individual ARV (usually within the same class) for toxicity, drug- drug interactions, or intolerance refers to SUBSTITUTION of individual (offending) drug. This does not indicate that a second-line regimen is being used even if second-line drugs like boosted PIs are used for substitution.

SWITCH: Treatment failure refers to the loss of antiviral efficacy to the current regimen. When the regimen is changed because of ARV treatment failure, it is referred as the SWITCH of the entire regimen.

Broad Principles and Objectives

All patients initiated on first-line ART need to be monitored carefully at every visit as per standard protocol on clinical and laboratory monitoring indicators. As emphasized early, a high index of suspicion is needed to detect first-line failure early. Whenever a patient develops new clinical manifestations (symptoms and /or signs) or is found to have a declining trend in CD4 counts (even before the counts reach the well- defined levels for immunological failure), one must start suspecting the possibility of failure of the regimen. Issues related to undetected OIs and sub-optimal treatment adherence need to be addressed. It is important to make appropriate timely referral to SACEP for evaluation of such patients following the simplified SACEP guidelines.

Once the patient has undergone viral load test and been evaluated by SACEP, if required, one of the following possible decisions will be conveyed by the SACEP of CoE / PCoE / ART plus centre to the referring ART centre.

- Switch to 'prescribed' second-line ART
- Not eligible for second-line ART; continue first-line ART, reinforce adherence and re-evaluate
- Evaluate for HIV-2

Once the decision has been made to start second-line ART, the decision will be communicated to the referring centre where the second-line will be initiated.

The objective of the second-line ART is to prolong the survival of the PLHIV as much as possible with complete suppression of viral replication. This requires regular monitoring with viral load every 6 months.

What to Switch:

When failure has been identified clinically or immunologically, many patients can be expected to have significant NRTI resistance at the time of switching. Thus, in the decision-making for a second -line regimen with maximal antiviral activity, one has to consider nucleoside class cross-

resistance and drug interactions. Some points to be noted are:

- Cross resistance exists between d4T and AZT
- High level AZT/ 3TC resistance reduces susceptibility to ABC
- TDF can be compromised by multiple nucleoside analogue mutations (NAMs) but often retains activity against nucleoside-resistant viral strains

▪ TDF/ ABC may facilitate evolution of the K65R drug resistance mutation,

which mediates resistance to non-AZT NRTIs

▪ NNRTI (such as EFV and NVP): usually there is complete cross-resistance

The details of certain expected mutations with different NRTIs are provided in the table 2.

Table 2: Expected resistance mutations with different NRTI backbone

Expected resistance mutations with different NRTI backbone	
Failing NRTI backbone	**Mutations**
AZT or d4T + 3TC and AZT + 3TC + ABC	M184V and then successive NAMs (cumulative, longer one waits to switch
TDF + 3TC	K65R and/or M184V
ABC + 3TC	L74V >K65R and/or M184V
AZT or d4T	TMs, Q151M, T69ins
TDF + ABC and TDF	K65R

Formulation of second-line ART for PLHIV failing to first-line ART

Formulation of second line ART is discussed in this section on the basis of:

- Current NACO treatment guidelines for the first-line ART in adults and adolescents recommend three drug combination therapy from two classes of ARV drugs for initial treatment i.e. 2 NRTI + 1 NNRTI

Current Recommendation for Second-line ART is based on:

- A new class of ARV, a Ritonavir boosted PI (Atazanavir/ritonavir or Lopinavir/ritonavir)
- Supported by at least one new and unused NRTI (Zidovudine or Tenofovir) or in an inevitable situation an integrase inhibitor (Raltegravir—presently after CoE-SACEP approval)
- Continued Lamivudine administration ensures reduced viral fitness

The steps to be followed in initiating second-line ART is given in Table 3

Table 3: Steps in Initiating Second-line ART

STEP 1	Define treatment failure	Define treatment failure by virological testing, see if adherence to treatment is adequate. Counsel and support. (SACEP will see these and take decision on providing second-line ART)
STEP 2	Decide on NRTI component of the second-line regimen	If AZT is used in first-line, NRTI choice in second-line is TDF. If TDF is used in first-line, NRTI choice could be AZT. Continuing Lamivudine reduces viral fitness and has to be part of second-line ART
STEP 3	Decide on the PI component of the second-line regimen	Give only boosted PI in combination. The preferred choice is ATV/r
STEP 4	Patient education and agreement on treatment plan including follow up and monitoring	Include counselling for adherence, linkages to specialist care, and follow-up monitoring plan.

Once it is decided to switch the ART regimen, following various scenarios should be considered and changes made as recommended below:

A. Second-line recommendations for patients with HIV-1, failing to first-line ART

1. Patients failing on AZT/d4T based first-line regimen, not exposed to any other NRTI will switch to TDF + 3TC + ATV/r
2. Patients failing on TDF/ABC based first-line, not exposed to any other NRTI:
    - TDF/ABC +3TC +EFV/NVP (if Hb is ≥ 9 g/dl) will switch to AZT + 3TC + ATV/r (TDF to be maintained, only if the patient is co-infected with HBV*)
    - TDF/ABC +3TC +EFV/NVP (if Hb is < 9 g/dl) will switch to RAL + LPV/r (TDF + 3TC to be maintained only if the patient is co-infected with HBV*)
3. Patients failing to TDF/ABC + 3TC + EFV/NVP (previous exposure to AZT/d4T in first-line regimen without evidence of immunologic failure at the time of substitution from AZT/d4T to TDF/ABC due to toxicity/d4T phase out):
    - When Hb is ≥ 9 g/dl, switch to AZT +3TC + ATV/r (TDF to be maintained only if the patient is co-infected with HBV*)
    - When Hb is < 9 g/dl, switch to LPV/r + RAL (TDF + 3TC to be maintained only if the patient is co-infected with HBV*)
4. Patients failing to all other multi-NRTIs exposed drug regimens will switch to LPV/r + RAL (TDF + 3TC to be maintained only if the patient is co-infected with HBV*)

* refer to appropriate physician for further monitoring like HBV DNA load and use of entecavir

The recommended second-line drug regimens for patients with HIV-1, failing to first-line ART are given in Table 4.

Table 4: Second-line ART recommendations for patients with HIV-1, failing to NNRTI based first- line ART

Failing First-Line ART	Recommended Regimens
AZT/d4T + 3TC+ NVP/EFV	TDF + 3TC + ATV/r
TDF + 3TC + EFV/NVP (not anaemic; Hb ≥ 9 g/dl)	AZT +3TC + ATV/r (TDF to be maintained, only if the patient is co-infected with HBV)
TDF + 3TC + EFV/NVP (anaemic; Hb < 9 g/dl)	RAL + LPV/r (TDF + 3TC to be maintained, only if the patient is co-infected with HBV)
TDF/ABC + 3TC + EFV/NVP (previous exposure to AZT/d4T in first- line regimen without evidence of immunologic failure at the time of substitution from AZT/d4T to TDF/ABC due to toxicity or d4T phase out) (Not anaemic; Hb ≥ 9 g/dl)	AZT+3TC + ATV/r (TDF to be maintained, only if the patient is co-infected with HBV)
TDF/ABC + 3TC + EFV/NVP (previous exposure to AZT/d4T in first- line regimen without evidence of immunologic failure at the time of substitution from AZT/d4T to TDF/ABC due to toxicity or d4T phase out) (Anaemic; Hb < 9 g/dl)	LPV/r + RAL (TDF + 3TC to be maintained, only if the patient is co-infected with HBV*)
All other cases of first- line failure and exposure to more than 1 NRTI (multi-NRTIs - AZT/d4T, TDF, ABC)	LPV/r + RAL (TDF + 3TC to be maintained, only if the patient is co-infected with HBV*)
AZT: Zidovudine; d4T: Stavudine; ABC: Abacavir; TDF: Tenofovir; 3TC: Lamivudine; EFV: Efavirenz; NVP: Nevirapine; ATV/r: Atazanavir/ritonavir; LPV/r: Lopinavir//ritonavir; RAL: Raltegravir * refer to appropriate physician for further monitoring like HBV DNA load and use of entecavir	

B. Second-line ART recommendations for patients with HIV-1, failing to PI based first-line ART (Not exposed to NNRTI)

- NACO guidelines do not recommend PI based first-line ART in adults and adolescents. However, patients who have received PI based first-line treatment outside the national programme (i.e. in private sector) and are failing to treatment are enrolled as part of the "universal access to treatment protocol". Patients belonging to this category are considered here.
- Change PI to NNRTI (Efavirenz). NRTI backbone to be changed as described earlier (as in previous section (A) Second-line recommendations for patients with HIV-1, failing to first-line ART)

The recommended second-line drug regimens for patients with HIV-1, failing to first-line ART are given in Table 5.

Table 5: Second-line ART recommendations for patients with HIV-1, failing to PI based first-line ART (Not exposed to NNRTIs)

Failing First-Line ART	Recommended Regimens
AZT/d4T + 3TC + ATV/r (OR) LPV/r	TDF + 3TC + EFV (routine viral load every 6 months)
TDF + 3TC + ATV/r (OR) LPV/r (not anaemic; Hb >9 g/dl)	AZT + 3TC + EFV (routine viral load every 6 months) (TDF to be maintained, only if the patient is co-infected with HBV) *
TDF + 3TC + ATV/r (OR) LPV/r (anaemic; Hb <9 g/dl)	RAL + DRV/r (TDF+3TC to be maintained, only if the patient is co-infected with HBV)
AZT: Zidovudine; d4T: Stavudine; ABC: Abacavir; TDF: Tenofovir; 3TC: Lamivudine; EFV: Efavirenz; NVP: Nevirapine; ATV/r: Atazanavir/ritonavir; LPV/r: Lopinavir//ritonavir; RAL: Raltegravir * refer to appropriate physician for further monitoring like HBV DNA load and use of entecavir	

C. Second-line ART recommendations for patients with HIV-1, failing to PI based first-line ART (intolerant to NNRTIs or where NNRTIs cannot be used)

- Change PI to NNRTI (Efavirenz). NRTI backbone to be changed as described earlier (as in previous section (A) Second-line recommendations for patients with HIV-1, failing to first-line ART)
- Since a boosted PI (Atazanavir/ritonavir or Lopinavir/ritonavir) is used in first-line ART, Darunavir/ritonavir has to be used as twice daily dose (BID)

The recommended second-line drug regimens for patients with HIV-1, failing to first-line ART are given in Table 6.

Table 6: Second-line ART recommendations for patients with HIV-1, failing to PI based first-line ART (intolerant to NNRTIs or where NNRTIs cannot be used)

Failing First-Line ART	Recommended Regimens
AZT/d4T + 3TC + ATV/r	TDF + 3TC + use DRV/r BID
TDF + 3TC + LPV/r (Not anaemic; HB > 9 g/dl)	AZT + 3TC + use DRV/r BID (TDF to be maintained, only if the patient is co-infected with HBV*)
TDF + 3TC + LPV/r (Anaemic; HB < 9 g/dl)	RAL + use DRV/r BID (TDF + 3TC to be maintained, only if the patient is co-infected with HBV*)
AZT: Zidovudine; d4T: Stavudine; TDF: Tenofovir; 3TC: Lamivudine; ATV/r: Atazanavir/ritonavir; LPV/r: Lopinavir//ritonavir; RAL: Raltegravir; DRV/r: Darunavir/ritonavir * refer to appropriate physician for further monitoring like HBV DNA load and use of entecavir	

D. Second-line ART recommendations for patients with HIV-2, having immunological failure to PI based (LPV/r) first-line ART

- Change Lopinavir/ritonavir to Darunavir/ritonavir. NRTI backbone to be changed as described earlier (as in previous section (A) Second-line recommendations for patients with HIV-1, failing to first-line ART)
- Since a boosted PI (Lopinavir/ritonavir) is used in first- line ART, Darunavir/ritonavir has to be used as twice daily dose (BID)

The recommended second drug regimens for patients with HIV-2, having immunological failure to LPV/r based first-line ART are given Table 7.

Table 7: Second-line ART recommendations for patients with HIV-2, failing to PI (LPV/r) based first-line ART

Failing First-Line ART	Recommended Regimens
AZT/d4T + 3TC +LPV/r	TDF+3TC + use DRV/r BID
TDF + 3TC +LPV/r (not anaemic; HB >9 g/dl)	AZT + 3TC + use DRV/r BID (TDF to be maintained, only if the patient is co-infected with HBV)
TDF + 3TC +LPV/r (anaemic; HB < 9 g/dl)	RAL + use DRV/r BID (TDF + 3TC to be maintained, only if the patient is co-infected with HBV*)
All other cases of first-line failure and exposure to more than 1 NRTI (Multi NRTIs- AZT, TDF, d4T, ABC)	RAL+ use DRV/r BID (TDF + 3TC to be maintained, only if the patient is co-infected with HBV*)
AZT: Zidovudine; d4T: Stavudine; TDF: Tenofovir; 3TC: Lamivudine; LPV/r: Lopinavir/ritonavir; RAL: Raltegravir; DRV/r: Darunavir/ritonavir * refer to appropriate physician for further monitoring like HBV DNA load and use of entecavir	

Toxicities of second line drugs

The major toxicities of the second line drugs are depicted in Table 7 below:

Table 8: Side effects related to the NACO Second Line Regimen:

ARV	Side effect/toxicity	Management
TDF	Usually well tolerated; Minor: weakness and lack of energy, headache, diarrhoea, nausea, vomiting and flatulence. More serious side effects include kidney failure and pancreas disease TDF can reduce bone mineral density	Monitor renal function test as per NACO protocol Symptomatic management of minor side effects. Calcium supplements may be used in patients with osteoporosis

ATV*	Apart from the PI-class specific side-effects like hyperglycaemia, fat maldistribution, hyper lipidaemia (especially with Ritonavir boosting), increased bleeding episodes in haemophiliacs etc. the unique side-effects of Atazanavir include indirect hyper bilirubinaemia (producing yellow discolouration of eyes), skin rash and nephrolithiasis (rare). Unique drug interaction involving Atazanavir: • In addition to all the drug interactions involving PI class • Atazanavir has significant drug interaction with antacids, H2 Receptor antagonists and proton pump inhibitors*	The patients need to be counselled that they may appear to be jaundiced with yellow eyes but they should not be afraid as it would only be a cosmetic problem (like Gilbert disease). It should not be taken as hepatotoxicity. However, LFT has to be done should someone appear to have jaundice. Also, they should be advised to consume plenty of water. Antacid: Give Atazanavir at least 2 hours before or 1 hour after antacids or any buffered medications (For details please refer to table 8)
LPV/r	Side effects include abdominal pain, abnormal stools or bowel movements, diarrhoea, feeling weak/tired, headache and nausea. In addition, patients taking Lopinavir should be monitored for possible liver problems. People who have liver disease, such as hepatitis B or hepatitis C, may experience a worsening of their liver condition. A small number of patients have experienced severe liver problems.	Symptomatic management of minor side effects. Supportive counselling and use of other drugs to manage GI effects should be done. These symptoms improve after a few weeks. Monitor LFTs, lipid profile and blood sugar regularly
3TC	Very minimal side effects. They include cough, diarrhoea, dizziness, headache, loss of appetite, mild stomach cramps or pain. More serious side effects include burning, tingling, or pain in the hands, arms, feet, or legs, chills, ear, nose, or throat problems, fever, muscle aches, nausea, pale skin, severe stomach pain, skin rash are seen rarely	Symptomatic management of minor side effects

CAUTION: We should be cautious in recommending the use of H2RA & PPIs with ATV/r as most of our patients are ARV-experienced; this is a black box warning for ATV; only systemic antacids can be co-prescribed.

*Side-effects of Atazanavir: Apart from the PI-class specific side-effects like hyperglycaemia, fat maldistribution, hyperlipidaemia (especially with Ritonavir boosting); the unique side effects of Atazanavir include indirect hyper bilirubinaemia (producing yellow discolouration of eyes), skin rash, prolongation of PR interval and nephrolithiasis.

For more detailed guidance on Atazanavir toxicity reader is referred to annexure 12.

Drug Interactions:

Avoid concurrent use of the following drugs:

Astemizole, Cisapride, Fluticasone, Indinavir, Lovastatin, Simvastatin, Midazolam, Terfenadine.

Unique drug interaction involving Atazanavir:

In addition to all the drug interactions involving PI class, Atazanavir has significant drug interaction with antacids, H2 Receptor antagonists and proton pump inhibitors. These are listed in table 8 below:

Table 8: Recommendations on major Drug Interaction with Atazanavir

Sl. No	Patients on following drugs concomitantly	Recommendation/points to remember for ATV
1	Antacids	Give ATV/r at least 2 hours before or 1 hour after antacids or buffered medications
2	H2 Receptor Antagonist	1. H2 receptor antagonist dose should not exceed a dose equivalent to Famotidine 40 mg BID in ART-naïve patients or 20 mg BID in ART-experienced patients 2. Give ATV 300 mg + RTV 100 mg simultaneously with and/or > 10 hours after the H2 receptor antagonist Example: If a patient on Zidovudine + Lamivudine + Atazanavir/ritonavir requires to be treated with Famotidine 20 mg BID or Ranitidine 150 mg BID; S/he should be instructed to take Tab. Famotidine/Ranitidine with Zidovudine + Lamivudine at 8.00 AM and in the evening take ZL and ATV/r at 8 PM and ensure that there is a gap of at least 2 hours before or 1 hour after Famotidine/ Ranitidine evening dose.
3	Proton pump Inhibitor	1. H2 receptor antagonist is not recommended with Tenofovir + Lamivudine + Atazanavir/ritonavir 2. PPIs should not exceed the dose of Omeprazole 20 mg daily or equivalent dose of Esomeprazole 20mg/ Pantoprazole 40 mg/ Rabeprazole 20 mg in PI-naïve patients, along with Ritonavir boosted Atazanavir. PPIs should be administered at least 12 hours prior to Atazanavir/ritonavir 3. PPIs are not recommended in PI-experienced patients Example: If a patient, on Tenofovir + Lamivudine + Atazanavir/ritonavir, requires to be treated with PPI, S/he should be instructed to take Tab. Omeprazole 20 mg / Esomeprazole 20mg / Pantoprazole 40 mg / Rabeprazole 20 mg OD at 8 AM and Tenofovir + Lamivudine + Atazanavir/ritonavir after 8 PM.

a. Prolongation of P-R and Q-Tc interval in the ECG can occur. Hence, PR interval needs to be monitored in patients with known conduction defects or with concurrent use of other drugs that alter conduction abnormalities (like diltiazem, clarithromycin, cisapride, ketoconazole etc.). However, routine ECG before starting Atazanavir based ART is not mandatory.

b. Atazanavir induced urolithiasis is also reported; presumably due to precipitation of the drug resulting in crystalluria in a manner analogous to Indinavir.

Counselling issues:

There is a need for enhanced counselling of PLHIV on these regimens particularly unique side effects of Atazanavir/ritonavir. Hence, the patients need to be counselled that they may appear to be jaundiced with yellow eyes but they should not be afraid, as it is only a cosmetic problem. It should not be taken as hepatotoxicity. However, LFT has to be done should someone appear to have jaundice. Also, they should be advised to consume plenty of water.

Important consideration in pregnancy

ATV/r is not to be used for pregnant women exposed to single dose-Nevirapine in the past; they shall be provided with Lopinavir/ritonavir based regimen.

Second-Line ART and TB Treatment

Tuberculosis is the most common opportunistic infection among PLHIV. While tuberculosis has to be treated appropriately and on priority, in the context of second-line ART, drug- drug interactions must be considered. Rifampicin alters the metabolism of protease-inhibitors, including Lopinavir, Atazanavir and Ritonavir, and reduces effectiveness of standard doses. However, another Rifamycin, Rifabutin, can be administered in the presence of PI-containing second-line ART regimen without compromising the efficacy of ART or anti-TB treatment. Therefore, NACP and RNTCP have recommended the substitution of Rifampicin with Rifabutin for the entire duration of anti-TB treatment.

The dosage of Rifabutin during the administration of Atazanavir/ritonavir or Lopinavir/ ritonavir based second-line regimen shall be 150 mg daily for all patients, weighing > 30 kg for the entire period of co-administration of anti-TB treatment and second-line ART, as presently NACO ART centres provide daily anti-TB treatment regimens. Whenever Rifabutin is prescribed, instead of the usual FDC packs, individual anti-TB drugs (without Rifampicin) have to be dispensed to the patients as per weight band.

Some of the common **side effects** of Rifabutin include orange-brown discolouration of skin, tears, saliva, sweat, urine and stools as long as Rifabutin is consumed. The ART centre SMO/MO should be contacted as and when the patient experiences chest pain, muscle aches, severe headache, fatigue, sore throat, flu-like symptoms, vision changes, unusual bruising or bleeding, nausea/ vomiting and/ or yellowing of the skin or eyes.

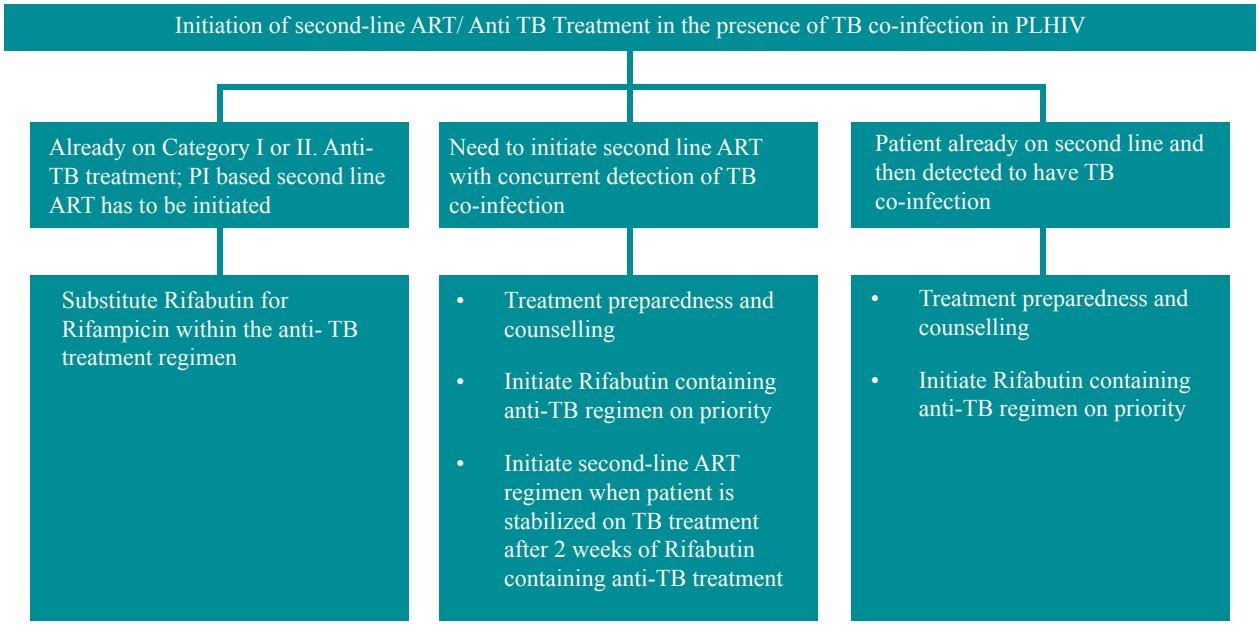
Initiation of second line ART in patient already on anti-TB treatment

If a patient is already on anti-TB treatment and needs to be initiated on second-line ART, then substitute Rifampicin with Rifabutin for 2 weeks prior to initiation of the second-line ART. This should be done to allow hepatic metabolism (induced by Rifampicin) to normalize prior to initiation of PI-containing regimens. While the patient is counselled and prepared for initiation of second-line regimen, the patient should still be given the first-line ART regimen.

Initiation of Anti-TB treatment in patients already on second line ART

If the patient is already on second-line ART (Atazanavir/ Ritonavir containing treatment protocol), and detected to have TB, substitute Rifabutin for Rifampicin within the category I or II anti TB regimen from the start of TB treatment.

Fig 4. Initiation of Second line ART and Anti TB Treatment in the presence of TB co-infection



Note:

- Whenever Rifabutin is prescribed, instead of the usual FDC packs, individual anti-TB drugs (without Rifampicin) have to be dispensed to the patients as per weight band with adequate counselling.
- The 2-weeks of Rifabutin containing anti-TB treatment allows hepatic function to normalize after induction of P 450 cytochrome enzymes by Rifampicin
- Patient should be counselled well for both anti-TB and second-line ART. Pill burden is high. If patient is not started on second-line ART immediately, then continue first-line regimen till patient is switched to second-line ART

Laboratory monitoring of patients on second line regimen

The protocol for laboratory monitoring of patients on second-line ART is described in table 9

Table 9: Monitoring patients on second line ART

Tests	Months						
	0	1	3	6	12	18	24
Hb, CBC	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Complete LFT	Yes		Yes	Yes	Yes	Yes	Yes
Renal function test	Yes		Yes	Yes	Yes	Yes	Yes
Fasting blood sugar	Yes				Yes		Yes
Fasting lipid profile	Yes				Yes		Yes
Viral Load (VL)	Yes			Yes	Yes	Yes	Yes
CD4 count	Yes			Yes	Yes	Yes	Yes

Timing for CD4 testing: CD4 testing should be done at 6 months.

- A baseline CD4 count at the time of ART initiation is necessary to understand presence of Opportunistic Infections (OIs) and to determine immunological failure in the future
- As and when routine virological monitoring becomes available:

1. CD4 testing should be done every 6 months till CD4 count reaches greater than 350 cells/cmm and viral load is less than 1000 copies/ml (when both tests are conducted at the same time).
2. CD4 monitoring should be re-started for any patient if (a) the patient has suspected treatment failure i.e. virological failure (VL >1000 copies/ml or (b) if the patient has undergone a switch in regimen

- The treating doctor can request for a CD4 test or viral load test when deemed necessary for clinical management

Second line ART Failure and Third line ART

Introduction

As the HIV (virus) is prone to error during replications, some patients on second-line ART may also develop resistance to their regimen. This is particularly if the adherence of the patients was not good or they underwent late switching to second-line drugs and there were either few Thymidine Analogue Mutations (TAMS) while on NRTIs or K65R while on NtRTI based regimen. These patients will eventually require third-line ARV drugs. These drugs have been introduced in the national ART programme now. The step-wise guidance for screening, referral, initiation and follow up of patients failing to second-line ART is given below:

Monitoring of patients on second line ART

All patients on second-line ART need to undergo viral load testing every six months.

Work up of patients with suspected line failure

All cases with suspected second-line failure need to be thoroughly evaluated for treatment adherence and presence of any major opportunistic infection. If adherence is good and there is no major OI, such patients with suspected second-line treatment failure should be referred to Centres of Excellence (CoE) first electronically with referral form, containing latest relevant reports and complete past history of treatment.

If treatment adherence is poor or major OI is identified, utmost steps need to be taken to improve adherence and/or treat OI. Such patients should be closely monitored clinically, immunologically and virologically. If no improvement is seen by 3 months, the case should be referred to CoE for further assessment.

After receiving electronic referral, SACEP at the CoE will give two appointments for these cases and the referring centre will confirm one after consultation with patient.

The patient will visit CoE as per the given appointment. SACEP will thoroughly examine the patient for issues like clinical signs-symptoms, investigations, adherence, OI treatment & prophylaxis.

SACEP will refer the patient for VL (if not available already). The VL report will be reviewed by SACEP (in absentia) and eligibility for third-line will be determined. All those with VL more than 10,000 copies /ml will be switched to third-line ART. But if PVL is between 1000 and 10,000 copies, CoE shall repeat VL after three months to confirm failure and exclude the possible blips in viral load readings. PLHIV found eligible for third line ART will be given appointment to come for initiation of third-line at the CoE / specified centers.

Initiation of third line ART

Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens such as Integrase strand transfer inhibitors (INSTIs) and second-generation NNRTIs and PIs. Under the national programme, it has been decided to provide INSTI (Raltegravir) and a new boosted PI (Darunavir/ritonavir). Accordingly, the regimen is **Raltegravir (400 mg) + Darunavir (600 mg) + Ritonavir (100 mg); one tablet each twice daily.**

As per WHO recommendations, in some cases the existing NRTI backbone can also be continued for the possible retention of some anti-retroviral activity; however, it is to be used judiciously for the possible risk of cumulative toxicities of NRTI backbone. Therefore, the third-line prescription has to be a more balanced one for the long-term management and acceptance.

The third-line ART will have to be initiated presently at the CoE only by the nodal officer himself / herself under his / her signature and stamp.

Once the decision of starting third-line ART has been taken by the CoE, the patient will be transferred out to the concerned CoE. The patient will continue third-line ART from CoE for at-least 3 months. Once the patient is stable and treatment adherence is > 95%, the patient can be transferred to the nearest CoE / ART Plus centre. Patients on third-line shall be monitored by viral load measurement every 6 months after initiation of third-line.

Supply chain management of drugs for third-line will be managed by CoE presently, for the initial period, and later on this will be the responsibility of SACS. SACS representative will also participate in SACEP meetings (as per existing guidelines) to address administrative issues.

In cases with difficulty in assessment of second-line failure, complicated prior treatment regimens, patients referred from private, multi-NRTI exposed cases, any intolerance to third-line drugs, cases requiring these third-line drugs as alternate within the second-line ART or any other query, SACEP at CoE can obtain expert opinion from National AIDS Clinical Expert panel (NACEP) electronically, by addressing to nacep.naco@gmail.com.

Follow up Protocol

The patients on third-line ART need strict monitoring for side effects at every visit as there is limited experience on the use of these drugs in the programme; one should keep eyes and the mind open for any new symptom and seek opinion if required. The guidelines for laboratory monitoring patients on third-line are given in table 10.

Table 10: Laboratory Monitoring of patients on third line ART

Tests	Time line			
	Baseline	1 Month after initiation	3 Months after initiation	Every 6 Months after initiation
Hb, CBC	√	√	√	√
Complete LFT	√		√	√
Renal function test	√		√	√
Fasting blood sugar	√			√
Fasting lipid profile	√			√
Viral Load (VL)	√			√
CD4 count	√			√

Adverse events with third-line drugs

Raltegravir:

- Rhabdomyolysis, myopathy, myalgia, nausea, headache, diarrhoea, fever, CPK elevation (statins to be used carefully)
- Rash, Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis (TEN)
- Hepatitis and hepatic failure
- Insomnia

Darunavir:

- Hepatotoxicity, underlying hepatic disease, HBV. HCV co-infections increase the risk of hepatotoxicity
- Skin rash (10%), Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis and erythema multiforme (darunavir has a sulphonamide moiety, so allergy to sulphonamide should be enquired)
- Diarrhoea, nausea, headache
- Hyperlipidaemia, serum transaminase elevation, hyperglycaemia
- Lipodystrophy

Ritonavir

- Gastrointestinal (including diarrhoea, nausea, vomiting, abdominal pain (upper and lower)
- Neurological disturbances (including paraesthesia and oral paraesthesia)
- Rash
- Fatigue/ asthenia

Recording and reporting tools for third line ART

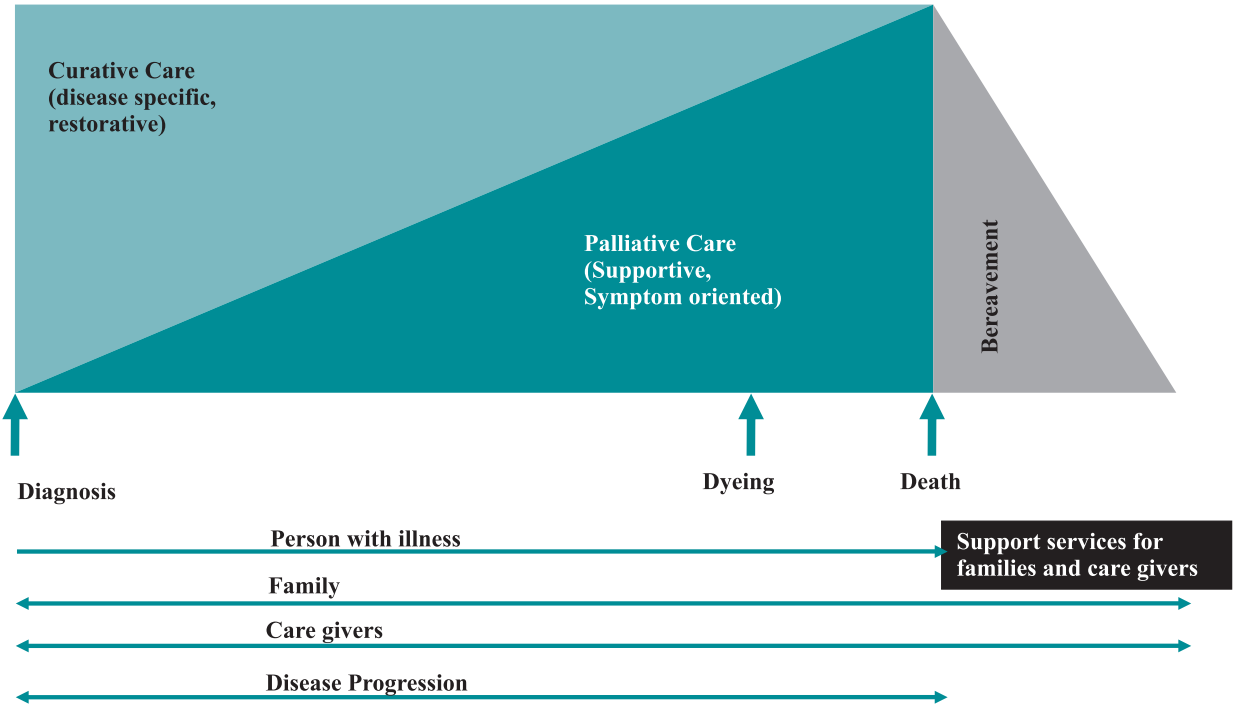
The third-line drugs will be initiated at CoE only; however, these patients will be transferred to the ART plus centres nearer to their homes. The detailed tools to be maintained are given in the M & E section of operational guidelines.

12. Palliative Care for Adults and Children with HIV

The Government of India has adopted WHO's definition of palliative care, which is the "active total care of patients whose disease is not responsive to curative treatment" (Manual on Palliative Care, MOHFW, November 2005). Palliative care is an "approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual".

Palliative care extends, if necessary, to support in bereavement

Relationship between disease-modifying, supportive and palliative care:



Palliative care in HIV:

- Is family and patient-centred
- Optimizes the quality of life by active participation, prevention and treatment of suffering
- Involves an inter-disciplinary team approach throughout the continuum of illness, placing critical importance on building of respectful and trusting relationships
- Addresses physical, intellectual, emotional, social and spiritual needs

The availability of ART and palliative care has made HIV a chronic, manageable disease for many. Apart from regular pain management, nutritional support and OI management, palliative care includes giving support for drug failure and severe toxicities due to ART.

Special attention needs to be given to the following HIV-related conditions, which may present as terminal illness. These conditions can be managed with proper medical care and support-

Severe oral and oesophageal candidiasis, leading to severe pain and weight loss, Cryptococcal meningitis and Toxoplasma encephalitis.

Components of Palliative Care

The main components include:

1. Pain management
2. Symptomatic management
3. Nutritional support
4. Psycho-social support
5. Spiritual support
6. End of life care
7. Bereavement counselling

Management of Pain

Step 1: Assess the patient for pain

- Determine the severity, site and nature of the pain (bone pain, mouth pain, shooting nerve pain, colicky pain, severe muscle spasms)
- If there is infection, prompt management of infection is the main step in controlling the pain (e.g. treating severe oral and oesophageal candidiasis with fluconazole relieves the pain)
- The severity of the pain can be graded with the help of the tools below. GO BY WHAT THE PATIENT SAYS IS HURTING: Do not disregard the patient's complaint of pain just because there is no apparent physical cause

Pain can be assessed by using the PQRST characteristics, given in table 1

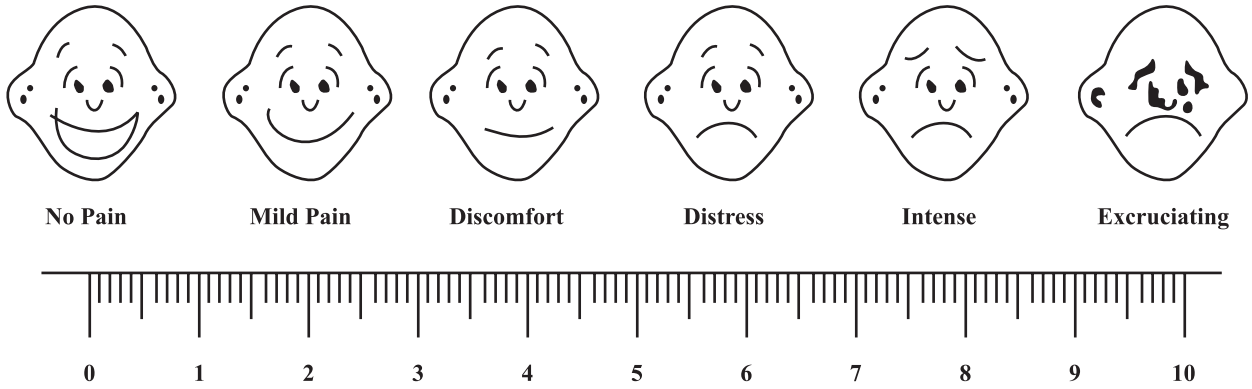
Table 1: PQRST characteristics in pain assessment

Factors for Assessment	Answer eliciting questionnaire
P- Palliative factors **Provocative factors**	'What makes it better?' 'What makes it worse?'
Q- Quality	'What exactly is it like?'
R- Radiation	'Does it spread anywhere?'
S- Severity	'How severe is it?' 'How much does it affect your life?'
T- Temporal factors	'Is it there all the time or does it come and go?' 'Is it worse at any particular time of the day of night?'

Table 2: Various scales for pain assessment

Various scales for pain assessment are	
• Descriptive Scale • Numeric Scale • Visual analogue Scale	• Percentage Scale • Coin Scale • Face Scale
The following format may be used for assessing pain in any given patient	

Pain Intensity Scale

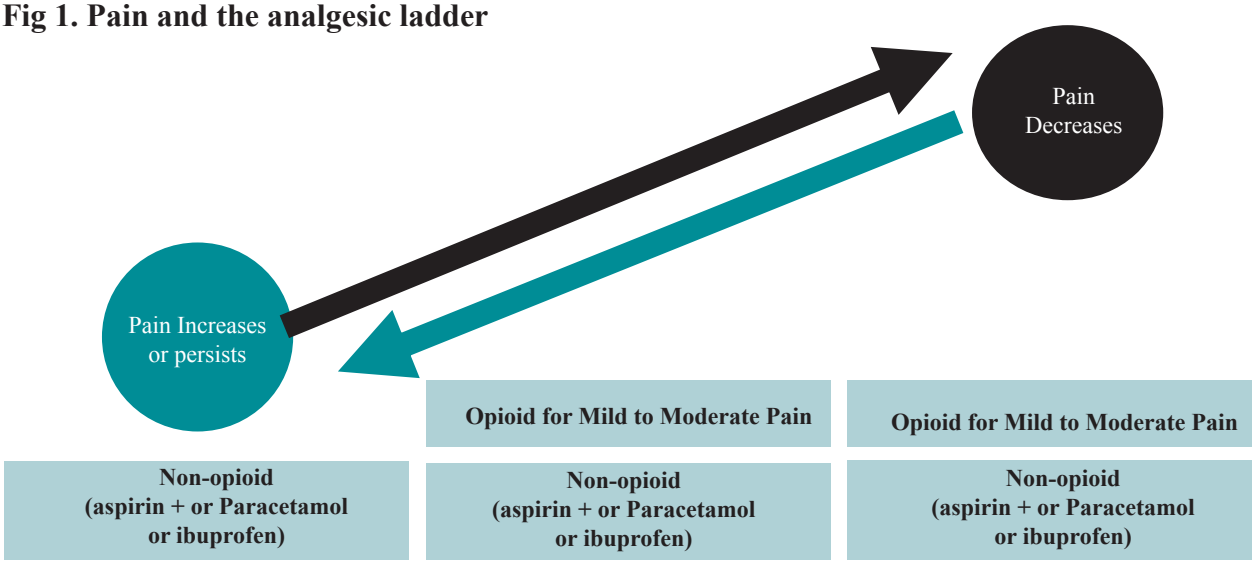


Step 2: Decide the treatment strategies for pain

Table 3: Strategies for treatment of pain

By mouth	By the Clock
If possible, administer pain killer by mouth • Rectal administration is an alternative- • Avoid intramuscular route)	1. Give pain killers at fixed time intervals (by clock or radio or sun) 2. Start with a small dose, then titrate the dose against the patient's pain, until the patient is comfortable 3. The next dose should be given before the effects of the previous on wears off 4. For breakthrough pain, give an extra "rescue" dose, in addition to the regular schedule

Fig 1. Pain and the analgesic ladder



The right dose is the dose that relieves the patient's pain Source: WHO ladder

Step 3: Prescribe analgesics - use of opioid and non-opioid

Give only one drug from the opioid and non-opioid groups at a time. The exception is if codeine cannot be given; use aspirin every four hours combined with paracetamol every four hours—overlap so one is given every two hours.

After adequate pain assessment and evaluation of parameters described above, the pharmacotherapy must be individualized so as to maximize pain relief and minimize adverse effects. WHO has devised a model paradigm for pain management approaches.

WHO Analgesic Ladder

Step 1: Non-opioid ± Adjuvant

⬇

Pain increasing or persisting

⬇

Step 2: "weak" opioid for mild to moderate pain

⬇ **± Non-opioid ± adjuvant**

Pain increasing or persisting

⬇

Step 3: 'Strong" opioids for moderate to severe pain

⬇

Freedom from pain ➡➡ ± Non-opioid ± adjuvant

The WHO approach advises the clinicians to match the patient's reported pain intensity with the potency of analgesic to be prescribed. For **mild pain**, one should use a non-opioid drug like acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) (Table A). A **moderate pain** not controlled by NSAID alone, a "weak" opioid like codeine phosphate or hydrocodone bitartrate should be used in combination with aspirin, another NSAID or acetaminophen (Table B). For **severe pain**, a "strong" opioid such as morphine, hydromorphone, methadone or fentanyl should be used (Table II). The various pain management scales described earlier should be used to assess the outcome of pain management.

Table 4: Partial list of Acetaminophen and Non-Steroidal Anti-inflammatory drugs used for cancer pain

Drug	Dosage Schedule
Acetaminophen	650 mg q4h p.o.
Aspirin	650 mg q4h p.o.
Ibuprofen	200-800 mg q6h p.o.
Diclofenac Sodium	50-75 mg q8-12h p.o.
Flurbiprofen	200-300 mg q4-8h p.o.

Naproxen	250-750 mg q12h p.o.
Piroxicam	10-20 mg q daily p.o
Ketoprofen	50 mg q6h p.o.
Ketorolac tromethamine	10 mg q4-6h p.o.
Ketorolac tromethamine	30 mg im. or iv. x 1 then 15 mg im. or iv. q6h

Table 5: Commonly used Opioids for Cancer pain

World Health Organization step I/II Opioids	**Usual starting dose**
Codeine phosphate	60 mg q3-4h p.o.
Hydrocodone bitartrate	10 mg q3-4h p.o.
Oxycodone hydrochloride	10 mg q3-4h p.o.
Tramadol hydrochloride	50 mg four times daily p.o.
World Health Organization step II/III Opioids	**Usual starting dose**
Morphine sulfate Immediate release	30 mg q3-4h p.o.
Morphine sulfate controlled release	10 mg q3-4h iv.
Morphine sulfate sustained release	30 mg q12h p.o.
Morphine sulfate suppository	As advised
Oxycodone hydrochloride immediate release	10 mg q4h p.o.
Oxycodone hydrochloride controlled release	20 mg q12th p.o.
Hydromorphone	6 mg q12h p.o.
Fentanyl: Duragesic (transdermal)	50 mg/h q72h
Fentanyl: Sublimaze	50 mg/h via continuous infusion
Methadone hydrochloride	20 mg q6-8h p.o.
Levorphanol tartrate	4 mg q6-8h p.o.

The NSAIDs act by inhibiting cyclo-oxygenase, thereby inhabiting prostaglandin synthesis, which are important mediators of inflammatory process. Recent introductions in NSAID therapy include two isoforms of enzyme cyclooxygenase, COX-I and COX-2. Ketoralac tromethadrine is available as oral, intramuscular and intravenous formulations. Various NSAIDs differ in their cost, dosing interval, analgesic ceiling and safety. The choice of NSAIDs must be individualized to the patient's need. The common adverse effects of NSAIDs include GI toxicity, ulceration and bleeding. NSAIDs and opioids have different mechanisms of action and logically would have additive analgesia.

The opioids form an essential component of pharmacotherapy of pain and can be classified as "weak" or "strong" depending on their relative efficacy in releasing pain (Table B). Morphine sulfate is the prototype opioid agonist and is designated by WHO, as "**drug of choice**" for treatment of severe pain associated with cancer. The half-life of morphine is approx. 2 hours, and it is available both as oral immediate release preparation as well as slow release preparations that permit once or twice daily drug regimens. Oral administration of opioids is a convenient, well-tolerated, inexpensive and effective therapy. Moreover, these can also be used in epidural and intrathecal space in selected cases.

The most common **adverse** effect of opiates is constipation that may be result of reduced gastric, biliary, pancreatic and intestinal secretions and a decrease in propulsive motility of stomach and intestines. The other effects include nausea and vomiting caused by direct stimulation of chemoreceptor trigger zone for emesis in medulla. Transient sedation is common when opioid

therapy is initiated but it withers off with prolonged usage.

The adjuvant drugs used include certain anticonvulsants as gabapentin, carbamazepine and clonazepam; oral local anaesthetics, topical therapies, α2 adrenergic receptors like Clonidine and Tizanidine; N-Methyl-D-Aspartate Receptor antagonists like Ketamine, dextromethorphan and amantadine. Certain neuroleptics like fluphenazine and haloperidol are also being used increasingly for various neuropathic pains.

Some of the commonly used non-pharmacological therapies finding increasing acceptance in pain management are quick distraction and imagery (hypnosis), music therapy, specialized Cognitive – Behavioural interventions, massage, thermal modalities, electrical stimulation etc. Certain future neurosurgical interventions that may be helpful in pain management include medullary or pontine tractomy, medullary trigeminal tractomy, mesencephalotomy, thalamotomy, myelotomy and anterolateral cordotomy etc.

Give medications to control special pain problems

There are nerve injury pains and pains from special conditions which can be relieved by specific medications. Provide specific treatment in combination with drugs from the analgesic ladder.

Table 6: Medications for special pain problems

Special pain problems	Medication-adolescent/adult
For burning pains; abnormal sensation pains; severe, shooting pains with relatively little pain in between, pins and needles	PREGABALAIN 75 mg twice a day or Low dose amitriptyline (25 mg at night or 12.5 mg twice daily; some start 12.5 mg daily) – wait 2 weeks for response, then increase gradually to 50 mg at night or 25 mg twice daily
For muscle spasms in end-of-life care or paralyzed patient	Diazepam 5 mg orally or rectally 2-3 times per day
Herpes zoster (or shooting pain following it) Refer patients with ophthalmic zoster	Low dose amitriptyline Early eruption: acyclovir if available; apply gentian violet if ruptured vesicles
Gastrointestinal pain from colic only after intestinal obstruction has been excluded (i.e. vomiting, no stool and gas passing, visible bowel movements)	Codeine 30 mg every 4 hours or Hyoscine 10 mg three times daily (can increase up to 40 mg three times daily)
Bone pain or renal colic or dysmenorrhoea	Ibuprofen (or other NSAID)
If pain is from: • Swelling around tumour • Severe oesophageal ulceration and cannot swallow • Nerve or spinal cord compression • Persistent severe headache (likely from increased intracranial pressure)	When giving end-of-life care and referral is not desired, one can consider use of steroids under careful clinical supervision

Additional methods for pain control

Combine these with pain medications if the patient agrees and it helps:

- Emotional support

- Physical methods: Touch (stroking, massage, rocking, vibration). Ice or heat
  - Deep breathing
- Cognitive methods: distraction such as radio, music, imagining a pleasant scene
- Prayer (with respect to patient's practice)
  - Traditional practices which are helpful and not harmful—get to know what can help in the local setting

Symptom Management

Table 7: Management of Symptoms with Medications and home care

Symptoms	Medications to give	Home care
Nausea and Vomiting	Give anti-emetic: Ondansetron 24 mg tid / Domperidone upto 20 mg tid / metoclopramide (10 mg every 8 hours). Give only for a day at a time or haloperidol (1- 2 mg 4- 6 hourly) or chlorpromazine (25- 50 mg every 6- 12 hours). Injectable anti-0emetics may be needed in several cases	• Eat small, frequent meals • Avoid an empty stomach as this makes the nausea worse • Eat bland foods • Avoid foods with strong or unpleasant odour • Drink plenty of liquids • Rest and relax after and between meals • Avoid lying down immediately after eating • Avoid coffee and alcohol • Assess for any signs of dehydration and consult the health care provider if there is dehydration
Painful mouth ulcers or pain on swallowing	• If Candida: give fluconazole, nystatin or miconazole orally. Topical anaesthetics can provide some relief. Pain medication may be required according to analgesic ladder • For Aphthous ulcers: crush one 5 mg prednisone tablet and apply a few grains • Smelly mouth/breath (halitosis) from oral cancer or other lesion: metronidazole 400 mg bid or chlorhexidine Gluconate 1 % 10 ml qid mouthwash or hexetidine 0.1 % 10 ml qid or Benzydamine 0.5 mouth wash or sodium bicarbonate mouthwash (1 tsp in 1-pint warm water) • For Herpes Simplex: 3 ml nystatin solution (500,000 U) + 2 tablets metronidazole +1 capsule acyclovir (if available)- paint on lesions	• Remove bits of food stuck in the mouth which cotton wool, gauze or soft cloth soaked in salt water • Rinse the mouth with diluted salt water (a finger pinch of salt or ½ teaspoon sodium bicarbonate in a glass of water) after eating and at bedtime • Mix 2 tablets of aspirin in water and rinse the mouth up to 4 times a day • Soft diet to decrease discomfort such as rice porridge, oat meals, depending on what the sick person feels in helpful • More textured foods and fluids may be swallowed more easily than fluids • Avoid extremely hot or cold or spicy foods

The **commonly administered antiemetic** agents are all 5-HT3 antagonists. Even metoclopramide which acts through a dopamine receptor (O23) probably works via 5-HT3 pathway at higher doses.

Use of the newer antiemetic agents has decreased the incidence and severity of nausea and vomiting induced by chemotherapy (Table 8). However, these agents have not totally solved the problem. Adequate control of nausea and vomiting is a must to ensure patient compliance and follow-up ultimately leading to a better quality of life.

Table 8: Commonly administered antiemetics: Classes, Drugs and Dosage Schedules

Antiemetics		
Class	**Drug**	**Dosage Schedule**
Serotonin receptor antagonists	Ondansetron	8 mg iv. x 1, 24 mg p.o. x 1
	Granisetron	10 µg/kg iv. x 1, 2 mg p.o. x 1
	Dolasetron	1.8 mg/kg iv. x 1, 200 mg p.o. x 1
	Tropisetron	5 mg iv. x 1
Substituted benzamide	Metoclopramide	1-3 mg/kg iv. x every 3 h
Phenothiazine	Prochlorperazine	10-20 mg iv. x 1 over 5 min.
Butyrophenone	Haloperidol	1-3 mg iv. q4-6h 1-2 mg p.o. q4-6h
Corticosteroid	Dexamethasone	10-20 mg iv. x 1 over 5 min.
Cannabinoid	Dronabinol	2.5-5.0 mg p.o. q3-6h
Benzodiazepine	Lorazepam	0.5-2.0 mg iv. q4-6h 0.5-1.0 mg p.o. 94-6h

Table 9: Handling of PLHIV with Hiccups and Bed-Sores

Hiccups	• First try to manoeuvre to control. If oral thrush, treat • If no response or recurrent: metoclopramide (10 mg tablet, 1- 2 tablets three or four times daily) OR – haloperidol (5 mg tablet: ¼ to ½ tablets once to three times daily) • If patient has brain tumour, consider anti-epileptic medication	• Manoeuvre to stop hiccups: • Stimulate the throat • Quickly eat 2 heaped teaspoons sugar, or • Drink cold water or eat crushed ice, or Rub with a clean cloth inside the top of the mouth (feel toward the back, where the top of the mouth is soft) • Interrupt the normal breathing by: hold breath or breathe into paper bag – stop when you feel uncomfortable • Pull knees to chest and lean forward (compress the chest)
Bed-Sores	• All patients need skin care to avoid pressure problems • Check for signs of infection • For smelly tumours or ulcers, sprinkle metronidazole powder – enough to cover the area and keep dry	• For small sores, clean gently with salt water and allow to dry • Apply honey to bedsores that are not deep and leave the wound open to the air • If painful, give pain killers such as paracetamol or aspirin regularly • For deep or large sores, every day clean gently with diluted salt water, fill the bedsore area with pure honey and cover with a clean light dressing to encourage healing

End-of-life Care

"How people die lives on the memory of those left behind."

The terminal phase is defined as the period when day-to-day deterioration, particularly of strength, appetite and awareness are occurring. Is it difficult to predict when death will occur and it is better not to do so? The aim of care at this stage should be to ensure the patient's comfort holistically, and a peaceful and dignified death.

Provide psycho-social and spiritual support to the patient:

- Other patients' active listening, counselling and social/emotional support
- Spiritual support is very important
- Be prepared to discuss all matters if the patient would like to
- Learn to listen with empathy
- Understand reactions to the losses in their life (the different stages of grief)
- Be prepared to "absorb" some reactions, for example anger projected onto the health care provider
- Do not impose your own views
- Share religious beliefs with the appropriate person (e.g. religious leader, spiritualcounsellor), as required
- Empower the family to provide care: see table 10
- Help the family come to terms with the fact that the patient is leaving them soon: let family members be around to see and talk to the patient
- Deal with their anxieties and fears gently
- Give information and skills

Table 10: Management of end-of-life care issues

Steps	Actions
Preparing for death	• Encourage communication within family • Discuss worrying issues such as custody of children, family support, future school fees, old quarrels, funeral costs • Tell the patient that they are loved and will be remembered • Talk about death if the patient wishes to (keep in mind cultural taboos if not in a close relationship) • Make sure the patient gets help with feelings of guilt or regret • Connect with spiritual counsellor or pastoral care as patient wishes
Presence	Approach, be present with compassion • Outreach visit regularly with home-based care • Someone needs to hold hand, listen and converse with the patient and family. This could be a volunteer, NGO worker, outreach worker, counsellor etc.
Caring	• Provide comfort and physical contact by light touch, holding hands (if appropriate)

Comfort measures near the life	• Moisten lips, mouth eyes • Keep the patient clean and dry and prepare for incontinence of bowel and bladder • Only give essential medications-pain relief, anti-diarrhoeal drugs, treat fever and pain (e.g. paracetamol round-the-clock) etc. • Control symptoms with medical treatment as needed to relieve suffering (including antibiotics and antifungal drugs) • Eating less is OK; Ensure hydration • Skin care; turning every 2 hours or more frequently to prevent bed sores • Make sure pain is controlled.
Signs of imminent death	• Decreased social interaction-sleeps more, acts confused, coma • Decreased food and fluid intake-no hunger or thirst • Changes in elimination-reduced urine and bowel movements, incontinence • Respiratory changes-irregular breathing, "death rattle" • Circulatory changes-cold and greyish or purple extremities, decreased heart rate and blood pressure
Signs of death	• Breathing stops completely • Heart beat and pulse stop • Totally unresponsive to shaking, shouting • Eyes fixed in one direction, pupils dilated, eyelids open or closed • Changes in skin tone-white to grey

For more details on end of life care, those interested can read Mathura declaration on EOLC 2017.

Palliative care in Children

WHO defines palliative care for children as a special, albeit closely related field to adult palliative care. WHO definition of palliative care appropriate for children and their families is as follows: the principles apply to all paediatric chronic disorders-

- The active total care of the child's body, mind and spirit; it also involves giving support to the family
- It begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease
- Health providers must evaluate and alleviate a child's physical, psychological, and social distress
- Effective palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited
- It can be provided in tertiary care facilities, in community health centres and even in children's homes

Physical needs of children infected with HIV may vary greatly. There is evidence that physical pain in children with HIV/AIDS has historically been underestimated and undertreated. The prevalence of pain in children with HIV/AIDS continues to be high, understudied and associated with poor quality of life and increased mortality. There is a significant need to recognize and manage pain in

children, as well as other physical needs.

Establishing a mutual trusting relationship between the child and family with the clinical team (counsellor/paediatrician/nurse/NGO volunteer) is essential and depends on factors unique to children:

- Child development: physical, emotional and cognitive development influences all aspects of care from drug dosages to communication skills and understanding of their disease and of death
- Care at home: most children are cared at home; if the parent is present, the family unit needs to be given support and be taught appropriate skills
- Assessing symptoms in children: Healthcare providers must provide an environment where children:
    - Do not fear repercussions from their honest expressions (especially if there is an authority figure like doctors / parents)
    - Understand that there is a possibility to reduce pain, if present
    - Learn to trust the health care providers and express future feelings and symptoms

Essential components in palliative care for children

Pain Management

It is important to note that pain is often not adequately treated in children because:

- Some children are unable to express their pain due to their age, lack of verbal skills or disability.
- Few health care professionals are trained and skilled at evaluating children's pain and suffering, and therefore pain is left unrecognised, ignored and untreated.
- Majority of health professionals lack competence in prescribing opioids in children.
- There is fear of using opioids for pain management due to common belief that it will lead to addiction.
- Acknowledgement and support for spiritual pain and conflict, and the impact of culture and language, is mostly ignored in children.

Successful pain management in HIV-infected children begins with efforts to diagnose and treat the underlying conditions causing pain.

Non-pharmacological measures: Various cognitive methods help relieve pain.

- Age-appropriate active distraction
- Older children can be encouraged to concentrate on a game, a conversation or special story
- Swaddling or carrying an infant, providing warmth, breastfeeding or feeding, stroking, rocking, massaging
- Relaxation techniques and behaviour modifications
- Environmental management, including play opportunities, music, scheduled (rather than random) medical and nursing interventions and structured opportunities for sleep and rest
- Nutritional support, adequate hydration, and electrolyte replacement

Pharmacological measures: Correct use of analgesic medicines will relieve pain in most children.

Although there are a limited number of analgesic medicines that can be safely used in children, it is still possible to provide adequate analgesia according to the child's level of pain severity: for children assessed as having mild pain, paracetamol and ibuprofen should be considered as first options and in children assessed as being in moderate to severe pain, the administration of an opioid should be considered.

Symptom management

HIV infection is associated with a variety of symptoms due to the infection itself, opportunistic infections, and treatment side effects. Common symptoms include fever, cough, diarrhoea, anorexia, sore mouth, nausea, vomiting and shortness of breath. They are major causes of discomfort and poor quality of life during the course of HIV infection in infants and children.

Many of these symptoms can be prevented, treated or controlled with basic medications and therapies. Non-pharmacological methods are an important adjuvant to symptom management. Alleviating symptoms enables patients to function, freeing them from the restrictions of the disease as much as possible.

Psycho-social and Spiritual support

In addition to coping with a life-threatening disease and debilitating symptoms, HIV infected children and their infected/ uninfected families may have to manage the changing family dynamics, stigma in the community, loss of their own physical functions, depression, and hopelessness. In this context, psycho-social support can significantly improve their quality of life.

This may need an inter-disciplinary team including doctors, social workers, psychotherapists, and counsellors who are trained to provide counselling and to address mental health issues. They may help them in dealing with the emotional effects of their illness, as well as the social environment in which they function.

Home-Based Care

Home based care means any form of care given to sick people in their own homes instead of a hospital setting. Home-based care covers physical, emotional, spiritual and social aspects, including self-care, care provided by the family members, peer counsellors, outreach workers (ORW), link worker or ASHA.

Home based care components:

The following components are an integral part of managing PLHIV in their homes by the caregivers:

- Symptom and pain management
- Clinic / hospital referral for routine visits and acute care
- Treatment support for adherence and side-effects management
- Nutrition support
- Emotional support, spiritual support (links with religious organisations as appropriate)
- Social services (income generation, child support, food support)
- Future planning for self / family preparing will, identifying guardian for child
- End-of-life care (pain management, funeral grieving support for family)

Caregivers to know:

The caregivers should be educated or imparted with information on basic knowledge of HIV/AIDS, personal and environmental hygiene, prevention of infections and injuries to themselves and others, management of infections at home and necessary information on essential nutritional needs and additional energy requirements. In addition, they should be equipped with information about medicines to be taken by the patient, their possible side effects and also on whom to call for help whenever necessary.

Symptoms management at home:

The caregivers, with the information and knowledge provided, will be able to address and manage the symptoms like cough, fever, hiccups, weight loss, nausea and vomiting, mouth ulcers, pain on swallowing, dry mouth, constipation and incontinence of stool and urine. They should be able to alleviate anxiety and trouble of sleeping, which might be bothering the patient on various issues. The caregivers should be in touch with the ART centres to seek advice on the suspected side-effects of ARV drugs.

Interventions in Home Based Care:

It would be more beneficial for the patients, if the caregivers were oriented with certain skills on prevention of bed sores, prevention of pain, stiffness and contractures in joints, bathing and handling the bed ridden. For managing PLHIV in their homes, there should be necessary materials made available as the part "Home health care kit".

Table 11: Home health care kit

Items	Quantity (minimum)
Sterile gauze pads	20
1-,2-,3-inch gauze rolls	2 each
Clean cotton	1 small package
Soap	1 bar
Scissors	1 pair
Calamine lotion	1 bottle
Bleaching powder	500 g
Petroleum Jelly or Vaseline	1 Jar
Gentian violet crystals or solution	1 small packet or bottle
Potassium permanganate crystals	1 small packet
Betadine ointment and common salt	
Rubber gloves or plastic bags	
Towels or clean cotton cloth	

Challenges faced by caregivers:

Over a period of time, the care givers are subjected to physical and emotional stress, burden of providing care and also taking care of household work, especially women, lack of income if the head of the family is sick and this will be more intense if there is only one caregiver and that too as and when he/she also falls ill.

Caregivers and their stress:

Symptoms of caregiver's stress: Stress in the caregivers can be identified by the surfacing emotional symptoms like crying, worry or anxiety, irritability, anger, feeling exhausted and/or lack of interest in their activities.

Approach to caregivers' stress:

- Encourage them to talk to friends and relatives whom they trust, participate in activities outside home – support groups, hobbies, make them eat well and take care of their own health, train them to become peer educators with positive attitude and approach
- Train more family members: Apart from the caregivers, other family members also should be educated on providing adequate and appropriate nutrition, nursing the patient according to his/her prevailing conditions, preventing complications, preventing transmission of infections like TB, linking with the community HBC provider for support and referrals, alleviating pain as much as possible, seeing that patient seeks medical care for any trivial infection, supporting the patient in order to avoid risk situations and providing emotional support and spiritual care. This helps in identifying additional caregivers within the family and provides needed relief and rest for the overburdened caregivers.

13. Post Exposure Prophylaxis for HIV

INTRODUCTION

Health care providers are prone to accidental exposure to blood and other body fluids or tissues while performing their work duties. Several factors contribute to the increased risk of occupational HIV exposure. First, with the scale-up of HIV testing and ART services more and more people with HIV are coming in contact with health care personnel (HCP). Second, as people living with HIV (PLHIV) receiving antiretroviral therapy benefit from living longer, they are more likely to survive and their chances of coming in contact with the HCP are increasing, thus the increased chances of accidental exposure to HIV infected blood and other body fluids.

Avoiding occupational exposure to blood and other body fluids is the primary way to prevent transmission of HIV, hepatitis B, hepatitis C and other blood borne pathogens in health care settings. Post exposure management protocols form an important element of work place safety. These guidelines describe the risks of infection, the preventive measures and the steps to be followed after accidental occupational exposure.

The term **"Health Care Personnel (HCP)"** is defined as any persons, paid or unpaid; working in healthcare settings who are potentially exposed to infectious materials (e.g. blood, tissue, and specific body fluids and medical supplies, equipment, or environmental surfaces contaminated with these substances). HCP include: emergency care providers, laboratory personnel, autopsy personnel, hospital employees, medical and nursing students and health care professionals at all levels. If required, PEP can also be given to public safety workers, including law enforcement personnel, sanitary workers, prison staff, fire-fighters, workers involved in needle exchange programmes, health care providers in private setting and even to attendants of patients after proper evaluation of exposure.

"Exposure" which may place an HCP at risk of blood-borne infection is defined as:

- A percutaneous injury (e.g. needle-stick or cut with a sharp instrument)
- Contact with the mucous membranes of the eye or mouth
- Contact with non-intact skin (when the exposed skin is chapped skin or afflicted with dermatitis)
- Contact with intact skin when the duration of contact is prolonged with blood or other potentially infectious body fluids

Occupational exposure refers to exposure to potential blood-borne infections (HIV, HBV and HCV) that occurs during performance of job duties.

Non-occupational exposure refers to exposure to potential blood-borne infections (HIV, HBV, HCV) outside of the work place setting like unsafe sex, sexual assault.

Post exposure prophylaxis (PEP) refers to the comprehensive management instituted to minimize the risk of infection following potential exposure to blood-borne pathogens (HIV, HBV, HCV).

This includes first aid, counselling, risk assessment, relevant laboratory investigations based on informed consent of the source and exposed person, depending on the risk assessment, the provision of short term (4 weeks) of antiretroviral drugs, with follow up and support including maintaining confidentially.

The term **"Needle Stick Injury"** is a broad term that includes injuries caused by needles or other sharp objects (e.g. glass vials, surgical blades, forceps) that accidentally puncture the skin.

The **"Exposed Person"** is the person who is potentially at risk of acquiring HIV infection due to exposure to blood or potentially infectious body fluids in his on her occupation.

The **"Source Person"** is the person who is (either identified or not identified as) the possible source of contamination through blood or potentially infectious body fluids. If the sero-status of the source person is unknown, he or she may be counselled to provide informed consent for HIV testing. The source person may be a patient if a health care provider is exposed or the perpetrator in the case of sexual assault.

The decision regarding whether to provide PEP should be based on the clinical consideration of risk only. Providers should give information, services and education without discrimination. The provision of information regarding PEP should be confidential including information about HIV testing, PEP provision and the reasons for seeking PEP.

Written Informed consent needs to be obtained as for any other surgical/medical procedure. Consent for HIV testing of source/exposed person in the context of HIV exposure and/or taking PEP, needs to be done in accordance with national HIV counselling and testing guidelines.

In special situations, where the individual has limited or no capacity to consent (e.g. children, or unconscious or mentally ill adults), a legally acceptable representative may be able to provide consent (e.g. parent / guardian / care taker).

NACP PEP guidelines provide PEP services for all occupational exposures and victims of sexual assault but not for those following unsafe sexual behaviour or having other high-risk exposure

WHO IS AT RISK

Professions with higher chances of blood exposure:

- Nursing staff and students
- Emergency care providers
- Labour and delivery room personnel
- Surgeons and operation theatre staff
- Laboratory technicians
- Physicians
- Interns and medical students
- Dentists
- Health facility cleaning staff, mortuary staff and clinical waste handlers

Table 1: Risk of Exposure from different body fluids

Exposure to body fluids considered `at risk'	Exposure to body fluids considered 'not at risk,' unless these fluids contain visible blood	
Blood Semen Vaginal secretions Cerebrospinal fluid Synovial, pleural, peritoneal, pericardial fluid Amniotic fluid Other body fluids contaminated with visible blood	Tears Sweat Urine & faeces Saliva Sputum Vomitus	Unless these secretions contain visible blood

Any direct contact (i.e. contact without barrier protection) to concentrated virus in a research laboratory requires clinical evaluation. For human bites, clinical evaluation must include the possibility that both the person bitten and the person who inflicted the bite were exposed to blood-borne pathogens. Transmission of HIV infection after human bites has been rarely reported.

Average Risk of Acquiring HIV, Hepatitis B, Hepatitis C after Occupational Exposure

The average risk of acquiring HIV infection following different types of occupational exposure is low compared to the risk of acquiring infection with HBV or HCV. In terms of occupational exposure, the important routes are needle stick exposure (0.3 % risk for HIV, 9-30 % for HBV and 1- 1.8% for HCV) and mucous membrane exposure (0. 09% for HIV).

Table 2: HIV transmission risk by different routes

Exposure route	HIV transmission rate
Blood transfusion	90- 95 %
Perinatal (without any intervention)	15- 40%
Sexual intercourse	0.1 to 10 %
Vaginal	0.05- 0.1 %
Anal	0.065- 0.5 %
Oral	0.005- 0.01 %
Injecting drugs use	0.67 %
Needle stick exposure	0.3 %
Mucous membrane splash to eye, oro-nasal	0.09 %
Comparative risk after needle-stick injury for HBV is 9-30 % and for HCV is 1- 1.8 %	

Figures 1 and 2 below demonstrate common type of needle stick injuries and the activities associated with them

Fig 1: How needle stick injuries occur

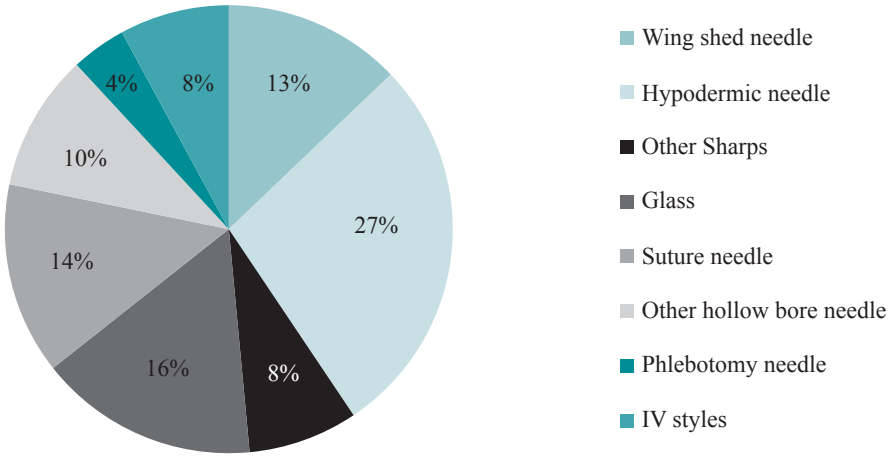


Figure 1. Hollow-bore needles and other devices associated with percutaneous injuries in CDC surveillance hospitals, by % total percutaneous injuries (n=4,951), June 1995-July1999.

Fig 2: Activities associated with needle stick injuries

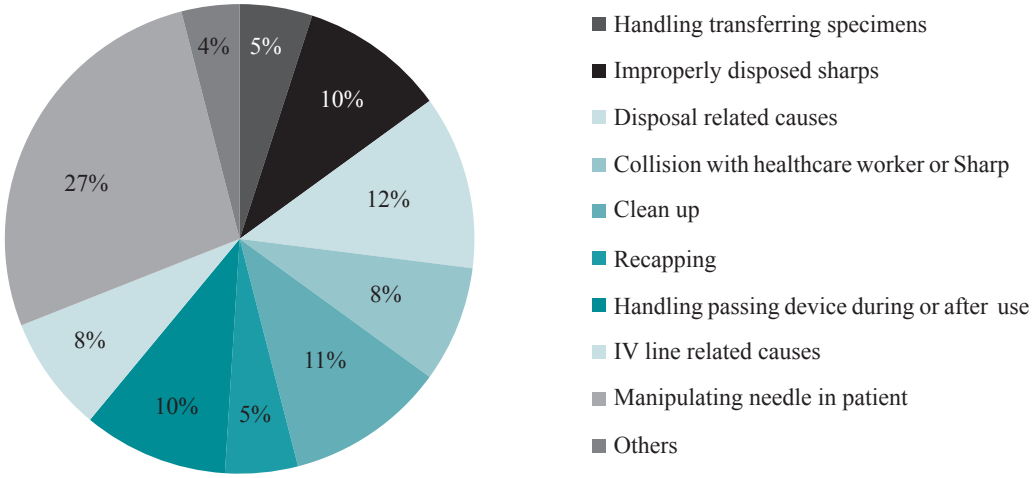


Figure 2. Causes of percutaneous injuries with hollow-bore needles in CDC surveillance hospitals, by % total percutaneous injuries (n=3,057), June 1995-July 1999 (NIOSH,1999).

PRACTICES THAT INFLUENCE RISK AND HOW TO REDUCE RISK TO OCCUPATIONAL EXPOSURE

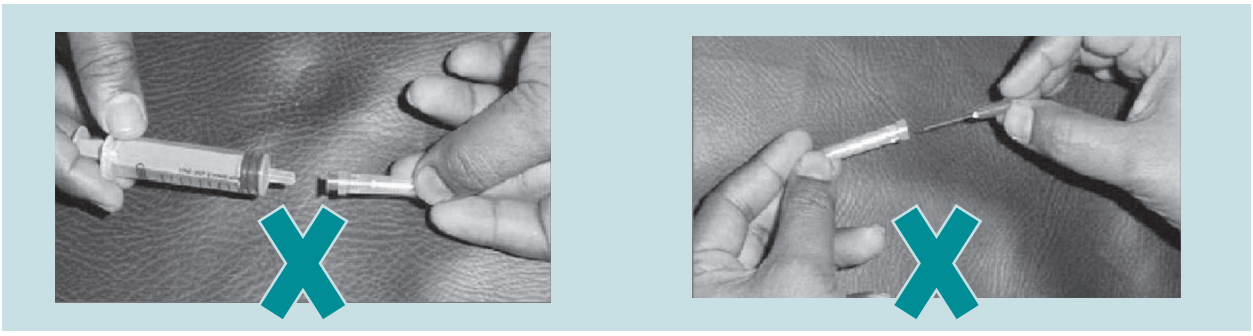
Certain work practices increase the risk of needle stick injury such as:

- Recapping needles (most important)
- Transferring a body fluid between containers
- Handling and passing needles or sharps after use
- Failing to dispose of used needles properly in puncture-resistant sharps containers
- Poor healthcare waste management practices

How to protect oneself from needle stick/sharps injuries:

- Strict compliance to universal work precautions
- Avoid the use of injections where safe and effective alternatives are available e.g. oral, drugs
- Avoid recapping needles
- Plan for safe handling and disposal of needles after use
- Promptly dispose of used needles in appropriate sharps disposal containers
- Report all needle stick and sharps- related injuries promptly to ensure that you
    - o Receive appropriate follow-up care
    - o Participate in training related to infection prevention
    - o Use devices with safety features provided by the institute (wherever possible)
    - o Record and monitor injuries with an injury register in each location of healthcare setting

Figure 3: "Do Not Recap Needle"



Performing activities involving needles and sharps, in a rush increases the likelihood of an accidental exposure

PREVENTING EXPOSURE TO AND TRANSMISSION OF HIV AND OTHER VIRUSES

Staff Information: All categories of HCP within the hospital should be trained on how to protect themselves against HIV and other pathogens transmitted by blood or body fluids. The information must be reinforced on a regular basis. All the staff members share an individual and collective responsibility in this regard. The Medical Superintendent (MS)/ Dean/ Principal/ In-charge of the hospital must constitute a hospital infection control committee which should conduct regular trainings and monitor hospital infection control including universal precaution and post-exposure prophylaxis implementation and quality control. The MS must ensure that the hospital has a written protocol and Standard Operational Procedures (SOP) to handle occupational exposure and that those are disseminated to all relevant personnel/departments.

The Medical Superintendent / Medical officer i/c of the hospital has the responsibility of informing the staff about:

- Universal precautions to be followed in health services (see table 3)
- Use of personal protective equipment (PPE)
- SOPs to be followed in case of accidental exposure to blood and body fluids
- Round the clock availability of PEP drugs –Drugs must be kept in atleast three locations— Emergency room / casualty, labour room and ICU / OT complex

All hospital staff members must know whom to report for PEP and where PEP drugs are available in case of occupational exposure

Minimize the use of sharps/ injections: All the medical staff should try to minimize the use of invasive interventions, for example —oral drugs must be used in place of injections, wherever possible. Whenever the use of sharps is indicated, try to use safer alternatives that are practical and possible, within the limitations of the system.

Protection against hepatitis B: All Health Care Providers (HCP) should be vaccinated against the hepatitis B virus. The vaccination for hepatitis B consists of 3 doses: baseline, 1 month, and 6 months. Most of the recipients (99 %) seroconvert after completing the full course. There is no vaccine or prophylaxis against hepatitis C.

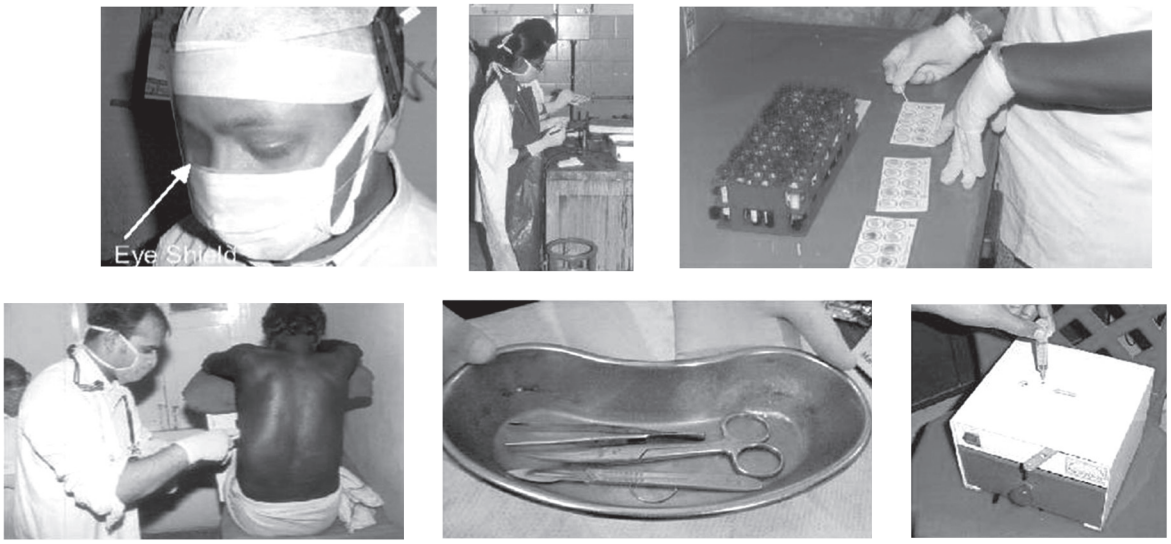
Table 3: Universal Precautions

Universal precautions are intended to prevent the exposure of health-care workers and patients to blood borne pathogens. These must be practised in regard to the blood and body fluids of all patients, regardless of their infection status.

Universal precautions include:

- Hand-washing before and after all medical procedures
- Safe handling and immediate safe disposal of sharps: not recapping needles; using special containers for sharp disposals; using needle cutter/destroyers; using forceps instead of fingers for guiding sutures; using vacutainers where possible
- Safe decontamination of instruments
- Use of protective barriers whenever indicated to prevent direct contact with blood and body fluid such as gloves, masks, goggles, aprons, and boots. A HCP who has a cut or abrasion should cover the wound before providing care
- Safe disposal of contaminated waste

Fig 4: Universal Work Precaution



Always use protective gear/Consider all blood samples as

Follow universal precautions practice-Practise safe handling of sharp instrument-Use needle destroyers

MANAGEMENT OF THE EXPOSED PERSON

Step 1: Management of Exposure Site-First Aid

For skin—if the skin is pierced by a needle-stick or sharp instrument:

- Immediately wash the wound and surrounding skin with water and soap and rinse
- Do not scrub
- Do not use antiseptics or skin washes
  - Don't use bleach, chlorine, alcohol, betadine
- **After a splash of blood or body fluids:**
- **To unbroken skin:**
  - Wash the area immediately
  - Do not use antiseptics
- **For the eye:**
  - Irrigate exposed eye immediately with water or normal saline
  - Sit in a chair, tilt the head back and ask a colleague to gently pour water or normal saline over the eye
  - If wearing contact lens, leave them in place while irrigating, as they form a barrier over the eye and will help protect it. Once the eye is cleaned, remove the contact lens and clean them in the normal manner. This will make them safe to wear again
  - Do not use soap or disinfectant on the eye
- **For Mouth:**
  - Spit fluid out immediately
  - Rinse the mouth thoroughly, using water or saline and spit again. Repeat this process several times
  - Do not use soap or disinfectant in the mouth
  - Consult the designated physician of the institution for management of the exposure immediately

Do not put pricked/ cut finger in the mouth- a childhood reflex

Step 2: Establish eligibility for PEP

The average rate of HIV sero-conversion afterafter an Accidental Exposure to Blood (AEB) (for per-cutaneous exposure) is 0.3 %. The real risk of transmission depends on the amount of HIV transmitted (= amount of contaminated fluid and the viral load).

A designated person/ trained doctor must assess the risk of HIV and HBV transmission following an AEB. This evaluation must be made rapidly, so as to start any treatment as soon as possible after the accident. This assessment must **be made thoroughly** (because not every AEB requires prophylactic treatment).

The first dose of PEP should be administered ideally within 2 hours (but certainly within the first 72 hours) of exposure and the risk evaluated as soon as possible. If the risk is insignificant,

PEP could be discontinued, if already commenced. PEP needs to be started as soon as possible after the exposure and within 72 hours. In animal studies, initiating PEP within 12, 24 or 36 hours of exposure was more effective than initiating PEP 48 hours or 72 hours following exposure. PEP is not effective when given more than 72 hours after exposure.

PEP must be initiated as soon as possible, preferably within 2 hours

Two main factors determine the risk of infection: the nature of exposure and the status of the source patient.

Assessing the nature of exposure and risk of transmission

Three categories of occupational exposure for HCW can be described based on the amount of blood/ fluid involved and the entry port. These categories are intended to help in assessing the severity of the exposure but may not cover all possibilities.

Table 4: Categories of Exposures 4: C

Category of Exposure	Definition and example
Mild exposure	Exposure to mucous membrane/non-intact skin with small volumes E.g. a superficial wound (erosion of the epidermis) with a plain or low calibre needle, or contact with the eyes or mucous membranes, subcutaneous injections following small-bore needles.
Moderate exposure	Exposure to mucous membrane/ non-intact skin with large volumes OR percutaneous superficial exposure with solid needle. E.g. a cut or needle stick injury penetrating gloves.
Severe exposure	Percutaneous exposure with large volume E.g. -an accident with a high calibre needle (> 18 G) visibly contaminated with blood - a deep wound (haemorrhagic wound and/or very painful); transmission of a significant volume of blood - an accident with material that has previously been used intravenously or intra-arterially
The wearing of gloves during any of these accidents constitutes a protective factor. Note: In case of an AEB with material such as discarded sharps/ needles, contaminated for over 48 hours, the risk of infection becomes negligible for HIV, but still remains significant for HBV. HBV survives longer than HIV outside the body.	

Assessing the HIV status of the source of exposure

A baseline **rapid HIV testing of the source of the exposed** should be done before starting PEP. Initiation of PEP where indicated should not be delayed while waiting for the results of HIV testing of the source of the exposure. Informed consent should be obtained before testing of the source as per national HIV testing guidelines.

Table 5: Categories of situations depending on results of the source

Source HIV Status	Definition of risk in source
HIV negative	Source is not HIV infected but consider HBV and HCV
Low risk	HIV positive and clinically asymptomatic
High risk	HIV positive and clinically symptomatic
Refer Annexure 13: Risk Assessment of the source person	

Routinely used HIV test, do not detect HIV during the "window period ", as the antibody level is still too low for detection - but the person can still have a high viral load. This implies that a positive HIV test result (of source) can help in taking the decision to start PEP, but **a negative test result does not exclude HIV infection.** In districts or some population groups with a high HIV prevalence, a higher proportion of HIV-infected individuals are found in the window period. In these situations, a negative result has even less value for decision-making on PEP.

Assessment of the exposed individual

The exposed individual should have confidential counselling and assessment by an experienced physician. The exposed individual should be assessed **for pre-existing HIV infection** (*see Step 5*) intended for people who are HIV negative at the time of their potential exposure to HIV. Exposed individuals who are known or discovered to be HIV positive should not receive PEP. They should be offered counselling and information on the prevention of transmission and referred for clinical and laboratory assessment for subsequent linkage to comprehensive HIV services. Besides the medical assessment, **counselling** (*see Step 3*) of exposed HCP is essential to allay fear and start PEP (if required) at the earliest.

Step 3: Counselling for PEP

For an informed consent, exposed persons (clients) should receive appropriate information about what PEP is and the risk and benefits of PEP. It should be clear that PEP is not mandatory. The client should understand details of window period, baseline test, drugs that are used, their safety and efficacy and issues related to these drugs during pregnancy and breast-feeding. He/ she should be counselled on safe sexual practices till both baseline and 3 months HIV test are found to be negative.

Psychological support: Many people will feel anxious after exposure. Every exposed person needs to be informed about the risks and the measures that can be taken. This will help to relieve part of the anxiety, but some may require further specialized psychological support.

Documentation on record is essential. Special leave from work, if required, should be considered for a period of time e.g. 2 weeks (initially), then as required based on assessment of the exposed person's mental state, side effects and requirements. For recording and reporting framework please refer to operational guidelines for ART services.

Step 4: Assessing Need for PEP and Prescribing PEP

Deciding on PEP regimen:

The decision on the need for PEP for HIV (following an occupational exposure in health care worker) will depend on the exposure as well as source person's HIV status and the extent of disease, if the source has been confirmed positive. It is decided based on exposure code and source code.

Figure 5: HIV Exposure Codes

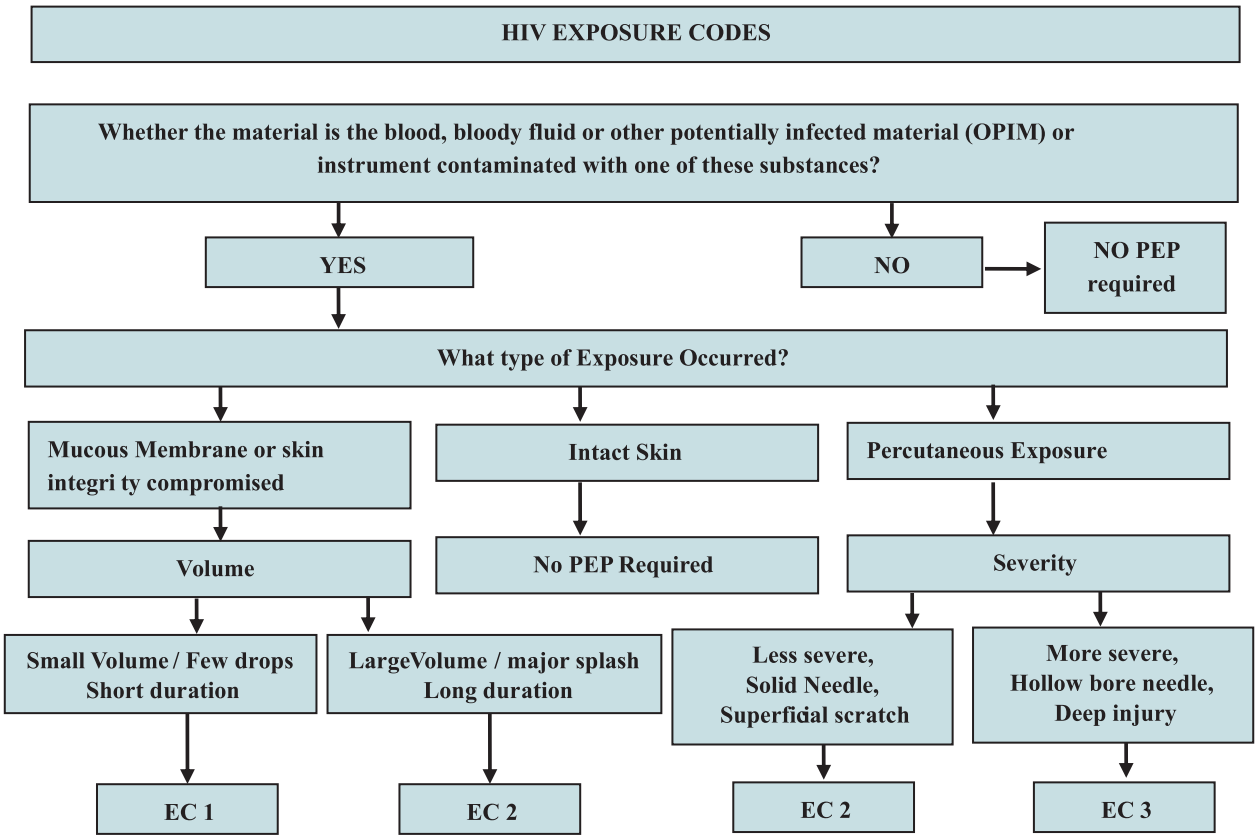
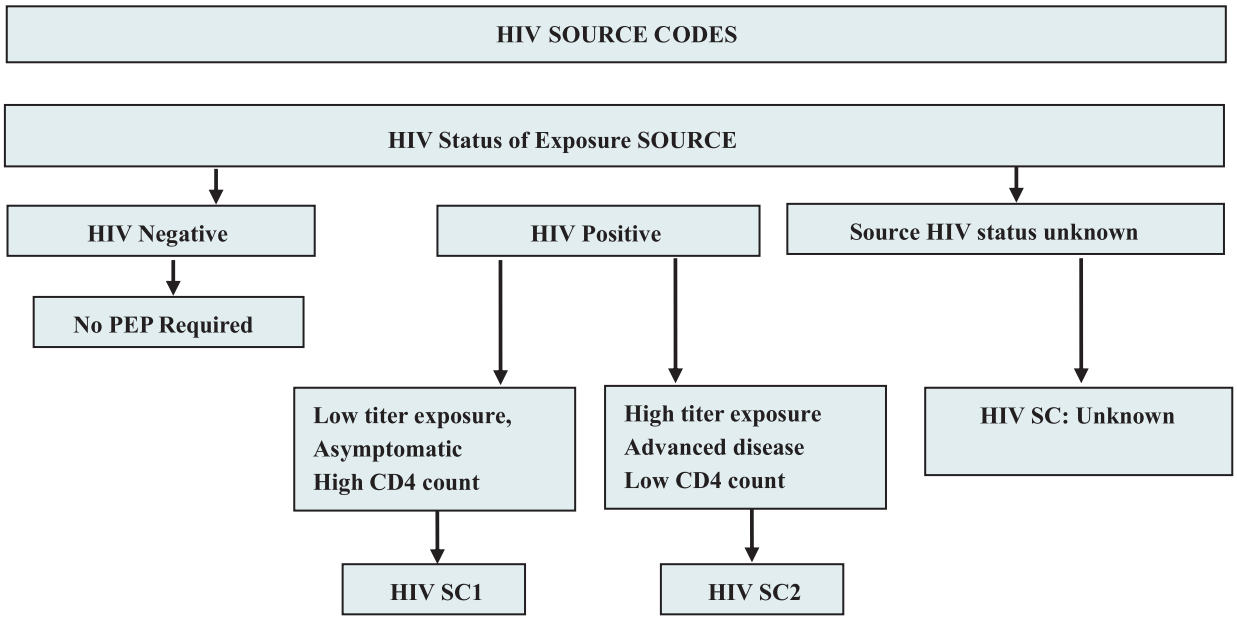


Figure 6: HIV Source Codes



Depending on the exposure and source code, the decision to offer PEP or defer it should be considered as provided in table 6.

Table 6: NACO Recommendations of PEP for HCP based on Exposure and HIV Source codes

Exposure Code	Source Code	Recommendation for PEP	Duration
1	1	Not warranted	
1	2	Recommended PEP	PEP is recommended for 28 Days
2	1		
2	2		
3	1 or 2		
2/3	Unknown	Consider PEP if HIV prevalence is high in given population and risk categorization	28 days

In cases of sexual assault, PEP should be given to the exposed person as a part of the overall package of post sexual assault care.

- HIV testing of the source patient should not delay the decision about whether or not to start **PEP.** Start PEP first if required, then send for consultation or refer
- In the case of a high-risk exposure from a source patient who has been exposed to or is taking antiretroviral medications, consult an expert to choose the PEP regimen, as the risk of drug resistance is high and a change of regimen may be required.

Expert opinion may be obtained for the following situations

- Delay in reporting exposure (> 72 hours)
- Unknown source: use of PEP to be decided on case-to-case basis after considering the severity of exposure and the epidemiologic likelihood of HIV transmission. Do not delay PEP initiation if indicated
- Known or suspected pregnancy: do not delay PEP initiation
- Breastfeeding issues in the exposed person: do not delay PEP initiation
- Source patient is on ART or possibly has HIV drug resistance: refer/consult as soon as possible
- Major toxicity of PEP regimen: minor side effects may be managed symptomatically. Refer to expert if non-tolerance or non-adherence
- Refer/ consult if in doubt or complicated cases (e.g. major psychological problem)

PEP must be initiated as soon as possible, preferably within 2 hours

What Regimen to Give for PEP

As post-exposure prophylaxis (PEP) for HIV has its greatest effect if begun within 2 hours of exposure, it is essential to act immediately. There is little benefit if > 72 hours have lapsed but PEP can still be used if the health care worker presents after 72 hours of exposure. **The prophylaxis needs to be continued for 4 weeks.**

- Report exposure immediately to appropriate authority
- Never delay the start of therapy due to debate over regimen. In cases with exposure from patient on ART, start available three drug regimens and seek opinion after that.
- PEP is indicated for health care providers based on exposure and HIV source codes NACO's recommended PEP regimens are tabulated below.

Table 6: Recommended PEP regimens

Dosages of the drugs for PEP for adults	Recommendation for PEP	Duration
Tenofovir (TDF) 300 mg + Lamivudine(3TC) 300 mg One Tab (FDC) once daily (1-OD)	One tab Immediately within 2 hours of accidental exposure, either at day time or at night time	Next day one tab once OD, continue for 4 weeks
Lopinavir (200 mg) + Ritonavir (50 mg) Two Tab (FDC) twice daily (2-BD)	Two Tab Immediately within 2 hours of accidental exposure, either at day time or at night time	Next day two-tab BD, continue for 4 weeks
If LPV/r is not available / can not be used, Tenofovir(300mg) + Lamivudine (300 mg) + Efavirenz (600 mg), One Tab OD may be given for 4 weeks.		

In case of highly treatment experienced source, initiate first dose as per above guidelines and expert opinion should be sought urgently by phone/e-mail from CoE/ART Plus centre.

In cases of sexual assault, the same principles need to be followed in adults and adolescents. For children who have suffered assault and have to be administered PEP, the dosage should be as per age and weight bands and haemoglobin levels.

Table 7: PEP Drugs for paediatric age group

3-Drug Regimen (as per weight band)	
Medication	**Dose**
Zidovudine (AZT)	Preferred choice. As per weight band
Abacavir (ABC)	If AZT contradicted. As per weight band
Lamivudine (3TC)	As per weight band
LPV/r	As per weight band
EFV (if LPV/r is not available or can not be used)	As per weight band below, in children with age > 3years and weight >10 Kg only.

* Refer to Annexure 2 for Pediatric Dosing schedule

In all cases, appropriate and adequate counselling must be provided regarding possible side-effects, adherence and follow-up protocol.

In practice and from HCP studies, it has been observed that many HCP do not complete the full course of PEP because of side-effects. Side-effects can be reduced by prescribing regimens that do not include a protease inhibitor (PI), by giving medications to reduce nausea and gastritis and by educating clients about how to reduce side effects e.g. taking PEP medications with food. It is important that side effects should be explained before initiating PEP so that the symptoms are not confused with symptoms of seroconversion to HIV.

Adherence information is essential with psychological support. More than 95% adherence is important in order to maximise the efficacy of the medication in PEP. Table 9 below gives guidance on management of common side effects of PEP drugs.

Table 9: Management of Minor ARV drug side effects

Sign or Symptom	Management at health facility
Nausea	Take with food; reassure that this is usually self -limited. Treat symptomatically.
Headache	Give paracetamol. If on EFV, reassure that this is common and usually self-limited. If persists more than 2 weeks, call for advice or refer.
Diarrhoea	Hydrate. Follow diarrhoea guidelines. Reassure patient that if it is due to ARV,it will improve in a few weeks. Follow up in 2 weeks. If it does not improve, call for advice or refer.
Fatigue	This commonly lasts 4 to 6 weeks. Take 'sick leave' from work. If severe or longer than this, call for advice or refer.
CNS side effects: Anxiety, nightmares, psychosis, depression	This may be due to EFV. Take EFV at night before sleeping; Counsel and support (usually lasts < 3 weeks). The initial difficult time can be managed with amitriptyline at bedtime Call for advice or refer if severe depression or suicidal tendencies or psychosis (stop EFV)
Rash	If on EFV, assess carefully. Is it a dry or wet lesion? Call for advice. If generalised or peeling, stop drugs and refer for expert opinion
Fever	Assess clinically for Hepatitis, see if this could be primary (acute) HIV infection or other non-HIV related infections e.g. concurrent common cold. Call for advice or refer
Jaundice or abdominal or flank pain	Stop drugs; Call for advice or refer If jaundice or liver tenderness is present, send for ALT test and stop ARVs. Call for advice or refer

Availability and Prescription for PEP

All clients starting on PEP must take 4 weeks (28 days) of medication. In all cases, the first dose of PEP should be offered as soon as possible, once the decision to give PEP is made. HIV testing of the client or results of the source HIV test can come later. As usage of PEP drugs is not frequent and the shelf life is 1 to 1.5 years, drugs for PEP should be made available in the emergency department, labour room and intensive care unit (ICU). Instructions must be given to the patient/client to go to the designated clinic/officer at the earliest for a complete risk assessment, HIV counselling and testing and receipt of the remaining medications and further management. It is important to monitor and regularly follow-up the patient/client once PEP is started (see step 6).

Hepatitis B

All health staff should be vaccinated against Hepatitis B. The vaccination for Hepatitis B consists of 3 doses- initial (zero) dose, 2nd at 1 month and 3rd dose at 6 months. Sero-conversion after completing the full course is 99%.

If the exposed person is unvaccinated or unclear vaccination status, give complete Hepatitis B vaccine series.

Table 10: HBV vaccination after an AEB

HBV vaccination after an AEB	
HBV vaccination status of exposes persons	**Action after AEB**
Never vaccinated	Give complete Hepatitis B vaccine series
Vaccinated, anti-HbS not known	Give Hepatitis B vaccine booster
Vaccinated more than 5 years ago	Give Hepatitis B vaccine booster
Note: If available, testing for the antibody level (anti-HbS) is not necessary. Hepatitis B vaccine should be given as soon as possible after the exposure. Do not wait for anti-HbS results, if the test is done. Adequate levels of serum Ab to HbSAg (i.e. anti-HbS) is >10 IU/L	

Vaccination for Hep B:

- All HCW must be immunized for Hepatitis-B
- ART staff can be immunized using contingency fund

7.4.10 Hepatitis C: Presently no prophylaxis is available against Hepatitis C. There is no evidence that interferon, pegalated or not, with or without Ribavirin is more effective when given during this time than when given at the time of disease. Post-exposure management for HCV is based on the early identification of chronic HCV disease and referral to a specialist for management.

Step 5: Laboratory Evaluation

The reason for HIV testing soon after an occupational exposure is to establish a "baseline" against which future test results can be compared. If the HCP is HIV-negative in the baseline test, it is, in principle, possible to prove that the subsequent infection identified by follow-up testing is related to the occupational exposure (depending on the timing of infection and consideration of other risks or exposure). When offered HIV testing, the exposed person should receive standard pre-test counselling according to the national HIV testing and counselling guidelines, and should give informed consent for testing. Confidentiality of the test result must be ensured.

There are possibly different reasons for delaying HIV testing: the HCP may be unable to give informed consent immediately after the exposure due to anxiety or the exposure occurs outside working hours or in settings where HIV testing is not readily available. The HIV test may be done up to several days after the exposure, depending upon the informed consent and with pre- and post-test counselling, ensuring confidentiality.

Do not delay PEP if HIV testing is not available.

Table 11: Recommended baseline laboratory investigations

Baseline laboratory investigations		
Timing	In person taking PEP (standard regimen)	In persons not taking PEP
Baseline	HIV, HCV, anti-HBs*, Complete blood count, Transaminases	HIV, HCV, anti-HBs *
* HIV, HBV and HCV testing of exposed staff within 6 days of an AEB is recommended (baseline sero-status). Offer an HIV test in case of an AEB, as a positive HIV status may indicate the need to discontinue PEP. The decision whether to test for HIV or not should be based on the informed consent of the exposed person.		

HIV RNA testing by polymerase chain reaction (PCR) during PEP has a very poor positive predictive value and should be strongly discouraged. Pregnancy testing should also be available, but its unavailability should not prevent the provision of PEP. Other laboratory testing such as haemoglobin estimation should be available, especially when AZT is used for PEP in areas where anaemia is common. Testing for other blood-borne diseases such as syphilis, malaria and kala-azar may also be useful, depending on the nature of risk, symptoms of the source patient, local prevalence and laboratory capacity.

Step 6: Follow-up of an Exposed Person:

Whether or not PEP prophylaxis has been started, follow-up is indicated to monitor possible infections and to provide psychological support.

Clinical follow-up: In addition, in the weeks following an AEB, the exposed person must be monitored for the eventual appearance of signs indicating an HIV seroconversion: acute fever, generalised lymphadenopathy, cutaneous eruption, pharyngitis, non-specific flu symptoms and ulcers of the mouth or genital area. These symptoms appear in 50-70% of individuals with a primary (acute) HIV infection, almost always within 3 to 6 weeks after exposure. When a primary (acute) infection is suspected, referral to an ART centre for an expert opinion should be arranged immediately.

An exposed person should be advised to use precautions (e.g., avoid blood or tissue donations, breastfeeding, unprotected sexual relations or pregnancy) in order to prevent secondary transmission, especially during the first 3 months following exposure. Condom use is essential.

Counseling regarding adherence and side-effects should be provided and reinforced at every follow-up visit. If PEP is prescribed, the exposed health care provider should be followed up every week with laboratory tests recommended below; psychological support and mental health counselling is often required.

CLINICAL MONITORING IN PEP

- **Monitor for acute sero-conversion illness**
  - **Within 3-6 weeks after exposure**
  - **If suspected, refer to ART centre**
- **Avoid:**
  - **Blood donation**
  - **Breast feeding**
  - **Pregnancy**
- **Person should use precautions:**
  - **Sexual relationship (CONDOM protection)**
- **Adherence & Adverse Drug Reaction counselling**

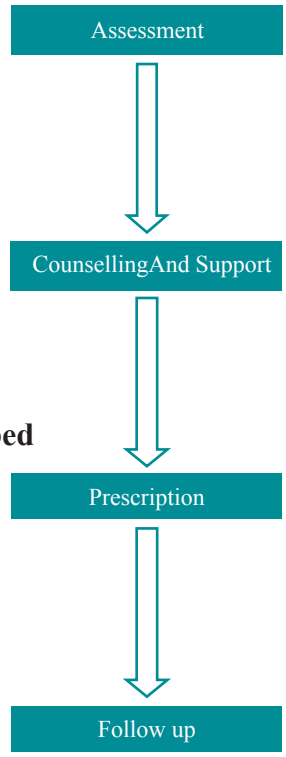
Laboratory follow-up: The exposed person should have follow-up HIV tests post-PEP . Testing at the completion of PEP may give an initial indication of seroconversion outcome, if the available antibody test is very sensitive. However, testing at 4-6 weeks may not be enough as the use of PEP may prolong the time required for seroconversion and there is not enough time to diagnose all

persons who seroconvert. Therefore, testing at 3 months and again at 6 months is recommended. Very few cases of seroconversion after 6 months have been reported. Hence, if the HIV test at 6 months is negative, no further testing is recommended.

Table 12: Recommended follow-up laboratory monitoring (during and after PEP)

Minimum Laboratory Follow-up recommended for PEP for HIV*	
Timing	**In person taking PEP (standard regimen)**
Weeks 2 and 4	Complete blood count (For patients on AZT, this is particularly useful)
Week 6	HIV-Ab
Week 12 (Month 3)	HIV-Ab,
Week 24 (Month 6)	HIV-Ab
It is important to remember that the person exposed to the risk of transmission of HIV is also at risk fof getting infected with HBV and HCV. Hence, that too needs to be addressed	

Fig 3: Care pathway for PEP



- **Clinical assessment of Exposure**
- **Eligibility assessment for Post-Exposure Prophylaxis**
- **HIV testing of exposed people and source, if possible**
- **Provision of first-aid in case of broken skin or other wounds**

- **Risk of HIV**
- **Risk and benefits of Post-Exposure Prophylaxis**
- **Side-Effects**
- **Enhanced counselling if Post-Exposure Prophylaxis to be prescribed**
- **Specific Support in case of sexual assault**

- **PEP should be initiated as early as possible following exposure**
- **28-day prescription of recommended age-appropriate ARV drugs**
- **Drug information**

- **Assessment of underlying co-morbidities & possible drug-drug interactions**
- **HIV test 3-months after exposure**
- **Link to HIV treatment, if possible**
- **Provision of prevention intervention as appropriate**

Source: Adapted from "HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: Recommendations for a public health approach, December 2014 supplement to the 2013 consolidated guidelines on the use of Antiretroviral drugs for treating and preventing HIV infection")

Section 3

Paediatric

14. HIV Exposure in infants and young children

Background

There are an estimated 2.1 million (2015) People Living with HIV (PLHIV) in India at present. Children account for 6.5% of these. Mother-to-child-transmission (MTCT), occurring during pregnancy, labour or during breastfeeding accounts for over 90 % of all HIV infections in children. In India, there are an estimated 27 million pregnancies every year and the current HIV prevalence in pregnant women is 0.29 % (HSS 2014-15). Thus, it is estimated that around 78,300 pregnancies occur in women with HIV infection annually. Infants born to these women are at risk of acquiring HIV infection. The term '***HIV exposed infants/children***" is used to refer to infants and children born to mothers infected with HIV, until HIV infection can be reliably excluded or confirmed in them.

Conventionally, MTCT is referred to as Parent to child transmission (PTCT) in India to emphasize the role of father in the transmission of the virus as well as management of the infected mother and child. Table 1 shows risk of HIV transmission through PTCT with and without any intervention.

Table 1: Risk of HIV transmission through PTCT with and without any intervention

Intervention	Risk of Mother to Child HIV Transmission
No ARV, breastfeeding	30-45%
No ARV, No breastfeeding	20-25%
Short course with 1 ARV, breastfeeding	15-25%
Short course with 1 ARV, No breastfeeding	5-15%
Short course with 2 ARVs, No breastfeeding	5%
3 ARVs (ART) with breastfeeding	2%
3 ARVs (ART), No breastfeeding	1%

Why are HIV exposed infants a vulnerable group?

Regardless of their own HIV status, HIV exposed infants are at a high risk of malnutrition, growth failure, developmental delay and repeated infectious disease related morbidity by common as well as unusual organisms. Adverse social and economic factors associated with parental HIV infection like poverty, broken families, parental sickness/drug abuse, and stigmatization by society are major reasons for this. Increased likelihood of replacement feeding, which may often be inappropriate and over-diluted, poor environmental sanitation and delayed introduction and poor quality of complementary feeds may further increase this vulnerability.

Exposed infants who themselves acquire HIV infection, are even more vulnerable to repeated infections, malnutrition and developmental delay. **HIV disease progresses very rapidly in young children, especially in the first few months of life, often leading to death. If HIV exposure is unknown, HIV infected infants frequently present with clinical symptoms in the first year of life.** Without care and treatment, about one third of infants living with HIV will die in their first

year of life and almost 50% of children by the second year of life.

Thus, it is very important to follow all HIV exposed infants with a structured plan to minimize risk of HIV transmission, ensure timely detection and management of HIV infection, and to give an optimal comprehensive care to improve their overall outcome. With the rapid and significant expansion of the national HIV programme, i.e. the PPTCT, ICTC, ART (for adults and children) programmes, including access to early diagnosis for HIV testing of infants and children < 18 months of age, it is now possible to ensure that HIV exposed, infected infants and children receive the required essential package of care.

Care of Exposed Infant/Child

Components of Care

Main components of care of HIV exposed infants are presented in Box 1.

Box 1: Components of Care of HIV-Exposed Infant/Child

- Immediate Care at Birth
- Infant feeding
- ARV prophylaxis
- Immunization and Vitamin-A Supplementation
- Co-trimoxazole prophylaxis
- Growth and Development
- Early infant diagnosis
- Follow up

Immediate Care at Birth

Care of HIV-exposed infants should follow standard neonatal care according to safe motherhood guidelines which includes the following:

- The baby's mouth and nostrils should be wiped as soon as the head is delivered
- Infants should be handled with gloves until all blood and maternal secretions have been washed off
- The cord should be clamped soon after birth, and milking should be avoided. Cover the cord with gloved hand and gauze before cutting to avoid blood splattering.
- Initiate feeding within the first hour of birth according to the preferred and informed choice

Infant Feeding

Feeding guidelines for infants < 6 months age:

Breastfeeding (BF) provides the infant with all the required nutrients and immunological factors that help to protect against common infections. However, it does carry a risk of transmission of HIV infection from HIV infected mothers to their infants. In accordance with the WHO recommendations, NACO has been providing free and life-long ART to all pregnant and lactating women regardless of their clinical and immunological stage since January 2014. Use of concomitant maternal ART not only decreases the maternal viral load, but also, upon transmission to the infant through placenta and breast milk, provides an effective pre-exposure prophylaxis to the infant preventing replication of any transmitted virions. Thus, the chances of HIV transmission to the foetus and the infant are

greatly reduced, and breast feeding is rendered even more safe. **Breastfeeding with concurrent ARV intervention offers HIV exposed infants the greatest chance of HIV-free survival and is the recommended feeding strategy for them in India.**

In concordance with the recommendation for HIV unexposed infants, it is therefore recommended that, exclusive breastfeeding (EBF) be provided to all HIV exposed infants; and at 6 months of age, these infants should be offered complementary foods along with breast milk.

However, given the fact that breast feeding still carries some risk of HIV transmission, however slight it may be, individual pregnant women should also be informed about the alternative infant feeding options and their advantages and disadvantages as compared to breastfeeding in the current era (table 2).

Exclusive Replacement Feeding (RF) is not a viable public health strategy in India and other developing nations for HIV exposed infants due to increased chances of non-HIV related morbidity and mortality negating the benefits of reduced HIV transmission. Thus, it cannot be recommended and promoted as the optimal infant feeding strategy for HIV-infected mothers in India.

The current national guidelines for feeding of HIV-exposed and infected infants < 6 months age are:

- **Exclusive Breast feeding for first 6 months of life is recommended. In a situation where the mother is practicing mixed feeding, Health-care workers and Counsellors should motivate her to exclusively breastfed.**
- **When exclusive breast feeding is not possible for any reason (maternal sickness, twins), Mothers and health care workers can be reassured that maternal ART reduces the risk of postnatal HIV transmission in the context of mixed feeding as well.**
- **Mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first six months of life, introducing appropriate complementary foods thereafter and continue breastfeeding."**
- **"Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided." Mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or beyond (similar to the general population) while being fully supported for ART adherence.**
- **Exclusive Replacement feeding may be considered only in situations where breastfeeding cannot be done* or upon individual mother's choice, *only if all the 6 criteria for replacement feeding are met (Box 2)***

(#EBF means that infants are given only breast milk and nothing else – no other milk, food, drinks and no water. The infant receives only breast milk and no other liquids, or solids with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines, as advised by authorized medical attendant. * Maternal death, severe maternal sickness, etc.)

Table 2: Benefits and Risks of Exclusive breastfeeding (EBF) and Replacement feeding (RF)

	Exclusive breastfeeding	Replacement feeding
Benefits	• Breast milk contains all the nutrients the baby needs in the first six months • Breast milk is easy to digest • Breast milk protects the baby from diarrhoea, pneumonia and other infections • Breast milk is readily available, does not require preparation • Breastfeeding helps in developing the mother-infant bonding • Exclusive breastfeeding helps the mother to recover from childbirth early • Exclusive breastfeeding protects the mother from getting pregnant again too soon*	• No risk of HIV transmission through feeding • Other family members may be involved in feeding when mothers need help
Risks/ Demerits	• Risk of acquiring HIV infection as long as the baby is breastfed	• Expense of obtaining appropriate milk, water, fuel, added task of cleaning utensils • Babies are at higher risk of contracting diarrhoea, pneumonia and other infections • Mother may be questioned about not breastfeeding her baby

Box 2: The 6 criteria to assess suitability for replacement feeding

Mothers known to be HIV-infected should give replacement feeding to their infants **only** when **ALL** of the following conditions are met:

1. **Safe water and sanitation** are assured at the household level and in the community
2. The mother, or any other caregiver can **reliably afford** to provide sufficient and sustained replacement feeding (milk), to support normal growth and development of the infant
3. The mother or caregiver can **prepare it frequently enough in a clean manner** so that it is safe and carries a low risk of diarrhoea and malnutrition
4. The mother or caregiver can, in the first six months **exclusively give replacement feeding**
5. The **family is supportive** of this practice
6. The mother or caregiver can **access health care** that offers comprehensive child health services

Counselling the mothers who decide to breast feed the infants:

Mothers who decide to breast feed the infants should be counselled to give breastfeed as often as the child wants, day and night, at least 8 times in 24 hours. The mother should be advised to continue breastfeeding if the child is sick. She should not give any other food, fluids or water to her infant during the first 6 months of life. Counselling should also include steps for appropriate breast care.

Counselling mothers who decide to give RF to the infants:

The options of RF include unmodified animal milk/ pre-packed processed toned milk (containing 3 % fat, 3.1 % protein and providing 58 Kcal/ 100 ml/ suitable infant formula reconstituted as per recommendation of the manufacturer. While animal milk is not ideally suited to meet the complete nutritional requirements of an infant below 6 months, it is easily available, economical and culturally acceptable. The infants receiving animal milk should additionally receive multi-vitamin and iron supplementation.

Mothers who decide to give exclusive RF to their infants need to be counselled about the hygienic way to prepare feeds and also about the amount of feeding the child will need at different ages.

They should wash their hands with soap and water before preparing the feed and use clean utensils. The child should be fed using katori-spoon or paladai. Bottle feeding should be strictly avoided since it carries a higher risk of causing diarrhoea.

Mixed Feeding:

It was earlier recommended that giving an infant a combination of both BF and RF is to be avoided since an artificially fed or breastfed child is at less risk of acquiring HIV than the child who receives mixed feeding. Use of animal milk / formula feed increases the chance of causing inflammation of gut mucosa due to allergy and infections, making it easier for the HIV in breast milk to gain access and cause HIV infection in the infant. However, current evidence suggests that in continued presence of maternal ART, mixed feeding is also rendered safe and may be preferred over no breastfeeding at all. Thus, **although exclusive breastfeeding is still recommended during first 6 months, practicing mixed feeding is not a reason to stop breast-feeding in the presence of ARV drugs.**

Thus, with ongoing maternal ART during pregnancy and lactation, there remains no difference in the feeding guidelines related to infant feeding of HIV exposed vs. unexposed infants.

Feeding guidelines for infants and children 6-18 months of age:

For all infants more than 6 months of age, complementary feeding should be started regardless of HIV status and initial feeding options.

Breast feeding beyond 6 months:

Beyond 6 months of age, breastfeeding should continue while complementary feeds are introduced. If an infant is confirmed to be HIV infected, the mother is strongly encouraged to continue breast-feeding upto 2 years or beyond as per the norm for general population. For HIV uninfected infants, it was earlier recommended that BF be stopped by 12 months of age. However, in the current era of universal ART for all pregnant and lactating women, and resultant increased safety of BF, this recommendation may not be valid. The WHO, in its 2016 guidelines on feeding HIV exposed infants recommends that **"In settings where health services provide and support lifelong ART, including adherence counselling, and promote and support breastfeeding among women living with HIV, the duration of breastfeeding should not be restricted. Mothers living with HIV should breastfeed for atleast 12 months and may continue breastfeeding for upto 24 months or longer (similar to the general population) while being fully supported for ART adherence. Also, if a mother living with HIV plans to return to work, she and health-care workers can be reassured that shorter duration of breastfeeding of less than 12 months are**

better than never initiating breastfeeding at all." NACO has endorsed this recommendation for use in India.

Complementary feeding:

The 10 guiding principles of complementary feeding are presented in box 3. (See section on nutrition for further details)

Box 3: Guiding principles of complementary feeding

- Introduce complementary foods at 6 months of age (180 days) while continuing to breast feed
- Start at 6 months of age with small amounts of food and increase the quantity and frequency as the child gets older, while maintaining frequent breast feeding
- Gradually increase food consistency and variety as the infant grows older, adapting to the infant's requirements and abilities
- Feed a variety of nutrient-rich and energy-dense food from the family pot to ensure that all nutrient needs are met; use iron rich complementary foods or vitamin-mineral supplements for the infant, as needed
- Practise responsive (active) feeding, applying the principles of psycho-social care, good hygiene and proper food handling
- All breast feeding should stop only when a nutritionally adequate and safe diet, without breast milk, can be provided by complementary feeds
- Assess the child's nutritional status regularly and, for HIV positive children, classify appropriately as one of the three - growing, poor weight gain/ conditions with increased nutritional needs or severe acute malnutrition
- In addition to age specific needs, HIV positive children who are growing appropriately will require additional 10 % energy, based on actual weight
- In addition to age specific needs, HIV positive children who have poor weight gain or have conditions with increased nutritional needs will require additional 20- 30 % energy, based on actual weight
- In addition to the age specific needs, HIV positive children who have severe acute malnutrition will need therapeutic feeding to provide 50- 100 % additional calories and should be referred to appropriate facility for management of Severe Acute Malnutrition (SAM)

ARV prophylaxis

Infant ARV prophylaxis when mother has been initiated on ART during pregnancy

ARV prophylaxis to the infant must be given according to the national PPTCT programme guidelines in place since January 2014 (See section A6 on PPTCT). According to these guidelines, lifelong ART is provided to all pregnant and breastfeeding women living with HIV regardless of CD4 count or clinical stage. Infants born to these mothers are to be given daily Nevirapine (NVP) from birth for 6 weeks regardless of the mode of feeding, to provide additional protection against HIV transmission during the perinatal period. The duration of Nevirapine prophylaxis should be increased to 12 weeks, if ART to the mother was started late in pregnancy, during or after delivery and she has, therefore, not been on adequate duration of ART to achieve optimal viral suppression (which is at least 4 weeks). The recommendation on extended Nevirapine duration (12 weeks) applies to infants of breast-feeding women only and not to those on RF. If in this situation the mother opts for RF, NVP prophylaxis for 6 weeks suffices. Dose of Nevirapine is given in table 3.

Table 3: Infant Nevirapine prophylaxis regimen

Infant age	Daily dosing
Birth* to 6 weeks • Birth weight 2000- 2500 g • Birth weight > 2500 g	 10 mg (1 ml) once daily 15 mg (1.5 ml) once daily
> 6 weeks - upto 6 months#	20 mg (2 ml) once daily
> 6 months - upto 9 months#	30 mg (3 ml) once daily
> 9 months - until breast feeding ends	40 mg (4 m) once daily
**Infants weighing < 2000 g; the suggested starting dose is 2 mg/kg once daily* *# NVP dose for older infants is provided in a situationwhere HIV exposure is identified during infancy, the mother is breastfeeding and the infant is either HIV uninfected or the status is yet to be determined*	

Infants of women with prior exposure to Nevirapine/ born to women with HIV-2 infection should be given syrup Zidovudine in place of syrup Nevirapine (table 4).

Table 4. Dose of Zidovudine for infants of Nevirapine exposed mothers / women infected with HIV-2

Infant Birth Weight	AZT Daily Dosage in mg	AZT Daily Dosage in ml	Duration
< 2000 g	5mg/dose twice daily	0.5 ml twice daily	6 weeks
2000- 2500 g	10mg/dose twice daily	1 mltwice daily	6 weeks
> 2500 g	15mg/dose twice daily	1.5 ml twice daily	6 weeks

Infant ARV prophylaxis when mother is diagnosed with HIV during labour

All infants born to women who present directly-in-labour and are initiated on intra-partum and subsequent life-long ART, should be started on daily NVP prophylaxis at birth and continued for a minimum of 6 weeks (if the infant is started on RF) or 12 weeks if the infant is initiated on breast feeding.

ARV prophylaxis for infants born to women who did not receive any ART (Home Delivery / detection of HIV during labour / lactation)

Infants should be started on daily NVP prophylaxis at their first encounter with health services. Daily infant NVP prophylaxis can be started even if more than 72 hours have passed since birth though its efficacy in preventing perinatal transmission will be lower. It will, however, still be protective towards transmission by breastfeeding. Daily infant NVP prophylaxis should continue for a minimum of 6 weeks, during which the mother should be linked to appropriate ART services. A longer duration (12 weeks) of prophylaxis is needed for infants on breast feeding.

Immunization and Vitamin A Supplementation

HIV infected infants and children are more susceptible to infections and more likely to develop serious complications thereof. Thus, there is an increased need for vaccination against all vaccine preventable diseases endemic in the area. However, the success of vaccination may be sub-optimal, depending upon the extent of immuno-deficiency at the time of immunization. In general, all inactivated vaccines can be administered safely, while live attenuated vaccines are contra-indicated in severely immuno-compromised infants and children (CD4 <15 %).

HIV-exposed infants and children should be immunized according to the routine national immunization schedule (table 5) with a few exceptions detailed below. It is Important to give all the recommended vaccines at the correct age, as delay may not only increase susceptibility of the

child to illness, but also decrease the immune response to the vaccine as the child's immune status deteriorates.

Points to be kept in mind:

- HIV exposed infants, like all other infants, should be given BCG at birth. However, If BCG has not been given at birth, it should not be given in symptomatic HIV-infected older infants and children
- Live vaccines should be avoided in all severely immune compromised infants. (CD4 <15 %, or in the range of severe immune-deficiency for older children). CLHIV and their caregivers should be counselled about not accepting any vaccination given during immunization campaigns in schools or otherwise without first seeking opinion of the ART centre medical officer.
- Rotavirus vaccine is recommended for use in HIV exposed infants due to their vulnerability to diarrhoea. The vaccine virus is a highly attenuated virus in the vaccine and immunization with the vaccine is given in early infancy when diagnosis of HIV infection is not confirmed in most infants and those infected are unlikely to have severe immune-deficiency. Nevertheless, like all live vaccines it should not be given in children with known severe immunodeficiency.
- Japanese Encephalitis (JE) vaccine is inactivated and found to be safe for use in children with HIV infection. A reduced immune response may be seen in HIV-infected children. However, most children with immune recovery after highly active antiretroviral therapy develop a protective antibody response
- Check for sero-conversion and give boosters as required especially for hepatitis B and hepatitis A. A 4-dose, double quantity schedule for hepatitis B has been recommended in view of poor sero-conversion with routine immunization
- Vitamin A supplementation should be as per the national immunization schedule

Desirable vaccines not currently available through the national schedule include:

- Inactivated Hepatitis A vaccine (2 doses 6 month apart between 12- 23 months)
- Pneumococcal conjugate vaccine (2, 4, 6-month, Booster 12- 15 month). Administer Pneumococcal polysaccharide vaccine (PPSV23) at least 8 weeks after the last dose of PCV to children aged 2 years or older
- Inactivated Influenza vaccine (starting at 6 months age: two doses 1 month apart; 9 years and above: single dose. Annual booster with single dose)
- Varicella vaccine: Administer the first dose at age of 15 months through 18 months and the second dose at age 4 through 6 years

Table 5: Current National immunization schedule

Age	Immunization Schedule (After introduction of Rotavirus Vaccine)
At Birth	BCG, OPV-0, Hep B Birth Dose
6 weeks (1 1/2 months)	OPV-1, RVV-1, fIPV1##, Pentavalent-1
10 weeks (2 1/2 months)	OPV-2, RVV-2, Pentavalent-2
14 weeks (3 1/2 months)	OPV-3, RVV-3, fIPV2/IPV, Pentavalent-3
9 months	MCV-1, Vit A*, JE-1#
15 Months	MCV-2
16-24 Months	DPT-B1, OPV-B, JE-2#, Vit A*
5-6 Years	DPT-B2

10 Years	TT
16 Years	TT
Pregnant Mother	TT-1 and TT-2
*Vitamin A to be given every six months till five years of age #JE vaccine given in selected endemic districts ## Schedule varies from state to state	
BCG; Bacillus Calmette-Guerin; DPT: Diphtheria-Pertussis-Tetanus; Hep B: Hepatitis B; Pentavalent vaccine: DPT+ HepB + Hib (Haemophilus influenza type b); JE: Japanese Encephalitis: MCV: Measles Containing Vaccine; OPV: Oral Polio Vaccine; TT: Tetanus Toxoid; IPV: Inactivated Poliovirus Vaccine; FIPV: Fractional Inactivated Polio Vaccine; RVV: Rotavirus Vaccine	

Co-trimoxazole (CTX) prophylaxis for HIV-Exposed/Infected infants and Children

Co-trimoxazole prophylaxis is an effective and proven strategy for reducing morbidity and mortality in children with HIV infection. It not only protects the infants and children from Pneumocystis jiroveci infection, but also from malaria, diarrhoea due to isospora and cyclospra, toxoplasmosis and other bacterial diseases. All HIV-exposed infants should get co-trimoxazole prophylaxis from the age of 6 weeks. The recommended dose is 5 mg/ kg/ day as a single daily dose. For details related to co-trimoxazole prophylaxis, refer to the chapter on prophylaxis for opportunistic infections in children.

Growth and Development

Growth monitoring:

Frequency of growth monitoring:

The child's weight should be recorded at every visit to the ART centre. Length should be recorded once in 3 months for all HIV exposed infants. It is recommended that the WHO growth reference standard be used for assessing a child's growth parameters. These are available as growth charts as well as reference tables for boys and girls separately (Refer annexures 14, 15 & 18). In a child growing normally, a serial recording of these parameters in a growth chart over time should yield a curve parallel to one of the standard growth curves on the growth chart. When the child's growth parameters falter, serial recordings on a growth chart will no longer be parallel to the standard growth curves. For practical purposes *weight for age* chart should be maintained for every child for serial weight monitoring. Z scores for other parameters like length for age and weight for length may be checked from the graph/ table as required for assessment of nutritional status.

If the child's growth curve is flattening, one should intensify the assessment of HIV related features and also screen for treatable causes e.g. nutritional deficiency, chronic infections such as respiratory, gastro-intestinal, urinary tract infection and **TB.**

Developmental Assessment:

Developmental milestones help in assessing development or maturation of the brain of an infant/ child. they refer to abilities that children are expected to possess at different ages. Delayed development or, loss of milestones after attaining them, may be the first sign of HIV infection suggesting HIV encephalopathy, if other common causes are ruled out. Early identification of

developmental delay and neurologic abnormalities can facilitate intervention and suitable remedial actions. Therefore, it is crucial to assess the development in an HIV-exposed / HIV-infected infant and child.

Developmental assessment at each visit should include assessment of the cognitive, motor, language and social skills by asking appropriate history from the mother, and observing the child during the examination, using a developmental check-list.

Diagnosis of HIV infection in Infants and Children

Early Infant Diagnosis

Maternal HIV antibodies transferred passively to the infant during pregnancy usually persist for nearly 9- 12 months in the infant. In some children, they may persist for as long as 18 months. Thus, children born to HIV-infected mothers will test positive for HIV antibodies regardless of their own infection status. A positive ELISA/ Rapid test that detects antibodies to HIV, therefore, does not necessarily indicate the presence of HIV infection in the infant/ child. Rather, a positive ELISA/ Rapid test indicates exposure to HIV. More reliable indicators of the status of HIV infection of the infant are tests that detect HIV DNA or antigens. Table 6 shows the various tests available for diagnosis of HIV infection and their relevance for children aged < 18 months.

Table 6: Options of diagnostic Test for Infants & Children < 18 Months of Age

Test	Recommendation	Reason
HIV antibody	No	False +ve due to persistent maternal antibodies
HIV DNA PCR	Yes	98 % sensitive from 6 weeks of age
HIV p24 Antigen	Yes, but	Lower sensitivity than PCR (27 % at 6 weeks)
HIV viral culture	Yes, but	Costly, result takes 2- 4 weeks, not readily available

NACO protocol for diagnosis of HIV-1 infection in infants and children < 18 months age

NACO recommends the use of DNA PCR test on a Dried blood sample (DBS) of the infant to detect viral DNA for diagnosis of HIV-1 infection during infancy. This test is performed at 6 weeks of age and thereafter until 18 months of age. At 6 months of age or therafter, DNA PCR has to be performed after screening for HIV antibodies, as depicted in the algorithm (Box 4). It is also important to take breast-feeding into consideration in the HIV testing algorithm. Since breastfed children have ongoing risk of HIV acquisition, they are re-tested 6 weeks after complete cessation of breast-feeding to reliably exclude HIV-1 infection. The choice of test(s) depends upon the age of the child at the time of re-testing. Thus, if cessation of breast feeding occurs beyond 18 months of age, rapid tests for HIV antibodies will suffice; a child between 6- 18 months would first be screened for HIV antibodies followed by DNA PCR, if found positive for antibodies.

As per the Early Infant Diagnosis (EID) protocol of NACO, HIV exposed infants are tested for HIV infection status as follows:

- The first HIV DNA PCR test for HIV-1 infection using a Dried blood spot (DBS) method is conducted at 6 weeks of age. If the DBS test is positive for HIV, the test is repeated on another DBS sample as early as possible for confirmation. In case the second DBS tests negative for HIV, the lab will request for another DBS sample for a second confirmatory HIV -1 DNA PCR test from the ICTC and rely on the result of this test for final diagnosis
    - If the first PCR is negative (before 6 months of age), the child is screened for HIV

antibodies (Rapid test) at 6 months age. Infants testing positive on rapid test are re-tested with a PCR test using DBS

- DNA PCR can be repeated earlier if the infant becomes symptomatic
- If the child is breastfed and initial PCR tests are negative, re-testing is carried out 6 weeks after cessation of breastfeeding
- If the infant is seen for the first time after 6 months of age, an HIV serology is performed as a screening test. A PCR on a DBS sample is performed only if serology for HIV is positive
- In 74 % and 96 % of HIV-uninfected exposed children, HIV antibody test will be negative at age 9 and 12 months respectively. Thus, if in a HIV exposed child > 6 months of age HIV antibody test is negative, there are two situations:

- If the infant/ child is not breastfed in last 6 weeks, the infant/ child is probably not infected and does not need HIV DNA PCR testing.
- In an infant/ child with negative HIV antibody test but receiving exclusive breastfeeding or mixed feeding, HIV antibody test should be repeated after 6 weeks of complete cessation of breastfeeding to rule out HIV infection.
- If symptoms develop at any time, the child should be tested appropriately (DNA PCR or Antibody test by ELISA/rapid) at that age.
- For National Testing Algorith for HIV exposed infants and children < 18 months refer to Annexure – 1.
- Co-trimoxazole Preventive Therapy (CPT) to be initiated for all HIV exposed babies from 6 weeks of age and continued until proven HIV negative on all three serological tests at 18 months of age or later if still being breastfed. In case the baby is found to be HIV infected at any stage, LPV/r-based ART should be initiated and CPT should be continued until 5 years of age.
- Initiate babies on exclusive BF/ RF till 6 months of age; add complementary food thereafter

Presumptive diagnosis where there is no virologic testing (DNA PCR) available

If the child is aged < 18 months and has symptoms and signs that are suggestive of HIV infection and there is no virologic testing available, it is possible to make a presumptive diagnosis by addressing the following issues:

- Does the child meet the clinical criteria for presumptive diagnosis of severe HIV infection?
- Is there evidence of HIV exposure - mother or baby's serology shows positive HIV antibody?
- Is there evidence of immune suppression (low CD4 count/ %) and/ or symptoms or illnesses consistent with HIV infection?

Box 5 shows the clinical criteria for presumptive diagnosis of HIV infection in children aged < 18 months when virological tests are not available. In a child meeting the presumptive criteria, ART is initiated as soon as possible without waiting for virological tests that, nevertheless, should be performed at the earliest.

Box 5: Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not available

A presumptive diagnosis of severe HIV disease should be made if:

The infant's HIV antibody test is reactive

and

Diagnosis of any AIDS-indicator condition(s) can be made

or

The infant is symptomatic with two or more of the following *:

- Oral thrush;
- Severe pneumonia;
- Severe sepsis.

Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include:

Recent HIV-related maternal death; or advanced HIV disease in the mother; CD4 in the child <2 0%.

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

Notes:

* As per IMCI definition:

1. Oral thrush: Creamy white to yellow soft small plaques on red or normally coloured mucosa which can often be scraped off (pseudo membranous), or red patches on tongue, palate or lining of mouth, usually painful or tender.

2. Severe pneumonia: Cough or difficult breathing in a child with chest in-drawing, stridor or any of the IMCI general danger signs; i.e., lethargic or unconscious, not able to drink or breast-feed, vomiting, and presence or history of convulsions during current illness; responding to antibiotics

3. Severe sepsis: Fever or low body temperature in a young infant with any severe sign such as fast breathing, chest in-drawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions, etc.

Discordance among the EID results and Rapid tests at 18 months

18-month antibody testing should not be done for HIV exposed infants who were 2 DBS PCR positive and initiated on-ART. However if tests are done and in case of discordance between EID result and rapid test at 18 months, ART is to be continued regardless of antibody test results at 18 months.The case to be referred to NACEP (National AIDS Clinical Expert Panel).

Diagnosis of HIV infection in children > 18 months

Children aged ≥ 18 months are tested according to the national adult testing strategies:

Two positive HIV antibody test results (done sequentially) in a **clinically symptomatic** child (symptoms suggestive of HIV infection) more than 18 months indicate HIV infection in the child.

Three positive HIV antibody test results (done sequentially) in **a clinically asymptomatic** child more than 18 months old indicate HIV infection in the child.

Two positive HIV antibody test results and one negative result **(done sequentially) in an asymptomatic child more than 18** months old is indeterminate HIV status. Follow up testing should be done in such a child to resolve the HIV status.

Box 6: Summary points for HIV diagnosis in infants:

- For infants < 18 months: confirm with PCR and check status of breast-feeding
- For infants > 18 months: Antibody testing as per adult diagnostic guidelines
- If testing if not available for infants < 18 months, then diagnose clinically using presumptive diagnosis method.

Follow-up of HIV exposed infants and children

HIV exposed infants are a vulnerable group irrespective of their own HIV status due to a combination of various adverse socio-economic and family factors including poverty, stigma, increased exposure to sickness due to parental ill-health/ death, exposure to ARV drugs and, in some cases, replacement feeding. A structured follow-up plan gives opportunity to clinically evaluate these children at regular intervals and give them comprehensive care including delivery of all the components discussed above.

The exposed infants and children should be followed up at ICTCs beginning at 6 weeks of life. Prior to this, they should have been given BCG, hepatitis B and OPV vaccine at birth. At the first visit at 6 weeks, the following activities are undertaken:

- Initiation of co-trimoxazole prophylactic therapy
- Checking adherence of infant NVP prophylaxis for the past 6 week and decision regarding continuation of NVP till 12 weeks depending upon duration of maternal ART
- First DBS for HIV DNA PCR
- Growth monitoring / development assessment
- Referral of any infant with medical problems for medical assessment
- For exclusively breastfed infants, the pattern of feeding, attachment and positioning and mother's breast condition is enquired for
- For infants on replacement feeding, parents /family are asked about any problems faced in infant feeding. The nature, frequency and amount of replacement feeds being given is enquired about and feed hygiene is emphasised
- Assessment of maternal health and her adherence to ART

The subsequent visits are at 10, 14 weeks, 6, 9, 12, 15 and 18 months, synchronized with the immunization visits. The activities at these visits are similar to those described for the 6-week visit. At any time, an infant is detected to be infected with HIV on laboratory testing or by presumptive WHO criteria, he/ she is referred to the ART centre without delay. Infants may also require a medical review during an acute episode of sickness, or if they show growth faltering over serial visits. At every visit, information is given to the mother or caregiver on potential common HIV related features, about availability of early infant diagnosis, and the importance of follow-up and adherence to ARV prophylaxis or treatment. Any psycho-social concerns are addressed and need for co-trimoxazole prophylaxis is reinforced. Age appropriate guidelines are given for infant feeding. At the 18-month visit, HIV serology is tested for all infants. In case the infant is breastfeeding beyond 18 months of age, he/ she should be followed-up till complete cessation of breastfeeding. An HIV test must be performed 6 weeks after complete cessation of breast feeding.

Table 7: Follow-up protocol of HIV exposed infant

Care of HIV Exposed Infants & Children									
Activities at each follow up visit									
Visit	**Birth**	**6 Wks**	**10 Wks**	**14 Wks**	**6 Mths**	**9 Mths**	**12 Mths**	**15 Mths**	**18 Mths**
Co-trimoxazole Prophylaxis Therapy		Start from 6 weeks (or first immunization visit) for all HIV-exposed infants and children • Continue CPT: for those tested to be HIV infected • Stop co-trimoxazole: for those tested to be HIV un-infected							
Counselling for Infant feeding	√	√	√	√	√	√	√	√	√
Growth monitoring	√	√	√	√	√	√	√	√	√
Developmental assessment	√	√	√	√	√	√	√	√	√
Immunization &Vitamin A supplements	BCG OPV-0 Hep B Birth Dose	OPV-1 RVV-1 fIPV-1## Pen-tava-lent-1	OPV-2 RVV-2 Pentava-lent-2	OPV-3 RVV-3 fIPV2/ IPV Pen-tava-lent-3		MCV-1 Vit A* JE-1#		MCV-2	DPT-B1 OPV-B JE-2# Vit A*
Clinical assessment	√	√	√	√	√	√	√	√	√
HIV testing (√-if required		√			√		√	√	√
Maternal Health & ART Adherence	√	√	√	√	√	√	√	√	√

Counselling and Psycho-Social Support

Success of any public health program depends upon effective & ongoing counselling. Parents and caregivers of HIV exposed infants need ongoing counselling beginning right from pregnancy and through labour, post-natal period and beyond. The key counselling areas are PPTCT, maternal ART and infant ARV prophylaxis, infant feeding, nutrition, Early Infant Diagnosis, co-trimoxazole initiation, vaccination, awareness of signs of sickness in an infant and adherence to ART (mother), ARV/Nevirapine prophylaxis (infant). The key persons responsible for counselling are the PPTCT and ART counsellors, ART centre MO, the paediatrician and the obstetrician. It is critical that all the key persons are well informed about the current national guidelines so that a consistent message is given to the affected family by anyone who interacts with them. (*Refer to counselling section for more details on counselling support in children)*

15. Assessment of Children with HIV Infection, Pre-Art Care and Follow Up

At the beginning of HIV care and prior to starting ART, thorough assessment should be performed to:

- Determine the clinical stage of HIV infection
- Identify history of past illnesses (especially those related to HIV; like pneumocystis pneumonia (PCP) or tuberculosis (TB). Identify current HIV-related illnesses including TB that require treatment. If opportunistic infection is suspected, then diagnosis and treatment of Opportunistic Infections (OIs) take priority over ART initiation.
- Determine the need for OI prophylaxis according to clinical stage and/or CD4 count or CD4 %
- Identify coexisting medical conditions and treatments that may influence the choice of therapy
- After appropriate counselling, take written consent of the primary caregiver for HIV care and ART initiation (Refer to Annexure 03)

1. Assessment of a newly diagnosed child with HIV

1.1 Anthropometric assessment

1.2 Clinical assessment (History / Physical Examination)

1.3 Developmental Assessment

1.4 Laboratory assessment

1.5 Psycho-social assessment

1.1 Anthropometric assessment

HIV infected children are at particular risk for problems related to growth. HIV and opportunistic infections often negatively influence the growth of young children. Faltering in growth often occurs even before opportunistic infections or other symptoms become overt. Early detection of growth faltering facilitates timely intervention to prevent further deterioration.

Anthropometric assessment is a valuable tool for assessing growth and nutritional status of children. It involves measuring a child's weight, length/height and mid-upper-arm circumference (MUAC) and comparing these measurements to growth reference standards. The purpose is to determine whether a child is growing "normally", or his/her growth pattern is different from the expected. It is recommended that WHO growth reference standards are used for assessing a child's growth upto 5 years. These are available as growth charts as well as reference tables for boys and girls separately (see annexures 14, 15 & 18). For children beyond 5 years of age IAP growth charts based on growth reference data from Indian children are recommended (Refer to annexures 16 & 17). Refer to the chapter on nutrition for details on anthropometric assessment and its interpretation.

1.2 Clinical Assessment

History

Ask for:

- Unusually frequent and severe occurrences of common childhood bacterial infections, such as otitis media, sinusitis, and pneumonia
- Recurrent fungal infections, such as candidiasis (thrush), that do not respond to standard antifungal agents
- Recurrent or unusually severe viral infections, such as recurrent or disseminated herpes simplex or zoster infection or cytomegalovirus (CMV) retinitis
- 4 symptoms screening for TB – current cough, fever, poor weight gain and contact history of TB
- Key age-appropriate developmental milestones. Failure to attain typical milestones at the appropriate age suggests a developmental delay; such delays, particularly impairment in the development of expressive language, may indicate HIV encephalopathy. Ask also about loss of any pre-acquired milestones
- Behavioural abnormalities (in older children), such as loss of concentration and memory, may also indicate HIV encephalopathy
- Assess immunization status
- Identify concomitant use of any medication that may have drug interactions with ART

Physical examination

Look for:

- Assessment of growth as above; for children > 10 years of age, assess for onset of pubertal development
- Visible severe wasting
- Vitamin deficiencies
- Oedema in extremities
- Anaemia
- Jaundice
- Fever
- Thrush in the oral cavity and posterior pharynx (observed in approximately 30 % of HIV-infected children)
- Linear gingival erythema and median rhomboid glossitis
- Oral hairy leucoplakia (OHL) and aphthous ulcers
- Parotid enlargement
- Herpetic infection with Herpes Simplex Virus (HSV); may manifest as herpes labialis, gingivo-stomatitis, oesophagitis, or chronic erosive, vesicular, and vegetating skin lesions; the involved areas of the lips, mouth, tongue, and oesophagus are ulcerated
- HIV dermatitis: An erythematous, papular rash, observed in about 25 % of children with HIV infection

- Dermatophytosis: Manifesting as an aggressive tinea capitis, corporis, versicolor, or onychomycosis
- Digital clubbing: As a result of chronic lung disease or pulmonary hypertension
- Generalized cervical, axillary, or inguinal lymphadenopathy
- Otitis media

Perform a thorough systemic examination especially for presence of pneumonia, involvement and other evidence of associated systemic disease

Clinical Staging

Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS. These stages are defined by specific clinical conditions or symptoms.

The clinical stage is useful for baseline assessment of patients and also in the follow-up of patients in care and treatment programs. It should be used to guide decisions on when to start co-trimoxazole prophylaxis and other HIV- related interventions.

1.3 Developmental Assessment

Developmental milestones help in assessing development or maturation of the brain of an infant / child. They refer to the abilities that children are expected to possess at different ages. Delayed development or, loss of milestones after attaining them, may be the first sign of HIV infection suggesting HIV encephalopathy, if other common causes are ruled out. Early identification of developmental delay and neurologic abnormalities can facilitate intervention and suitable remedial actions. Therefore, it is crucial to assess the development in an HIV-infected infant and child.

A thorough history including the pre-natal, perinatal and post-natal factors, which can affect the development of the child, should be noted. A complete examination including physical examination, anthropometric parameters, assessment of vision and hearing and other factors that affect development should be undertaken.

Developmental assessment at each visit should include assessment of the cognitive, motor, language and social skills by asking appropriate history from the mother and by observing the child during the examination, using a developmental check-list.

Certain red flags suggest that development is seriously disordered and needs prompt referral.

Red Flags in Developmental Screening

Positive indicators (the presence of any of the following):

- Loss of previously acquired developmental skills at any age
- Parental or professional concerns about vision, fixing or following an object or a confirmed visual impairment at any age (simultaneous referral to paediatric ophthalmology)
- Hearing loss at any age (simultaneous referral for expert audiologic or ear, nose, and throat assessment)
- Persistently low muscle tone or floppiness
- No speech by 18 months, especially if the child does not try to communicate by other means such as gestures (simultaneous referral for urgent hearing test)
- Asymmetry of movements or other features suggestive of cerebral palsy, such as increased

muscle tone

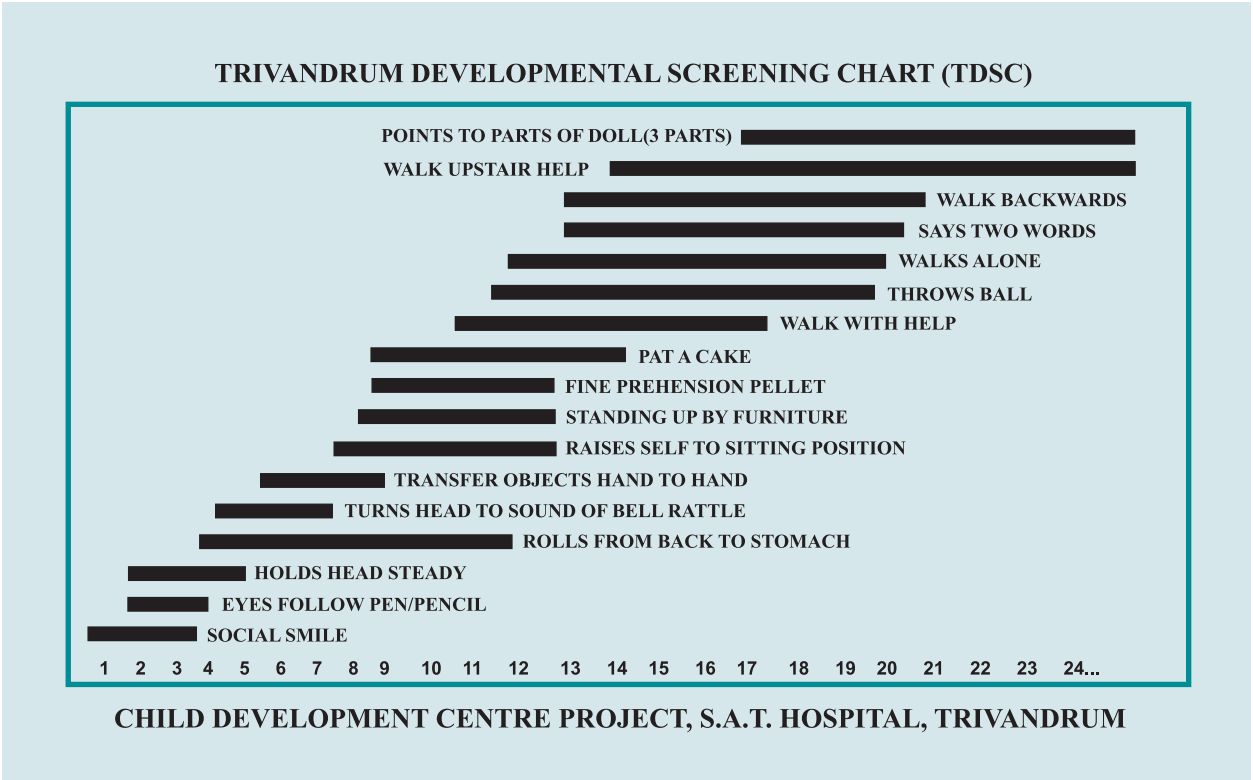
- Persistent toe walking
- Complex disabilities
- Head circumference above +3 SD or below -3 SD. Also, if the circumference has crossed 2 centiles (up or down) on the appropriate chart or is disproportionate to the parental head circumference
- An assessing clinician who is uncertain about any aspect of the assessment but thinks that development may be disordered

Negative indicators (activities that the child cannot do)

- Sit unsupported by 12 months
- Walk by 18 months (check creatine kinase urgently)
- Walk other than on tiptoes
- Run by 2.5 years
- Hold object placed in hand by 5 months (corrected for gestation)
- Reach for objects by 6 months (corrected for gestation)

Use of development screening tools helps detect developmental delay (Figure 1). Children with developmental disorders are at increased risk for behavioural problems. For example, temper tantrums or disruptive behaviour may be a manifestation of language delay.

Figure 1: Trivandrum Development Screening Chart



Adapted from Journal of Pediatric association of India.New Indian Journal of Pediatrics. Development and Validation of Trivandrum Development Screening Chart for Children aged 0-3 Years by TDSC (0-3). Chauhan VH, Vilhekar KY, Kurundwadkar M.

1.4 Laboratory Assessment

The purpose of the baseline laboratory evaluation is to (1) determine the stage of the disease, (2) rule out concomitant infections and (3) determine baseline safety parameters. The following are recommended tests for monitoring of CLHIV at ART centres (Table 1)

Table 1: Laboratory Monitoring for patients at ART centre

Baseline Investigations: Essential tests for all patients registering in HIV care at ART Centre
• Haemogram/CBC • Urine for routine and microscopic examination • Fasting blood sugar • Blood urea, Serum creatinine • Serum Bilirubin, ALT (SGPT) • VDRL • CD4 count • HBsAg and Anti- HCV IgG (if available) • X-ray Chest PA view • Pregnancy test (if required in adolescents) • rk 39 strip test to confirm or rule out leishmaniasis (especially in patients with HIV infection who live in or travel to endemic areas i.e. Bihar, Eastern Uttar Pradesh, Jharkhand and West Bengal)
Additional tests at baseline as per the physician's decision
• Symptoms and signs directed investigations for ruling out Opportunistic Infections, including M. tuberculosis by testing sputum/appropriate specimen by CBNAAT (Cartridge Based Nucleic Acid Amplification Test) and/or other required investigations • Complete LFT (Liver function test) for those being initiated on ATT and for patients with Hepatitis B or C co-infection • Lipid profile (if available) • USG whole abdomen
NON-AVAILABILITY / NON-FEASIBILITY OF ANY OF THESE TESTS SHOULD NOT DELAY THE INTIATION OF ART Note: All above investigations other than CD4 estimation shall be done from the health facility where the centre is located, with support from State Health Department.

Additional tests

Depending on clinical presentation

- Sputum / gastric aspirate / other body fluids as applicable for AFB / CBNAAT
- USG Abdomen / CT scan chest / CT scan Brain
- CSF Analysis

Tests for special situations

- For patients with Hepatitis B or C co-infection: further tests may be required to assess for chronic active hepatitis
- For patients started on PI based regimen: Baseline investigations including blood Sugar, LFT

and lipid profile to be done

Cascade screening

- Screen the family for HIV and other Opportunistic Infections

Normal CD4+ counts are higher in infants and young children than in adults due to relative lymphocytosis and decline over the first few years of life. In addition, children may develop opportunistic infections at higher CD4+ levels than adults. A value of 1500 CD4 cells/cmm in children < 1 year of age is indicative of severe CD4 depletion and is comparable to < 200 CD4 cells/cmm in adults. Classification based on age-specific CD4 levels (Table 2) is useful for describing the immunologic status of HIV-infected children.

Table 2: Immunologic categories based on age-specific CD4+ T-lymphocyte counts and percent of total lymphocytes

Immunologic Category		Age of the Infant / Child					
		12 months		1-5 years		6-12 years	
		uL	%	uL	%	uL	%
1	No evidence of suppression	>= 1500	>= 25	>= 1000	>= 25	>= 500	>= 25
2	Evidence of Moderate suppression	750- 1499	15- 24	500- 999	15- 24	200- 499	15- 24
3	Severe suppression	< 750	< 15	< 500	< 15	< 200	< 15

1.5 Psycho-social Assessment

- • Identify primary caregiver for the child and his/ her ability and willingness to adhere to follow-up and to administer medications, especially ART
- • Assess family members' understanding of HIV disease and treatment
- • Assess child's adherence to previously started medication including anti-TB treatment
- • Assess the family's financial status including its ability to pay for transportation to clinic, and to afford adequate food/nutritional supplements for the child.
- • Assess disclosure of HIV status within the family (whether the child knows his/ her status or whether anyone else knows; also whether the child knows the parent/s' HIV status).

2. Pre-ART Care

Pre-ART period is the period between a child testing positive for HIV and initiation of ART as per the national guidelines. In the current era of 'test and treat', the pre-ART period is very short, just the time taken for complete assessment, evaluation and initiation of the management of co-morbidities and stabilizing the general condition. This is also the phase when the child and caregivers are counselled regarding the need for ART, its benefits and limitations, and the need for life-long adherence.

Pre-ART care of the infected child with support to the family, as well as comprehensive care for the family unit, is important as this sets the stage for future care and response to treatment.

Components of Pre-ART Care

2.1 Prevention, recognition and management of Opportunistic Infections

It includes co-trimoxazole and Isoniazid prophylaxis, 4-symptom tuberculosis screening and initiation of anti-TB treatment two weeks ahead of ART initiation.

2.1.1 Co-trimoxazole prophylaxis for HIV Infected infants and Children

Co-trimoxazole prophylaxis is an effective and proven strategy for reducing morbidity and mortality in children with HIV infection. It not only protects the infant from Pneumocystis pneumonia, but also from malaria, diarrhoea due to isospora and cyclospora, toxoplasmosis and other bacterial diseases. All HIV-exposed infants should get co-trimoxazole prophylaxis from the age of 6 weeks. The recommended dose is 5 mg/kg/day as a single daily dose. The details of co-trimoxazole prophylaxis in children have been provided in the chapter on "Prophylaxis of opportunistic infections in children".

2.1.2 4-Symptom Screening for TB

All patients coming to the ART centres should be actively screened for opportunistic infections, particularly tuberculosis. All children living with HIV (CLHIV) should be regularly screened for four symptoms viz., current cough, fever, poor weight gain and contact history of TB, during every visit to a health facility and every contact with a health-care provider. Those who have one or more of the following symptoms should be evaluated for TB.

2.1.3 Isoniazid preventive therapy (IPT) for HIV infected children

Isoniazid Preventive Therapy is the administration of INH to individuals with latent TB infection in order to prevent progression to active TB Disease. The details of IPT for HIV infected children are provided in the section on "HIV-TB co-Infection"

2.2 Monitoring of Growth and Nutritional status and nutritional counselling

Regular measurement of weight and height is an essential activity to be undertaken for every HIV infected child. Serial assessments and plotting of weight and height on a growth chart help in early detection of growth faltering.

The weight should be recorded at every visit and height / length once in 3 months for all HIV infected children upto 5 years of age. For children beyond 5 years of age, height can be taken at 6 monthly intervals since the rate of growth is slower. Mid-upper arm circumference (MUAC) is also a good indicator of a child's general nutritional status.

Faltering in growth, especially a weight lower than that expected for the child's height often occurs even before opportunistic infections or other symptoms become overt in HIV infection. Early detection of growth faltering allows scope for timely intervention to prevent further deterioration.

2.2 Referral for Immunization and timely follow up

HIV infected children are more susceptible to infections and more likely to develop serious complications thereof. Thus, there is an increased need for vaccination against all vaccine preventable diseases endemic in the area. However, success of vaccination may be sub-optimal, depending upon the extent of immuno-deficiency at the time of immunization. In general, all inactivated vaccines can be administered safely, while live attenuated vaccines are contra-indicated in severely immuno-compromised children (CD4 < 15 %). See chapter on exposed infant care for

details of recommended immunizations for HIV exposed and infected children.

2.3 Developmental assessment at every visit and appropriate referrals

Developmental assessment using red flags or screening tools should be done at each visit for early identification of developmental delay and neurological deficit. Such children should be referred for a detailed assessment and appropriate management for better prognosis.

2.4 Counselling and timely referrals for Psychological / Social support if needed

HIV infection affects all dimensions of a person's life: physical, psychological, social and spiritual. Counselling and social support can help CLHIV and their caregiver cope more effectively with each stage of the infection and enhance the quality of life. With adequate support, they are more likely to be able to respond adequately to the stress of being infected and are less likely to develop serious mental health problems.

HIV infection can also result in stigma and fear for those living with the infection, as well as for those caring for them, and may affect the entire family. Psycho-social support can assist people in making informed decisions, coping better with the illness and dealing more effectively with discrimination. It improves the quality of their lives, and prevents further transmission of HIV infection.

For people with HIV/AIDS who must adhere to multi-drug therapy including TB treatment, long-term prophylaxis and antiretroviral therapy, on-going counselling can be critical in enhancing adherence to treatment regimens.

The physician must realize that initiating ART is never an emergency. The child and the caregiver need to be prepared for ART by giving the pre-treatment information and plan including benefits and limitations of ART, and the need for life-long adherence. This is also the time to consider disclosure of HIV status in an older child/ adolescent if not already disclosed.

A supportive and non-judgemental attitude of the health care workers during the first encounter with the newly diagnosed HIV positive patients is crucial in order to build rapport and establish partnership of care with each other. Patients are encouraged to discuss about their concerns and worries openly and frankly with the health care workers. Referrals to other professionals, including clinical psychologist or social worker may be necessary, when needs are identified in the interview.

Psychological intervention can be in the form of individual treatment and group treatment. Individual treatment involves individualized treatment plan for an issue identified by patient and the psychologist during assessment. On the other hand, group treatment delivers intervention in the form of group using a specific topic and theme. Patient support groups provide a forum to share feelings and experiences with each other, share information on treatment and resources, thereby lessening feelings of isolation and neglect.

Further details on counselling children and their caregivers are given in the section on "Issues related to paediatric counselling".

2.5 Promoting Healthy / Positive living

CLHIV and their caregivers should be counselled regarding basic healthy habits that will help them to stay healthy and avoid infections such as:

a) Eating healthy / nutritious foods

b) Washing hands well and often

c) Exercising good dental hygiene

d) Getting enough sleep

e) Doing moderate exercise

With "test & treat policy" in place, it is important to realize that the term "Pre-ART Care" still remains relevant. In fact, all the activities listed under this head would still need to be carried out, or atleast initiated, before starting ART and continued along-side ART.

16. Prophylaxis for OI in children

Treatment and prevention of opportunistic infections is an important component of comprehensive care of CLHIV. Prophylaxis given before the appearance of opportunistic infections is called as *primary prophylaxis* whereas the one given after the successful completion of treatment of opportunistic infections is called as *secondary prophylaxis*.

Co-trimoxazole Preventive Therapy (CPT) for HIV-Exposed/Infected infants and Children

Co-trimoxazole Preventive Therapy (CPT) protects the infant from Pneumocystis jiroveci pneumonia (PCP), toxoplasmosis and other bacterial diseases. It is the standard component of HIV care to reduce the morbidity and mortality of children less than five years of age. All HIV-exposed infants should receive CPT from the age of 6 weeks until HIV is reliably excluded. In all those confirmed to be HIV-infected, CPT should be continued till 5 years of age. The recommended dose is 5 mg/kg/day of Trimethoprim (TMP) of co-trimoxazole (sulfamethoxazole and Trimethoprim combination) once daily.

Children with history of severe adverse reaction (grade 4 reaction) to co-trimoxazole or other sulfa drugs as well as children with G6PD (glucose-6-phosphate dehydrogenase deficiency) should not be initiated on CPT. The alternative drug , in this case, is Dapsone 2 mg/kg once daily (not to exceed 100 mg/day) orally.

Table 1: Indications for CPT prophylaxis

Group	When to start Co-trimoxazole?	When to discontinue CPT prophylaxis?
All HIV-exposed infants/children	From 6 weeks of age (or at first encounter with health services)	HIV infection has been reliably excluded by a negative antibody test at 18 months, regardless of ARV initiation
All HIV-infected infants and children upto 5 years of age	Regardless of WHO stage or CD4 counts or CD4 %	At 5 years of age, when clinical or immunological indicators confirm restoration of the immune system for more than 6 months i.e. in a child > 5 years of age with a WHO T - stage 1 or 2 and CD4 count of > 350 cell/cmm on two occasions not less than 6 months apart
All HIV-infected children >5 years of age	WHO Stage 3 and 4 regardless of CD4 OR CD4 < 350 cells/cmm regardless of WHO staging	When clinical or immunological indicators confirm restoration of the immune system for more than 6 months i.e. in a child > 5 years of age with a WHO T- stage 1 or 2 and CD4 count of > 350 cells/cmm on two occasions not less than 6 months apart
As secondary prophylaxis	After completion of treatment for PCP	• < 5 years old: do not stop • > 5 years old: with a WHO T- stage 1 or 2 and CD4 count of >350 cells/cmm on two occasions not less than 6 months apart

Co-trimoxazole desensitization

Co-trimoxazole desensitization has been shown to be successful and safe in approximately 70 % of patients with previous mild to moderate hypersensitivity. If the patient reports a history of hypersensitivity to sulpha-containing drugs, desensitization regimen should be attempted only in a hospital setting.

Desensitization should not be attempted in individuals with a history of severe co-trimoxazole or other sulphonamide reaction. Desensitization can be attempted two weeks after a non-severe (grade 3 or less) co-trimoxazole reaction which has resulted in a temporary interruption in the use of the drug. If any reaction occurs, the desensitization regimen should be stopped. Once the patient recovers fully, dapsone at a dosage of 100 mg per day shall be tried. Some patients may be allergic to both co-trimoxazole and dapsone.

Table 2: Desensitization procedure for co-trimoxazole

Day	Step	Dosage
Day 1	80 mg SMX* + 16 mg TMP*	2 mL oral suspension
Day 2	160 mg SMX + 32 mg	4 mL oral suspension
Day 3	TMP 240 mg SMX + 48 mg	6 mL oral suspension
Day 4	TMP 320 mg SMX + 64 mg TMP	8 mL oral suspension
Day 5	400 mg SMX + 80 mg TMP	One single-strength SMX-TMP tablet
Day 6	800 mg SMZ + 160 mg TMP	Two single-strength SMX or One double-strength SMX-TMP tablet

*SMX: Sulfamethoxazole; TMP: Trimethoprim

Table 3: Dose of Co-trimoxazole for PCP Prophylaxis

Weight and Age based dosing for Co-trimoxazole (TMP/SMX) prophylaxis					
Weight (kg)	Approx. Age	Co-trimoxazole once a day			
		Syrup 5 ml (40 TMP / 200 SMX)	Child tablet (20 TMP, 100 SMX)	Single strength adult (80 TMP/400 SMX)	Double strength adult tablet (160 TMP/800 SMX)
< 5	6 weeks - 2 months	2.5 ml	1 tablets	-	-
5- 10	2- 12 months	5 ml	2 tablets	½ tablet	-
10- 15	1- 2 years	7.5 ml	3 tablets	½ tablet	-
15- 22	2- 5 years	10 ml	4 tablets	1 tablets	½ tablet
> 22	> 5 years	15 ml	-	1 ½ tablet	½ to 1 tablet depending on weight

Dosage: 5mg/kg of TMP/day orally once daily *splitting the tablets into quarters is not recommended, unless there is no syrup available.

- Patients and families should be emphasized upon the fact that Co-trimoxazole does not treat and cure HIV Infection.
- Counsel caregivers well for side-effects to CPT
- Discontinue CPT if: Stevens-Johnson syndrome, severe liver disease, severe anaemia, severe pancytopenia or completely excluded HIV Infection.

Prevention of TB in HIV infected children and adolescents

TB is the most common Opportunistic Infection in HIV infected children in India. The true burden of HIV-associated TB in children worldwide is unknown. This is due to difficulties in diagnosis and poor reporting of paediatric TB cases by national programmes. Co-infection with both organisms, the 'cursed duet', is an increasing global emergency. The vast majority of co-infected children live in resource-limited countries, with HIV prevalence rates of 10- 60 % among TB-infected children. The four main TB preventive strategies are :

- Intensified TB Case Finding (ICF) with high quality ATT (to cut TB transmission)
- Isoniazid Preventive Therapy (IPT)
- Airborne Infection Control in health-care facilities and congregate settings
- Early ART initiation among PLHIV

Isoniazid is one of the most effective bactericidal anti-TB drugs available currently. Isoniazid protects against the progression of latent TB infection to active disease (against endogenous reactivation). It also prevents TB re-infection post exposure to an open case of TB (against exogenous re-infection / super infection / nosocomial transmission)

INH prophylaxis in HIV-infected children has the potential to play a major public health role by reducing TB incidence and death. A randomized clinical trial in which 263 HIV-infected children were randomized to INH and co-trimoxazole or placebo, given daily or three times a week showed a marked reduction in TB incidence (3.8 % vs. 9.9 %) and death (8 % vs. 16 %) in the INH group.

Based on the evidence and the potential benefit of concomitant use of IPT with ART, the guidelines group strongly recommends that IPT be given regardless of the immune status (CD4) and whether or not a person is on ART. The duration of effectiveness of IPT in CLHIV in the absence of ART (not receiving concomitant ART) is limited due to ongoing progressive immunodeficiency. With the concomitant administration of both ART and IPT, there is a likelihood of restoration of tuberculosis-specific immunity by ART and the prolongation of the beneficial effect of IPT.

Concern regarding Isoniazid resistance was one of the important barriers for the implementation of this strategy. However, IPT does not promote Isoniazid resistance when used to treat latent TB infection. In latent TB, Mycobacterium tuberculosis bacilli are fewer in number, dividing slowly and therefore, the risk of selecting drug-resistant mutants is extremely low. In the study conducted by Van Halsema et al in 2010, prevalence of INH resistance amongst IPT- exposed is similar to the background population.

IPT Indications:

Children and adolescents living with HIV (more than 12 months of age) who do not report current cough, fever, poor weight gain and history of contact with a TB case are unlikely to have active TB and should be offered IPT. Additional investigations will help in ruling out active TB (X-ray chest and Tuberculin skin test), but are not mandatory. The dosage of Isoniazid for eligible children above 12 months for 6 months is given in the table x. In addition, to prevent the symptoms of peripheral neuropathy, pyridoxine (Vitamin B6) must be given for 6 months according to weight bands (25 mg daily for children weighing between 14- 25 kg and 12.5 mg for infants and children weighing between 1 and 13.9 kg) along with Isoniazid.

Contraindications

IPT is contraindicated among children and adolescents living with HIV with active Tuberculosis

disease, active Hepatitis, signs and symptoms of peripheral neuropathy, (persistent tingling, numbness and burning sensation in the limbs), poor adherence to Co-trimoxazole Preventive Therapy (CPT), poor understanding of IPT by guardian, contacts of MDR-TB and CLHIV who have completed DR-TB treatment.

Table 4: Dosage of Isoniazid in children

Weight range (kg)	Number of 100 mg tablets of INH to be administered per dose (total dose 10 mg/kg/day)	Dose (mg)
< 5	½ tablet	50
5.1– 9.9	1 tablet	100
10– 13.9	1 ½ tablet	150
14– 19.9	2 tablets	200
20– 24.9	2 ½ tablets	250
> 25	3 tablets or one adult tablet	300

Initiation and Follow up care

The counsellor will screen all the 4S negative patients and refer to the ART SMO/MO to determine their eligibility for IPT. The ART MO will initiate IPT if not contradicted. 4S screening must be done for all patients on IPT to exclude active TB during every visit. In case the patient becomes 4S positive during the IPT course, he/ she should be referred for TB diagnosis and if found positive, IPT should be stopped and appropriate ATT should be initiated. If IPT has to be used in conjunction with antiretroviral therapy, a rational approach would be to start IPT after completion of 3 months of antiretroviral therapy (delayed IPT).

IPT in special situations

1. **Patients previously treated for TB (secondary prophylaxis)**

All CLHIV who have successfully completed treatment for TB disease recently or earlier should receive INH for six months.

2. **IPT with ART**

Combined use of IPT with ART is recommended for all CLHIV regardless of the degree of immune suppression and previous treatment for TB. ART should not be delayed while starting or completing a course of IPT.

3. **IPT in children born to microbiologically confirmed TB mothers**

If a baby is born to a microbiologically confirmed TB mother, assess the newborn for active TB. Non-specific features suggestive of neonatal TB include: fever, low birth weight, hepato-splenomegaly, irritability, feeding intolerance. If the child has any of these features, investigate for active TB infection and treat accordingly. If the child has none of the above features or is negative for active TB infection, give IPT for six months.

4. **IPT and MDR-TB**

Contacts of MDR-TB and CLHIV who have completed DR-TB treatment are not eligible for IPT.

5. **Patient on IPT develops TB during IPT**

If a patient develops TB symptoms during IPT treatment, evaluate for TB and do DST. Based on the DST result, treatment will be provided. If the patient is sensitive to all the drugs then based on history of ATT and duration of IPT decide the following:

- If the patient has taken IPT for less than 1 month and has not taken ATT in the past, then provide the patient with a New case (Category I) regimen
- If the patient has taken IPT for more than 1 month OR has taken anti-TB treatment in the past, then provide the patient with Re-treatment (Category II) regimen. Whenever patients develop TB after > 1 month of IPT, category II anti-TB treatment must be provided because this duration of isoniazid usage is considered as isoniazid monotherapy in these patients.

If the patient has drug-resistant TB, refer to DR-TB Centre.

6. **Patients develop TB after IPT completion**

If the patient develops TB after IPT, IPT is not to be considered as past history of TB treatment in such cases. Treat TB episode as New or Previously treated case (based on the previous TB treatment history or Rifampicin resistance pattern) (whenever available).

Table 5: Restarting IPT after interruption

Scenario	Action
If a patient has taken **IPT for less than 1 month** in total and has discontinued it for any reason (like toxicity or loss to follow up)	Conduct adherence counselling, address reasons for discontinuation Conduct ICF and if asymptomatic, restart INH afresh Ensure they complete a 6-month course
After taking IPT for more than 1 month: If the patient has discontinued IPT for less than 3 months	Conduct adherence counselling Conduct ICF and if asymptomatic, restart INH Ensure they complete a 6-month course within a 9-month period
After taking IPT for more than 1 month: If the patient has discontinued IPT for more than 3 months, or has discontinued more than once	Do not re-initiate IPT

Preventing Vaccine-Preventable Diseases in HIV-Infected Children and Adolescents

Vaccines are extremely effective primary prevention tool. Vaccines that protect against 11 diseases are included in the national immunization schedule by Government of India, for routine use in children and adolescents in India. The **immunization protocol has been discussed in chapter on "Care of HIV exposed infants and children."**

17. Antiretroviral Therapy (ART) for Children

Paediatric formulations of Anti-Retro Viral (ARV) drugs have greatly improved the care of HIV infected children. Initiation of Antiretroviral Therapy (ART) at the earliest is crucial in reducing mortality and morbidity among infants and children. Recommendations for the care of those who are HIV infected will change over time, but the challenges in providing this care are the major hurdles in managing both acute and chronic conditions. ART is a life-long therapy and owing to its benefits, HIV-infected infants and children have been able to survive upto adolescence and adulthood today.

When to start ART for infants and children?

ART should be initiated in all children and adolescents living with HIV, regardless of the age, CD4 count and WHO clinical staging

Considerations before Initiation of ART

All people with confirmed HIV infection should be referred to the ART centre for registration in HIV care, comprehensive clinical and laboratory evaluation to assess baseline status, (ref to Chapter 15) treatment of pre-existing opportunistic infections, treatment preparedness counselling and timely ART initiation.

The following principles need to be kept in mind:

- Treatment should be started based on a parent's/guardian's informed decision and preparedness to initiate ART with an understanding of the benefits of the treatment, lifelong medication, issues related to adherence and positive prevention. Informed consent should be taken from the parent or legal guardian of children or adolescents aged less than 18 years.
- When it is decided to start ART, one should also consider the child's social environment, including identification of a clearly defined caregiver who understands the prognosis of HIV and the requirements of ART. A caregiver should be identified for each person to provide adequate support. Caregivers must be counselled and trained to support treatment adherence, follow-up visits, and shared decision-making.
- Co-trimoxazole Preventive Therapy (CPT) should be started in children as per the paediatric guidelines (Refer Chapter 16). All patients should be screened for TB, using the 4-symptom tool (current cough, fever, weight loss and history of contact with TB) and those who do not have TB should be started on Isoniazid Preventive Therapy (IPT) in addition to ART.
- **ART should not be started in the presence of an active OI.** In general, OIs should be treated or stabilized before commencing ART. Mycobacterium Avium Complex (MAC) and Progressive Multifocal Leukoencephalopathy (PML) are exceptions, in which, commencing ART may be the preferred treatment, especially when specific MAC therapy is not available. For details on starting ART in patients with HIV-TB co-infection, see the section on 'Management of HIV-TB. Some conditions, which may regress following the commencement of ART, include candidiasis and cryptosporidiosis. The following OIs and

HIV-related illnesses need treatment or stabilization before commencing ART.

Table 1: Management of Clinical Conditions

Clinical Picture	Action
Any undiagnosed active infection with fever	Diagnose and treat first; start ART when stable
TB	Treat TB first; start ART as recommended in TB section
PCP	Treat PCP first; start ART when PCP treatment is completed
Invasive fungal diseases: oesophageal candidiasis, cryptococcal meningitis, penicilliosis, histoplasmosis	Treat oesophageal candidiasis first; start ART as soon as the patient can swallow comfortably Treat cryptococcal meningitis, penicilliosis, histoplasmosis first; start ART when patient is stabilized or OI treatment is completed
Bacterial pneumonia	Treat pneumonia first; start ART when treatment is completed
Malaria	Treat malaria first; start ART when treatment is completed
Drug reaction	Do not start ART during an acute drug reaction
Acute diarrhoea which may reduce absorption of ART	Diagnosis and treat first; start ART when diarrhoea is stabilized or controlled
Non-severe anaemia (Hb < 9 g/dl)	Start ART if no other causes for anaemia are found (HIV is often the cause of anaemia); avoid AZT
Skin conditions such as PPE and seborrhoeic dermatitis, psoriasis, HIV- related exfoliative dermatitis	Start ART (ART may resolve these problems)
Suspected MAC, cryptosporidiosis and microsporidiosis	Start ART (ART may resolve these problems)
Cytomegalovirus infection	Treat CMV; Start ART after induction phase of treatment for CMV
Toxoplasmosis	Treat; start ART after 6 weeks of treatment and when the patient is stabilized
Severe acute malnutrition	ART should be started as soon as possible after stabilization of metabolic complications and sepsis (after establishment of F-100 diet; i.e. usually after seven days)

Utility of CD4 measurement in the context of "Treat All"

- Baseline CD4 is important to monitor treatment response, identify complications like IRIS, anticipate OI infections, identify the need for OI prophylaxis and offer immunization advice.
- CD4 levels in children are considerably higher than in adults; however, the CD4 levels slowly decline to match adult values by the age of 5 years. Therefore, immunologic criteria in HIV infected children upto the age of 5 years are different from those in HIV infected adults. Compared to absolute CD4 counts, the CD4 percentage in young children varies less within age groups. Therefore, in children < 5 years of age, CD4 % is considered a more reliable marker of immune-deficiency.

Baseline Clinical and Laboratory Assessment

Following confirmation of HIV infection, a baseline clinical assessment for children should be undertaken, as detailed in Chapter 15 (Assessment of Children with HIV Infection, Pre-Art Care and Follow Up).

General guidance

- Assessing the family's psychosocial readiness for ART
  - o Initiation of ART is not an emergency
  - o When deciding to start ART, one should also consider the child's social environment, including identifying a clearly-defined caregiver who understands the prognosis of HIV and the implications of ART (i.e. lifelong therapy, importance of adherence and also mode and frequency of administration, toxicities and storage of drugs)
  - o Identifying a second (back-up) informed caregiver is also advised
  - o Disclosure of HIV status to older children and their family members improves adherence and should be encouraged with support from trusted health professionals
  - o A family's access to adequate nutrition and support is equally important.

ART initiation

Confirm HIV infection serologically or virologically (< 18 months of age)

⇩

Treat and stabilize acute conditions and opportunistic infections;
Baseline CD4 count; Assessment of family and treatment preparedness

⇩

Initiate appropriate First line ART, regardless of WHO clinical staging or immune staging (CD4 count or CD4%)

Recommended first-line antiretroviral regimens for infants and children

Antiretroviral drugs are not a cure for HIV; but they reduce mortality and morbidity, and help to improve the quality of life of HIV-infected infants, children and their families. The current standard treatment for HIV infection uses three ARV medications (triple drug therapy) in order to suppress viral replication as much as possible and to arrest the progression of HIV disease. It is important to actively support adherence to first-line regimen, in order to maximize the durability and efficacy of the regimen.

Drug formulations and doses for infants and children

Important considerations for ART regimens for infants and children include: the availability of suitable paediatric drug formulations that can be taken in appropriate doses; simplicity of the dosage schedule; and the taste and palatability. All these are the potential factors for better treatment adherence in young children.

Fixed-dose combinations (FDCs) are increasingly available for younger children and are preferred

to syrups and individual multiple drugs because they promote and support treatment adherence. Adult formulations that require breaking into half, one third, etc., can result in under dosing or overdosing when given to children and this may lead to an increased risk of resistance or toxicity. In view of the availability of paediatric formulations, use of adult formulations is usually not resorted to in young children and in those with lower bodyweight.

Dosing of antiretroviral drugs in children is usually based on either body surface area, or weight, or more conveniently by weight band (as in the national programme). As these children gain weight, drug doses must be re-adjusted in order to avoid under-dosing.

Anti-Retro-Viral drugs (ARV)

Table 2: Classes of ARV Drugs

Nucleoside reverse Transcriptase inhibitors (NsRTI)	**Non-nucleoside reverse transcriptase inhibitors (NNRTI)**	**Protease inhibitors (PI)**
Zidovudine (AZT/ZDV)*	Nevirapine* (NVP)	Saquinavir (SQV)
Stavudine (d4T)	Efavirenz*(EFV)	Ritonavir (RTV)*
Lamivudine (3TC)*	Delavirdine (DLV)	Nelfinavir (NFV)
Abacavir (ABC)*	Rilpivirine (RPV)	Amprenavir (APV)
Didanosine (ddl)	Etravirine (ETV)	Indinavir (INV)
Zalcitabine (ddC)	**Integrase Inhibitors**	Lopinavir (LPV)*
Emtricitabine (FTC)	Raltegravir (RGV)*	Fosamprenavir (FPV)
Nucleotide reverse Transcriptase inhibitors (NtRTI)	Elvitegravir (EVG)	Atazanavir (ATV)*
	Dolutegravir (DTG)	Tipranavir (TPV)
Tenofovir (TDF)*		Darunavir (DRV)*
Fusion inhibitors (FI)	**CCR5 Entry Inhibitor**	
Enfuvirtide (T-20)	Maraviroc	
***Available in the national programme**		

For clinical pharmacology refer to 'ART for adult and adolescent' section

Paediatric ART regimens

The choice of drugs depends on the child's age, weight and presence or absence of anaemia (Hb: < 9 g/dl). If anaemia is present, always identify type of anaemia, by the examination of peripheral blood smear and RBC indices. In case of microcytic hypochromic anaemia which is very common in children, iron supplementation may be necessary. In children with HIV infection, Zidovudine (AZT) is the preferred NRTI for initiation at present. If a child is anaemic, then Abacavir (ABC) is to be considered as the drug of choice for initiation. For all children above 10 years and above 30 kg body weight, Tenofovir (TDF) is the preferred drug for initiation. This harmonizes with the adult ART regimen. Stavudine (d4T) is phased out from paediatric first line regimen; however, it is being used in special situations. In case of dual toxicity for both AZT & ABC, use of d4T may be considered as an alternative in children less than 10 years and less than 30 kg body weight. Lopinavir/ritonavir (LPV/r) is recommended as the preferred third drug in all children less than 3 years of age. For children older than 3 years, Efavirenz (EFV) is recommended as the preferred third drug.

First-line regimen for infants and children < 3 years of age

Table 3: First line ART regimens for infants and children aged < 3 years

Particulars	Recommended Regimen
Hb > 9 g/dl and not on concomitant Rifampicin containing ATT	Zidovudine + Lamivudine + Lopinavir/ritonavir
Hb < 9 g/dl and not on concomitant Rifampicin containing ATT	Abacavir + Lamivudine + Lopinavir/ritonavir
Hb > 9 g/dl and on concomitant Rifampicin containing ATT	Zidovudine + Lamivudine + Lopinavir/ritonavir as per weight; In addition, super boosting with Ritonavir If super boosting is not possible, use NVP as per body surface area
Hb < 9 g/dl and on concomitant Rifampicin containing ATT	Abacavir + Lamivudine + Lopinavir/ritonavir as per weight; In addition, super boosting with Ritonavir If super boosting is not possible, use NVP as per body surface area
Those with intolerance or contraindication to both Zidovudine and Abacavir	Stavudine based regimen can be used as alternative after e-approval by p-CoE / CoE / ART plus SACEP
Please note: Any regimen initiated for an infant or child must be based on the bodyweight; At every visit, check bodyweight of the infant / child before writing the prescription. Even though the drug regimen remains the same, drug dosages have to be modified according to the change in bodyweight. Please refer to annexure 02 for dosage schedule	

Rationale of using Lopinavir (LPV)- based Regimen in children aged < 3 years

There is a need for a potent first-line regimen in young children in the context of high viral load and rapid disease progression. Hence this recommendation is based on the evidence of the superiority of Lopinavir/ritonavir (LPV/r) based regimen for young children. New evidence is suggestive of the superiority of LPV/r-based regimen for children less than 3 years regardless of PMTCT exposure, given the high prevalence of NNRTI resistance. (Kuhn et al. Abstract # V-108)

A systematic review of two randomized trials shows that children younger than 36 months have a reduced risk of discontinuing treatment and virological failure or death at 24 weeks.LPV/r was demonstrated to be superior to NVP regardless of NNRTI exposure for PMTCT. LPV/r has a low failure rate and better resistance profile that protects against the selection of NRTI resistance without compromising the use of other Protease Inhibitors (PIs) in second-line regimens. (Violari et al. Glasgow 2012)

An additional advantage of considerable reduction in the incidence of malaria among children receiving LPV/r-based is offered, as recently demonstrated in a randomized trial comparing the use of LPV/r versus NVP or EFV among children in Uganda, receiving an Artemether + Lumefantrine combination for treating malaria episodes. Another reason is the desirability to have one preferred regimen for children younger than three years while providing alternative strategies that remain less costly, preserving second-line options.

Choice of a first-line regimen for children > 3 years – upto 10 years of age

Table 4: First line ART regimens for children aged 3 to 10 years

Particulars	Recommended Regimen
Hb > 9 g/dl (regardless of concomitant Rifampicin containing ATT or not)	Zidovudine + Lamivudine + Efavirenz
Hb < 9 g/dl (regardless of concomitant Rifampicin containing ATT or not)	Abacavir + Lamivudine + Efavirenz
For children with intolerance or contraindication to both Zidovudine and Abacavir	Stavudine based regimen can be used as alternative after e-approval by CoE / PCoE / ART plus SACEP
Please note: Any regimen initiated to an infant or child must be based on bodyweight; At every visit, check body weight of the infant / child before writing the prescription. Even though the drug regimen remains the same, drug dosages have to be modified according to changes in bodyweight. Please refer to annexure 02 for dosage schedule	

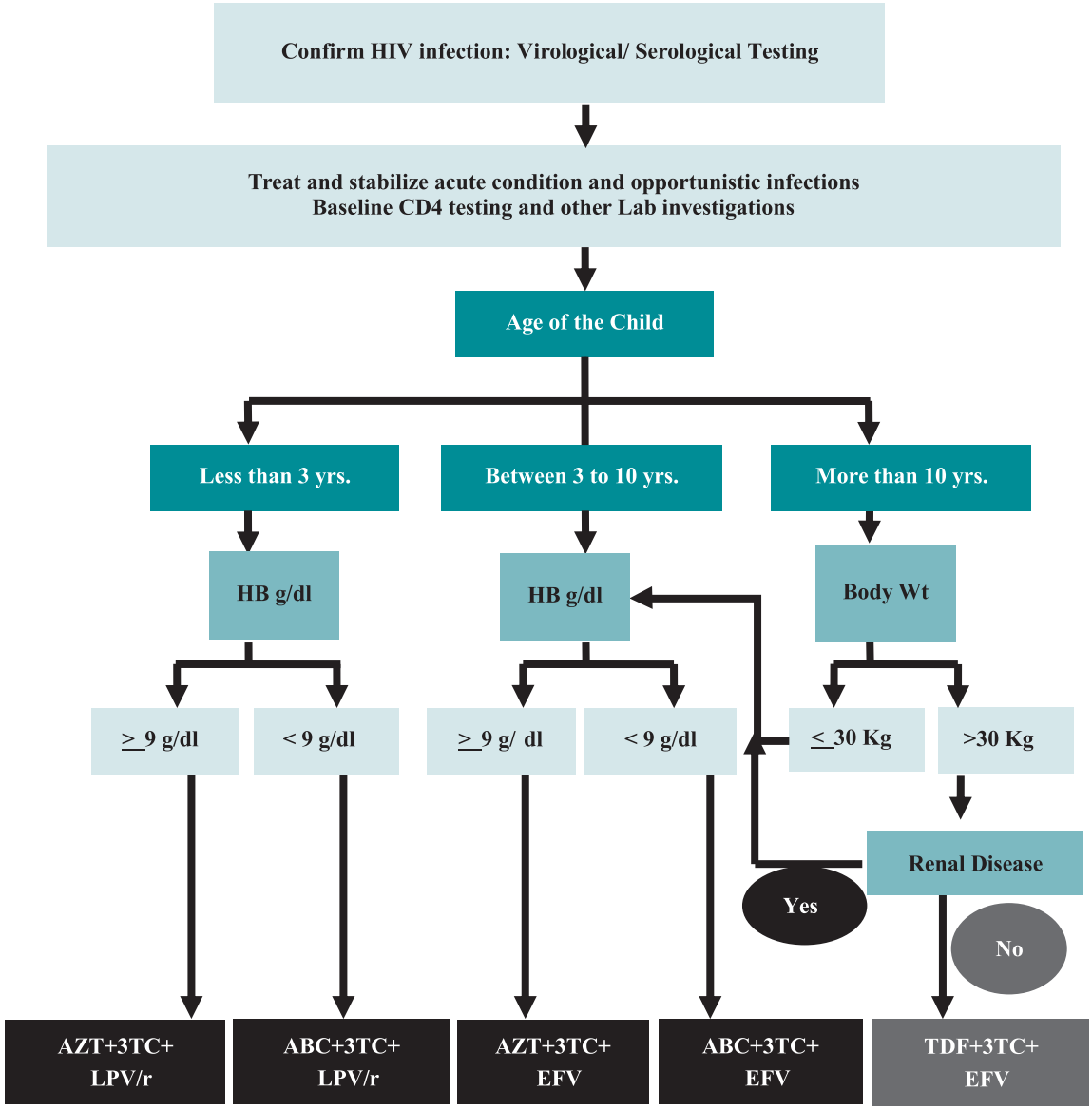
Choice of a first-line regimen for adolescent > 10 years and weighing > 30 kg

The guiding principles remain the same i.e. use fixed dose combination of three antiretroviral drugs (Tenofovir + Lamivudine + Efavirenz); use simplified, less toxic and more convenient regimen. This regimen has the advantage of harmonization of treatment of children above 10 years and > 30 kg with the treatment regimen for adults with HIV infection. It is a simple, potent and safe regimen that offers the advantage of a decentralized service delivery and monitoring. It also simplifies the supply chain and minimizes the monitoring requirements.

Table 5: First line ART regimens for adolescents (aged > 10 years)

ART Regimen	Recommended For
Tenofovir + Lamivudine + Efavirenz	First-line ART Regimen for: All new children aged above 10 years and weighing > 30 kg except those with known renal disease OR those with confirmed HIV-2 or HIV-1 & 2 infections
Zidovudine + Lamivudine + Efavirenz	1. First-line ART Regimen for: All children aged above 10 years and weighing > 30 kg with Hb > 9 g/dl with known renal disease 2. First-line ART Regimen for: All children aged above 10 years and weighing < 30 kg with Hb > 9 g/dl
Abacavir + Lamivudine + Efavirenz	1. First-line ART Regimen for: All children aged above 10 years and weighing > 30 kg with Hb < 9 g/dl with known renal disease 2. First-line ART Regimen for: All children above 10 years and weighing < 30 kg with Hb < 9 g/dl
Tenofovir + Lamivudine + Lopinavir/ritonavir	First-line ART regimen for: All children above 10 years and weighing > 30 kg with confirmed HIV-2 or HIV- 1 & 2 infections, except those with known renal disease

Fig: Choice of ART regimen in Children



ART in special situations: HIV-TB co-infection

In TB co-infected HIV children, initiation of anti-TB treatment is priority. CLHIV with all forms of TB shall be initiated after two weeks of anti TB treatment. This "two-week" guideline is to enable the patient to get adjusted to the effects and side-effects of anti-TB drugs. It also helps to reduce the antigenic load of M. tuberculosis as much as possible at the time of ART initiation so as to reduce ART related complications, including IRIS. In cases of moribund patients and in children aged > 5 years of age with CD4 less than 50 cells/cmm, ART can be initiated earlier than two weeks of ATT initiation with strict clinical monitoring which may be decided on individual basis. However, it is advisable to initiate ART in all cases at least within two months of starting anti-TB treatment.

Table 6: Management of HIV-TB co-infection in infants and children

Patients' details	Timing of ART in relation to initiation of TB treatment	ART recommendations
HIV infected Infants, children and adolescents co-infected with all forms of TB	• Start ART regardless of the CD4 count: • Start ATT first, initiate ART as soon as TB treatment is tolerated (between 2 weeks and 2 months)	Appropriate ART Regimen*
	• HIV-TB co-infected patients with CD4 count < 50 cells/cmm (in children aged > 5 years of age), need to be started on ATT first and then ART within 2 weeks with strict clinical monitoring	
*Efavirenz is the preferred drug, whenever children are being treated with Rifampicin containing drug regimen for TB co-infection *However, in children aged < 3 years and in children weighing < 10 kg, Efavirenz is not recommended; Super-boosted Lopinavir/ritonavir must be given		

All CLHIV with all forms of TB shall be initiated on Efavirenz based first-line ART, if the children are aged > 3 years and > 10 kg. In children < 3years and/or < 10 kg, receiving TB treatment, Nevirapine may not be an optimal choice because of drug interactions with Rifampicin. Similarly, Efavirenz is not recommended in children less than 3 years and less than 10 kg. Also, paediatric formulations of Rifabutin are non-available. Hence, the preferred regimen is super-boosted LPV/r based regimen in children less than 3 years and/or less than 10 kg with TB co-infection and on Rifampicin based ATT. The ART should be initiated at least after two weeks of starting anti-TB treatment.

Table 7: Management of HIV-TB co-infection in infants, children and adolescents in relation to Age groups and bodyweight

Age Group/Body weight	ART regimen
Age < 3 years AND Body weight: < 10 kg	Zidovudine + Lamivudine + Super boosted Lopinavir/ritonavir; Preferred for children with Hb > 9 g/dl
	Abacavir + Lamivudine + Super boosted Lopinavir/ritonavir; Preferred for children with Hb < 9 g/dl
Age between ≥ 3 years and < 10 years AND Body weight: between > 10 kg and < 30 kg	Zidovudine + Lamivudine + Efavirenz Preferred for children with Hb > 9 g/dl and body weight >10 kg
	Abacavir + Lamivudine + Efavirenz Preferred for children with Hb < 9 g/dl and Body weight > 10 kg
Age ≥ 10years AND Body weight: > 30 kg	Tenofovir+ Lamivudine + Efavirenz

Monitoring after initiation of ART in children

Follow-up and monitoring including clinical, adherence and laboratory, is essential in children initiated on ART. These children should be monitored at specified intervals by clinical and laboratory evaluations for clinical progress, side effects of the ARV and adherence counselling. The follow-up for children on ART is recommended as below:

Clinical monitoring

- Monthly clinical evaluation: growth, development and nutrition
- TB screening: 4 symptoms screening (4S screening)
- Treatment adherence evaluation: at every visit
- For adverse reactions of ART / OI drugs
- For drug interactions
- For IRIS (Immune Reconstitution Inflammatory Syndrome)

Immunological monitoring

- CD4 count (%) to be monitored every six months for children upto 5 years. After that follow adult guidelines

Virological monitoring

- Viral load testing at 6 months and 12 months after ART initiation and then once every year

At each monthly visit, the patient should be monitored for clinical symptoms, nutritional assessment including weight, height, head circumference (children less than 5 years) and mid upper arm circumference (in HIV infected children upto 14 years), developmental assessment, 4S screening, development of any new OI and adverse drug reactions. Adherence to ART must be assessed at each visit and adherence must be reinforced through counselling at each visit.

The laboratory monitoring of CLHIV on ART is also very important. Regular monitoring of patients' laboratory parameters is crucial to identify ARV related toxicities, inter-current illnesses and drug-drug interactions. The frequency of monitoring and the parameters to be monitored depend upon the ARV's used in the regimen, clinical symptoms and duration of ART exposure. The summary of the laboratory monitoring recommended under the programme is presented below in the tables. Additional laboratory tests outside this schedule may be performed as clinically indicated by the ART Medical Officer.

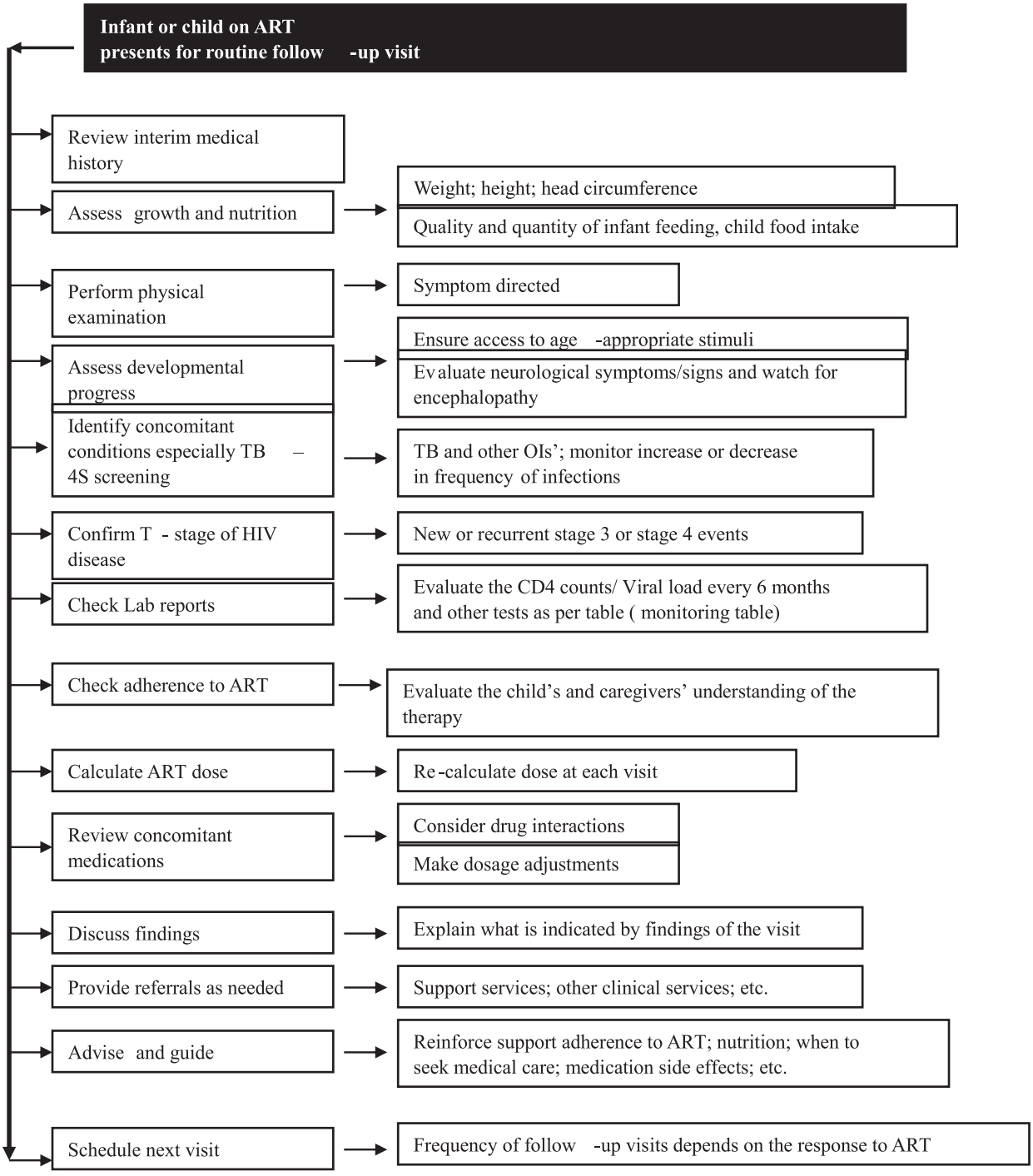
Table 8: Laboratory parameters for HIV-infected infants and children at baseline and monitoring during ART

For all patients on ART, need to do CD4, Hb, TLC, DLC, ALT (SGPT), Serum creatinine once in every six months								
Tests for monitoring patients on ART (Follow up tests) Drug specific tests frequency as below								
Monitoring ARV Drug in regimen	**Monitoring Test**	**Baseline**	**15th Day**	**First Month**	**Third Month**	**Sixth Month**	**Then every 6 months**	**At 12 months**
On Zidovudine based ART	CBC	Yes	Yes	Yes	Yes	Yes	Yes	--
On Tenofovir based ART	Serum Creatinine	Yes	--	--	--	Yes	Yes	--
Nevirapine containing ART	ALT							
(SGPT)	Yes	Yes	--	--	Yes	Yes	--	
Efavirenz containing ART	Lipid profile	Yes	--	--	--	--	--	Yes
Atazanavir containing ART	LFT							
Lipid profile	Yes	--	--	--	Yes	Yes	--	
Lopinavir containing ART	Lipid Profile & Blood sugar	Yes	--	--	--	Yes	Yes	--

More frequent visits or monitoring may be required, if the patient develops any symptoms, side effects of the ARVs or experiences difficulties in adherence to ARVs due to any reason, including clinically indicated reason as per the discretion of the Medical Officer.

Once the patient has stabilized and the CD4 starts improving, he/ she does not have any OI or adverse events, and has been adherent to ART for at least 1 year, the frequency of visit can be reduced to once in 2 months. NACO has defined stable patients as those who are on ART for at least one year, have good treatment adherence, an increasing CD4 count and are devoid of any active OI. Such patients should be encouraged to get linked out to the nearest Link ART centre (LAC) or be given 2 months of drugs, subject to the availability of sufficient stocks.

Monitoring of children on ART - Routine Follow up Visit



ARV Drugs adverse effects and its management

Adverse Events is the term used to describe side-effects due to normal dose of medications whereas toxicities are due to abnormal dose of medications. It is, however, not uncommon to use side-effects to describe both types of events. The manifestations of ARV related adverse events or toxicities overlap with many HIV associated conditions, opportunistic infections, other common childhood diseases or similar side- effects of medications that are used concomitantly. HIV associated organ dysfunction also mimics ARV adverse events or toxicities. Hence the differentiating ARV related adverse events or toxicities from these overlapping conditions pose a great challenge. There remains limited data in children when it comes to drug adverse events or toxicities; much is extrapolated

from adult studies. The majority of the common ARV related side effects is self-limiting and resolve on continued ARVs with simple supportive measures. It has been found in adults that ARV related adverse events or toxicities are the most important barriers for optimal adherence, especially in the early phase of ART initiation. Hence, a 'proactive' approach is required to limit non-adherence. A proper counselling explaining the ARV related adverse events or toxicities, which is self-limiting in nature, before initiation of ART allows the patient to self-manage towards an improved adherence to medications.

Substitutions vs. Switch

The general rule is that when one has identified an adverse event or toxicity due to a particular drug, then substitute the particular drug with another. When clinical features and/or lab evidence suggest treatment failure, then the rule is to switch the entire regimen.

Severity of adverse effect

Depending on the temporal relationship between the initiation of ART and onset of ARV related adverse events or toxicities, these can be described as follows:

- Acute, immediately after drug use
- Sub-acute, few weeks up to 6 months after drug use
- Late, prolonged drug use (> 6 months)
- The severity of these ARV related adverse events or toxicities, required for effective management can be described as follows:

Grade 1 Mild reactions: Symptoms are mild and transient, which do not require medical intervention / therapy.

Grade 2 Moderate reactions: Mild to moderate limitation of activity, some assistance needed, no or minimal medical intervention / therapy required. Some moderate reactions (e.g. lipodystrophy or peripheral neuropathy) do require substitution. For other reactions consider continuation of ART as long as feasible; if the patient does not improve on symptomatic therapy, consider single drug substitution.

Grade 3 Severe reactions: Limitation of activity, some assistance required usually, medical intervention/ therapy required with possible hospitalization. May need substitution of the offending drug without discontinuing ART.

Grade 4 Severe life-threatening reactions: Extreme limitation of activity, significant assistance required, significant medical intervention / therapy needed; hospitalization or hospice care needed. Immediate discontinuation of all ARV drugs is recommended. Manage the medical event (i.e. symptomatic and supportive therapy) and re-introduce ARVs using a modified regimen (i.e. with an ARV drug substitution for the offending drug) when the patient has stabilized.

Table 9: Adverse effects of ARVs

ARV drug	Major types of toxicity	Risk factors	Suggested management / substitution
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 allele	Substitute with AZT or TDF
AZT	Severe anaemia, neutropenia	CD4 cell count of ≤ 200 cells/ cmm	Substitute with TDF or ABC
	Lactic acidosis or severe hepatomegaly with steatosis Lipoatrophy Lipodystrophy Myopathy	BMI > 25 Prolonged exposure to NRTIs	Substitute with TDF or ABC
EFV	Persistent CNS toxicity (such as dizziness, insomnia, abnormal dreams) or mental symptoms (anxiety, depression, mental confusion)	Depression or other mental disorder (previous or at baseline)	For CNS symptoms, give dose at night-time. Consider substitute with NVP. For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (boosted PIs)
	Convulsions	History of seizure	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs	
	Severe skin and hypersensitivity reactions	Risk factor(s) unknown	
	Gynaecomastia	Risk factor(s) unknown	Substitute with NVP or another therapeutic class (boosted PIs)
	ECG abnormalities (PR and QRS interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome Hypokalaemia	Use with caution in people with pre-existing conduction disease or those on concomitant drugs that may prolong the PR or QRS intervals

LPV/r	Hepatotoxicity	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs	If LPV/r is used in first-line ART for children, substitute with NVP or Raltegravir (RAL) for children younger than 3 years and EFV for children 3 years and older. If LPV/r is used in second-line ART for children who has treatment failure with NNRTI in first-line ART, consider RAL
	Pancreatitis	Advanced HIV disease	
	Dyslipidaemia	Cardiovascular risk factors such as obesity and diabetes	Substitute with another therapeutic class (integrase inhibitors)
	Diarrhoea		Substitute with NNRTI or integrase inhibitors
NVP	Hepatotoxicity Severe skin rash and hypersensitivity reaction, including Stevens-Johnson syndrome	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs High baseline CD4 cell count (CD4 count > 250 cells/cmm in women or > 400 cells/cmm in men)	If hepatotoxicity is mild, consider substitution with EFV, for children 3 years and older. For severe hepatotoxicity and hypersensitivity, and in children under the age of 3 years, substitute with another therapeutic class (boosted PIs)
	Chronic kidney disease Acute kidney injury and Fanconi syndrome	Underlying renal disease BMI < 18.5 or low body weight (< 50 kg) Concomitant use of nephrotoxic drugs or a boosted PI	Substitute with AZT or ABC. Do not initiate TDF at eGFR < 50 ml/ min
TDF	Decreases in bone mineral density	History of rickets (in children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss Vitamin D deficiency	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity Liver disease	

ABC: Abacavir, AZT: Zidovudine, CNS: central nervous system, EFV: Efavirenz, eGFR: estimated glomerular filtration rate, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, LPV: Lopinavir, NNRTI non-nucleoside reverse-transcriptase inhibitor, NVP Nevirapine, PI protease inhibitor, r: ritonavir, RAL: Raltegravir, TDF: Tenofovir.

Monitoring ABC toxicity in adolescents and children

The use of ABC has been limited due to its toxicity profile, including an increased risk of hypersensitivity reaction (HSR) in children. Monitoring for HSR in children initiated on first-line/ second-line ART especially within the first 6 weeks of treatment is important .HSR, which is associated with the presence of the HLA-B*-5701 allele, represents a main concern in children.

However, the prevalence of the HLA-B*-5701 allele genotype in people of Asian origin was reported to be 4.0 %. In the meantime, because HSR remains rare, and HLA-B*5701 screening is not feasible under the national programme, appropriately trained clinical staff should manage patients clinically, with education provided to caregivers and older children.

Children exhibiting two or more of the following symptoms after initiation on an ABC based ART should discontinue therapy immediately and call for medical attention:

- Fever
- Skin rash
- Constitutional symptoms (malaise, fatigue, aches, arthritis, oedema)
- Respiratory symptoms (e.g., pharyngitis, dyspnoea, cough), and
- Gastro-intestinal symptoms (such as abdominal pain, diarrhoea, nausea, vomiting etc.)

Abacavir should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible and regardless of HLA-B*5701 status. Abacavir SHOULD NOT be restarted because more severe symptoms may occur within hours, including LIFE-THREATENING HYPOTENSION AND DEATH.

Monitoring TDF toxicity in adolescents and children

The systematic review indicated that TDF toxicity among children and adolescents could be similar to that seen in adults. However, data are still lacking and renal and bone toxicities in growing children and adolescents remain a concern. In the context of lack of paediatric formulations, increasing monitoring for TDF toxicity should be considered, including in adolescents.

Dual-energy X-ray absorptiometry testing is not possible in most settings, but careful growth monitoring is recommended while adolescents are receiving TDF. When serum phosphate testing is available, by extrapolation, low serum phosphate should give rise to concern about bone mineral density loss. Increasing dosing accuracy in children and adolescents is extremely important for reducing toxicity.

Principles of Management of Adverse Events

The identification of ARV related adverse events or toxicities and the determination of its severity is the important step in the management. However, distinguishing ARV related adverse events or toxicities from other HIV related conditions or adverse events due to concurrent use of other drugs pose a great challenge.

If the ARV related adverse events or toxicities is severe or life threatening, then consider stopping ART immediately. Symptomatic / supportive management should be provided. Never reintroduce the drug responsible for such a severe, life-threatening complication. If the ARV related adverse events or toxicities are severe but not life threatening, then substitute the offending drug without stopping ART. In case the ARV related adverse events or toxicities are moderate , continue ART and provide symptomatic / supportive management. If it does not resolve, substitute the drug responsible for moderate ARV related adverse events or toxicities. In mild ARV related adverse events or toxicities, continue ART and provide symptomatic / supportive management.

Table 10: Symptomatic management of adverse effects

Adverse Event	Symptomatic / supportive Measures	Specific Measures
Headache	Rest Hydration	Step 1: Non-opioid +/- adjuvants Paracetamol Step 2: Weak opioid +/- adjuvants Paracetamol + Codeine Step 3: Strong opioid +/- adjuvants Morphine
Peripheral Neuropathy	Rest Warmth	Step 1: Non-opioid +/- adjuvants Paracetamol Step 2: Weak opioid +/- adjuvants Paracetamol + Codeine Step 3: Strong opioid +/- adjuvants +/- Anticonvulsants
Nausea and Vomiting	Depends on cause Environment Smell Food Calm Small frequent feeds	Step 1: Select anti-emetics Domperidone / Metoclopramide Haloperidol Step 2: Select broad or combination anti-emetics Ondansetron Cyclizine + Haloperidol
Insomnia	Depends on cause Review day activity Environment Warm milk Restrict frightening TV programmes Story telling Parent/Guardian's presence	Sedatives Benzodiazepine Chloral hydrate

Table 11: Substituting with alternative first line ARV drugs in the event of dual toxicities

First line ARV causing the toxicity	Alternative substitute	Remarks
Intolerance to both AZT and ABC Patient exposed to both AZT and ABC with documented intolerance to both: d4T +3TC can be used		
AZT + 3TC ABC + 3TC	TDF (if age > 10 years and weight > 30kgs) d4T (if age < 10 years and weight < 30kgs; seek approval from PCOE/COE)	Continue the same NNRTI/ PI (either NVP/ EFV or LPV/r)
For intolerance to both NVP and EFV Patient should have been tried on both NVP and EFV (except if there is a history of Stevens Johnson Syndrome) and has been documented as not tolerating, before requiring substitution for the NNRTI component.		
NVP or EFV	LPV/r	Continue with the same NRTI backbone i.e. AZT/ 3TC or ABC/ 3TC if no problems
Essentially this moves the patient to the PI-based regimen. Counsel for good adherence. ART centre shall manage and provide LPV/r as substitution for intolerance to NNRTI		

18. ART Treatment Failure in Children and when to switch?

Treatment Failure refers to the loss of antiviral efficacy and triggers the SWITCH of the entire first-line regimen to the second line or beyond. It is identified by virological, immunological and/or clinical indicators.

Second-line ART is the next regimen used in sequence immediately after first-line therapy has failed. The ARV treatment failure may be due to poor adherence, inadequate drug levels, prior existing drug resistance and / or lower potency of the drugs. To identify treatment failure, certain factors like duration of ART, adherence need to be considered.

In children, the antiretroviral drug options are limited and poor adherence plays a significant role in the emergence of drug resistance and subsequent treatment failure. It is also important to note that the cost and the adverse effects of the drugs used in the subsequent regimens are high. Hence, all efforts should be made to ensure optimal adherence to the first-line ART regimens. Checking for adherence at each visit, clinical monitoring and T-staging at every visit must be ensured by the treating clinician, besides the defined laboratory parameters described earlier in the section.

Identifying the treatment failure

The virological criteria, immunological criteria and /or clinical criteria as per T-staging while on treatment should be considered for identification of treatment failure and a switch to a second-line regimen is recommended only after consulting SACEP at Paediatric Centres of Excellence (PCoE), Centres of Excellence (CoE) or ART plus centres. The following points need to be considered before failure of existing treatment regimen is concluded.

- The child should have received the regimen for at least six months
- Adherence to therapy should be assessed and should be optimal
- Any acute or opportunistic infections should be treated and resolved before interpreting CD4 counts
- Immune Reconstitution Inflammatory Syndrome (IRIS) must be excluded
- Primary malnutrition which can mimic clinical treatment failure should be ruled out
- Adverse effects of the drugs manifesting like clinical treatment failure should be ruled out

Table 1: Definitions of treatment failure in children

Failure	Definition	Comments
Virological failure	Plasma viral load above 1000 copies/ml	An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed

Immunological failure*	**Children between 12- 35months** CD % falls below 15 %. Persistent CD4 levels below 200 cells/ cmm **Children between 36- 59 months** CD % falls below 10 % Persistent CD4 levels below 200 cells/ cmm **Children aged 5 years and above** **<u>Atleast any one of the following three criteria</u>** 1. Fall of CD4 count to pre-therapy baseline 2. 50 % fall from peak "on treatment" level 3. Persistent CD4 levels below 100 cells	Concomitant or recent infection may cause a transient decline in the CD4 cell count
Clinical failure	New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment	The condition must be differentiated from IRIS. Some WHO stage 3/4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not indicate treatment failure

Virological treatment failure

Virological treatment failure, as defined by Plasma Viral Load (PVL) value of more than 1,000 copies/ml in any children on treatment for six months or more, indicates incomplete suppression of the virus. Viral rebound after being undetectable is also considered as virological failure. Low-level viral rebound, termed blips, usually indicates a statistical variation in the determination of PVL and not the need to alter therapy. The viral load remains the most sensitive indicator of ART failure. Recognizing early failure facilitates the decision to switch drugs before multiple resistance mutations develop to drugs of the first-line regimen.

Immunological treatment failure

The CD4 cell count is the strongest predictor of HIV-related complications, even after the initiation of therapy. Immunological criteria for recognizing treatment failure are most important as immunological failure almost always precedes clinical failure. In the context of any new clinical events occurring after 6 months of appropriate and regular ART, immunological criteria assist in differentiating clinical treatment failure from other overlapping conditions like IRIS, opportunistic infections and drug toxicities. The baseline pre-treatment value is informative; lower baseline CD4 counts are associated with smaller and slower improvements in the count over time. CD4 cell counts can also be used to determine when not to change therapy. One should keep in mind the phenomenon of virological- discordance as well. In children younger than 5 years, the absolute CD4 count is physiologically higher and gradually declines to adult level by 6- 8 years of age. Hence, immunological criteria of more than 50 % drop from "on-treatment" peak value or fall below pre-therapy baseline may result in an erroneous diagnosis of treatment failure especially

when ART was initiated before 5 years of age. In this scenario, the virological failure is essential for decision-making on switching over to second-line ART. Comparing the present CD4 counts with the previous CD4 values is required to recognize treatment failure. The decision to switch ART to second-line should always be based on virological criteria.

Clinical Treatment Failure:

Treatment failure should be considered if the child has been on therapy for at least 6 months. Adherence should be assessed and optimized, inter-current OIs treated and resolved, and IRIS should be excluded before diagnosing clinical treatment failure. The development of new or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with the exception of TB) after 6 months of effective treatment is considered functional evidence of the progression of HIV disease.

TB can occur at any CD4 level and does not necessarily indicate ART failure. The response to TB therapy should be used to evaluate the need to switch ARV drugs. In the case of pulmonary TB and some types of extra-pulmonary TB (e.g. simple lymph node TB), the response to TB therapy is often good and the decision to switch ARV drugs can be postponed and monitoring can be stepped up. The clinical criteria as per T- staging while on treatment should be considered for a switch to the second-line regimen only after consulting SACEP (PCoE / CoE / ART plus centre), as shown in the table below:

Table 2: Using the WHO Paediatric clinical staging events to guide decision-making (for referring patients to SACEP for the consideration of targeted viral load assessment)

New or recurrent event on ART[a,b,c]	Management options [d]
No new events or stage 1 events (T1)	Continue the same regimen Maintain regular follow-up
Stage 2 events (T2)	Treat and manage staging event Continue the same regimen Assess and offer adherence support Assess nutritional status and offer support Schedule earlier visit for clinical review and consider CD4
Stage 3 events (T3)e	Treat and manage staging event and monitor response Check if on treatment for 6 months or more Assess and offer adherence support Assess nutritional status and offer support Check CD4 Institute more frequent follow-up Refer to SACEP (PCoE / CoE / ART plus centre) for considering “targeted viral load assessment”
Stage 4 events (T4)	Treat and manage staging event Check if on treatment 6 months or more Assess and offer adherence support Assess nutritional status and offer support Check CD4 Refer to SACEP (PCoE / CoE / ART plus centre) for considering “targeted viral load assessment”

[a] A clinical event refers to a new or recurrent condition as classified in the WHO clinical staging at the time of evaluating the infant or child on ART.

[b] It needs to be ensured that the child has had at least 6 months of treatment and that adherence to therapy has been assessed and considered adequate before considering the possibility of treatment failure. All children with suspected treatment failure should be referred to SACEP (PCoE / CoE / ART plus centre) for considering "targeted viral load assessment".

[c] Differentiation of opportunistic infections from IRIS and adverse drug reaction is important.

[d] In considering the possibility of treatment failure because of growth failure, it should be ensured that the child has adequate nutrition and that any inter-current infections have been treated and resolved.

[e] Pulmonary or lymph node TB, which are clinical stage 3 conditions, may not be an indication of treatment failure, and thus may not require consideration of second-line therapy. The response to TB therapy should be used to evaluate the need for switching therapy.

SOP for Determining Failure:

Before diagnosing 'treatment failure' and switching the ART regimen, the following factors need to be considered.

Adherence: Optimal adherence to ART is the single most important factor determining the success of ART. As poor adherence is responsible for treatment failure in majority of cases, a detailed assessment of adherence should be done. The factors influencing poor adherence and barriers for optimal adherence should be explored and addressed before switching to second-line ART. Unless these factors/ barriers are addressed, a patient will also find it difficult to adhere to the second-line regimen.

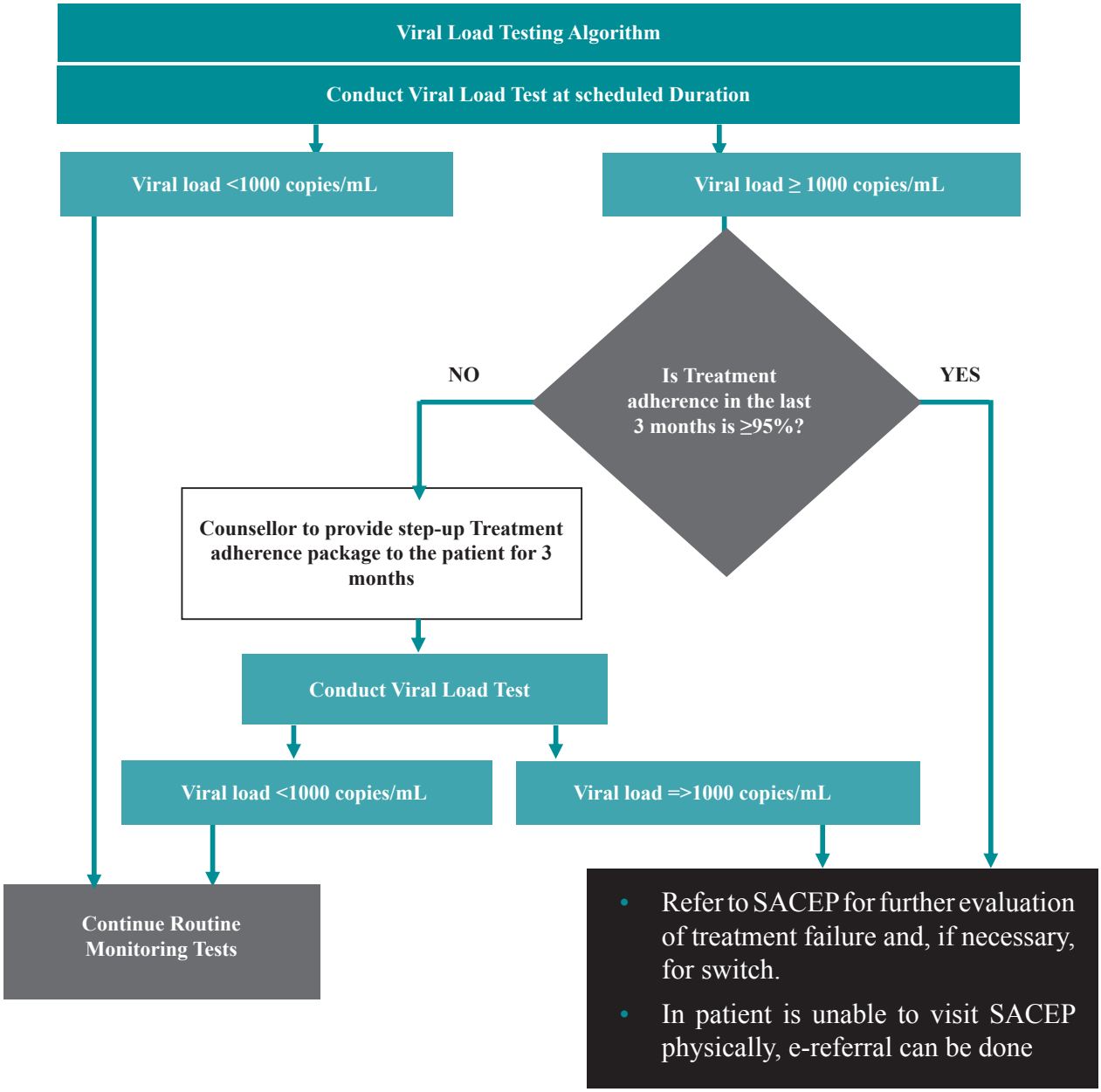
Drug-drug interactions: Assessing whether the patient is concomitantly taking medications that interfere with ARV activity is important. For example, many patients may not reveal that they take herbal treatments along with the prescribed ART regimen. These drugs not only reduce the efficacy of ART but may lead to poor adherence due to overlapping toxicities. Some of the **drug toxicities** like bone marrow suppression due to AZT may mimic treatment failure. This needs to be differentiated before switch to second-line ART.

Certain **Opportunistic infections** may lead to decline of the CD4 count, which may revert after treating those infections. **Immune Reconstitution Inflammatory Syndrome** (IRIS) needs to identified and managed appropriately before diagnosing treatment failure.

In children, **severe acute malnutrition** may sometime mimic treatment failure due to overlapping clinical features. Hence, it is advised to adequately treat nutritional deficiency and initiate nutritional rehabilitation before diagnosing treatment failure.

The sequence of treatment failure is virological failure followed by immunological and clinical failure. The time-lag between virological and immunological failure is around 6 months and few months of time-lag before clinical failure as indicated by the appearance of new or recurrent clinical event. Hence, compared to clinical or immunological monitoring, viral load provides an early and more accurate indication of treatment failure and the need to switch from first-line to second-line drugs, reducing the accumulation of drug resistance mutations and improving clinical outcomes. Measuring viral load can also help to distinguish between treatment failure and non-adherence. Studies suggest that around 70 % of patients on first-line ART who have a first high viral load will be suppressed following an adherence intervention, indicating non-adherence as the reason for the initial high viral load in the majority of cases.

Fig 1. Viral Load Testing Algorithm



* In case clinician feels discrepancy, a repeat Viral load, after three months step up adherence, may be done.

Formulating second-line regimen in children

Definitions

First-Line and Second-Line ART Regimen:

The working definition of First and Second-Line ART Regimen is as follows:

First-line ART:

First-line ART is the initial regimen prescribed for ART naïve children as soon as HIV infection is diagnosed after the stabilization of any concurrent illness, if any, and after ensuring adequate preparedness.

Second-line ART:

Second-line ART is the subsequent regimen used in sequence immediately after first-line therapy has failed.

SWITCH: Treatment Failure refers to the loss of antiviral efficacy to the current regimen. It triggers the SWITCH of the entire regimen from the first to the second-line. It is identified by clinical and/or immunological criteria and confirmed by virological criteria.

Broad Principles and Objectives

All patients initiated on the first-line ART need to be monitored carefully at every visit as per the standard protocol on clinical and laboratory monitoring indicators. As emphasized earlier, a high index of suspicion should be kept in mind whenever a patient has some symptoms or there is a declining trend in the CD4 count, even before it reaches the immunological failure criteria. Issues related to OI as well as adherence need to be addressed. It is important to follow the protocol for all patients with "Suspected Treatment Failure" and make appropriate timely referrals to SACEP for evaluation of such patients following the simplified SACEP guidelines. Once the decision has been made to start second-line ART, the decision will be communicated to the referring centre where the the ART SMO/ MO will initiate the second-line treatment as per the guidelines given by CoE/ PCoE/ ART plus centre..

The **objective of second-line ART** earlier was to prolong the survival of PLHIV rather than complete viral suppression as no further regimens were available. Now with the availability of third-line ART, the objective is **complete suppression of viral replication** just as in the first-line ART; this requires regular monitoring with viral load every 6 months.

What to Switch?

When failure has been identified, virologically, immunologically or clinically, many patients can be expected to have significant NRTI resistance at the time of switching. Thus, in the decision-making for a second-line regimen with maximal antiviral activity, one has to consider nucleoside class cross-resistance and drug interactions. Some points to note are:

- Cross resistance exists between AZT and d4T
- High level AZT/ 3TC resistance reduces susceptibility to ABC
- TDF can be compromised by multiple nucleoside analogue mutations (NAMs) but they often retain activity against the nucleoside-resistant viral strains
- TDF/ ABC may facilitate evolution of the K65R drug resistance mutation, which mediates resistance to non-AZT NRTIs
- NNRTI (such as EFV and NVP): usually there is complete cross-resistance
- NNRTI exposure (single drug) to children through infant ARV prophylaxis can result in arcHIVed NNRTI resistant mutations

Once it is decided to switch the regimen, following four steps outlined in Table 4 below need to be followed for decision making:

Table 3: Steps to be followed for review by SACEP for suspected treatment failure

STEP 1	Define treatment failure	Define treatment failure by virological testing, see if adherence to treatment is adequate, counsel and support. (SACEP will see these and take decision on providing second-line ART)
STEP 2	Decide on NRTI component of the second-line regimen	Select NRTI backbone as per the table 5 below
STEP 3	Decide on the third component of the second-line regimen	Select the third drug as per the table 5 below
STEP 4	Patient education and agreement on treatment plan including follow up and monitoring	Including counselling for adherence, linkages to specialist care, and follow-up monitoring plan

The current recommendation for second-line ART in children is based on previous exposure to ARV. A new class of ARV, unused in the first-line ART, either a Ritonavir-boosted PI (Lopinavir/ ritonavir) or NNRTI (Efavirenz), supported by at least one new and unused NRTI (Abacavir or Zidovudine or Stavudine or Tenofovir) should be used. Lamivudine administration should be continued to ensure reduced viral fitness.

For children who failed on the first-line AZT or d4T containing regimen, the recommended second-line regimen is ABC/TDF based regimen. TDF as the second-line option is recommended for children aged > 10 years with body weight > 30kg who were on AZT based first-line ART. For those on ABC/ TDF based first-line regimen, the second-line will be AZT based, but in cases, where AZT cannot be used because of anaemia, Stavudine can be used.

For children on LPV/r based regimen, NNRTI (Efavirenz) can be used as the third drug in second-line regimen. However, concerns remain about the effectiveness of this approach, given the potential for re-emergence of arcHIVed resistance as a result of NNRTI exposure during breastfeeding and post-natal prophylaxis.

Similarly, for children on EFV based first-line regimen, boosted PI can be used as the third drug in the second-line regimen. For children less than 6 years and weight less than 25 kg ritonavir boosted lopinavir should be used as the third drug in second-line ART.

There are limited options of second-line drugs for children aged 1 to 3 years receiving LPV/r based regimen with first-line treatment failure. These children should be continued with the existing regimen with careful monitoring except in the case of advanced clinical disease progression or lack of adherence specifically due to poor palatability of LPV/r. In such cases, switching to a second-line NVP-based regimen should be considered. However, concerns remain about the effectiveness of this approach, given the potential for re-emergence of arcHIVed resistance as a result of NNRTI exposure during breastfeeding and post-natal ARV prophylaxis.

Table 4: Second-line Regimens

First-line regimen	Current age	First-line regimen	Second-line regimen
LPV/r based first line regimen	Younger than 3 years	AZT +3TC +LPV/r	No change in regimen is recommended, unless in the case of advanced clinical disease progression or lack of adherence specifically due to poor palatability of LPV/r. In such case, switching to a second-line NVP-based regimen should be considered. (ABC+ 3TC + NVP)
		ABC +3TC +LPV/r	AZT+ 3TC + NVP, if Hb > 9 g/dl d4T + 3TC + NVP, if Hb < 9 g/dl
	Children aged between 3- 10 years (body weight > 10 kg)	AZT +3TC +LPV/r	ABC +3TC +EFV
		ABC +3TC +LPV/r	AZT +3TC +EFV, if Hb > 9 g/dl d4T +3TC +EFV, if Hb < 9 g/dl
	Children aged > 10 years with body weight > 30 kg	AZT +3TC +LPV/r	TDF+ 3TC +EFV
		ABC +3TC +LPV/r	AZT +3TC +EFV, if Hb > 9 g/dl d4T + 3TC +EFV if Hb < 9 g/dl
NNRTI based regimen	Children aged < 10 years and/or < 30 kg	AZT +3TC +EFV	ABC +3TC +LPV/r[a]
		ABC +3TC +EFV	AZT +3TC +LPV/ra, if Hb > 9g/dl d4T + 3TC +LPV/r, if Hb < 9 g/dl
	More than 10 years and > 30 kg	AZT +3TC +EFV	TDF +3TC +LPV/r
		ABC/ TDF +3TC +EFV	AZT +3TC +LPV/r or, if Hb > 9g/dl d4T +3TC +LPV/r or, if Hb < 9 g/dl
[a] for children with HIV-TB co-infection receiving Rifampicin based ATT, super boosted LPV/r should be used. This super-boosting should be continued until 2 weeks after stopping Rifampicin based ATT.			

ART options for Multi NRTI exposed patients

1. Patients failing on AZT based first-line, not exposed to any other NRTI will switch to TDF/ ABC + 3TC +LPV/r.
2. Patients failing on ABC/ TDF based first-line, not exposed to any other NRTI will switch to AZT+ 3TC+ LPV/r. If anaemic, or develops anaemia, they receive RAL+LPV/r or ATV/r+ ABC/TDF +3TC (if weight > 25kgs). If anaemic and weight < 25 kgs d4T+3TC+ LPV/r.
3. The patients who have failed on TDF/ABC based regimen and previously exposed to d4T/ AZT (CD4 count was not suggestive of immunological failure at the time of substitution from AZT to TDF)-The recommended II line is ZL + LPV/r. If anaemic or develops anaemia, the recommended regimen is RAL+LPV/r or ATV/r+ ABC/TDF + 3TC (if weight >25 kgs). If weight <25 kgs and anaemic or develops anaemia, d4T+ 3TC+ LPV/r.
4. All other cases of First line failure and exposure to more than 1 NRTI (AZT, TDF, d4T, ABC) – Raltegravir + LPV/r + last NRTI backbone.

Second-Line ART in HIV-TB co-infected children

In HIV-infected adults co-infected with TB, on protease-inhibitor containing ART, Rifabutin is being used as a substitution for Rifampicin, if they have to be treated with Rifampicin containing category 1 or 2 anti-TB treatment. However, there is inadequate data on the pharmacokinetics, therapeutic levels and efficacy of Rifabutin in infants and children. Furthermore, there are no Rifabutin paediatric formulations available at present. In HIV-infected children on paediatric second-line regimens, which require concurrent TB treatment, the current practice globally is *'super boosting of LPV/r'* with additional doses of Ritonavir with the target ratio of LPV/r as 1:1. This will ensure adequate protease-inhibitor levels during concurrent TB treatment with Rifampicin. However, the problems are- enhanced pill burden and the possible side-effects to Ritonavir (usually GI intolerance). These children need symptomatic relief and careful monitoring during the course of super boosting LPV/r treatment.

In the event of a child being identified with first-line ART failure presenting with tuberculosis simultaneously, appropriate anti-TB treatment should be started, as a priority according to RNTCP guidelines first and super boosted PI or EFV based second-line ART regimen should be started after 2 weeks and within 2 months of initiation of anti-TB treatment.

If the child is already on second-line ART regimen and develops TB, appropriate anti-TB treatment should be initiated immediately. If necessary, ART regimen should be modified simultaneously, as and when the child is treated with Rifampicin containing category 1 or 2 anti-TB regimen as per the following guidelines:

- If child is on boosted PI based second-line ART regimen, the PI should be super-boosted, as detailed in table 6.
- If child is on EFV based second-line ART regimen, there should be no change in the ART.

Table 5: Super boosting of Lopinavir (LPV/r +r) in HIV-TB co infection

Weight (kg)	Drug Schedule			If Super-boosting in TB-HIV (LPV/r +r) Ritonavir tab 100 mg
3 – 5.9	Morning	ABC/ 3TC (60/30) Syp LPV/r (80/20)	2 tabs 1 ml	Add Tab Ritonavir 100 mg ½ tab
	Evening	ABC/ 3TC (60/30) Syp LPV/r (80/20)	2 tabs 1 ml	Add Tab Ritonavir 100 mg ½ tab
6 – 9.9	Morning	ABC/ 3TC (60/30) Syp LPV/r (80/20)	2 tabs 1.5 ml	Add Tab Ritonavir 100 mg 1 tab
	Evening	ABC/ 3TC (60/30) Syp LPV/r (80/20)	2 tabs 1.5 ml	Add Tab Ritonavir 100 mg 1 tab
10 – 13.9	Morning	ABC/ 3TC (60/30) LPV/r (100/25)	2 tabs 2 tabs	Add ritonavir 1 tab
	Evening	ABC/ 3TC (60/30) LPV/r (100/25)	2 tabs 1 tab	Add ritonavir 1 tab
14 – 19.9	Morning	ABC/ 3TC (60/30) LPV/r (100/25)	2.5 tabs 2 tabs	Add ritonavir 2 tab
	Evening	ABC/ 3TC (60/30) LPV/r (100/25)	2.5 tabs 2 tabs	Add ritonavir 1 tab

20 – 24.9	Morning	ABC/ 3TC (60/30) LPV/r (100/25)	3 tabs 3 tabs	Add ritonavir 2 tab
	Evening	ABC/ 3TC (60/30) LPV/r (100/25)	3 tabs 2 tabs	Add ritonavir 1 tab
25 – 29.9	Morning	ABC/ 3TC (60/30) LPV/r (100/25)	4 tabs 3 tabs	Add ritonavir 2 tab
	Evening	ABC/ 3TC (60/30) LPV/r (100/25)	4 tabs 3 tabs	Add ritonavir 2 tab
30 – 34.9	Morning	ABC/ 3TC (60/30) LPV/r (200/50) adult dose	5 tabs 2 tabs	Add ritonavir 2 tab
	Evening	ABC/ 3TC (60/30) LPV/r (200/50) adult dose	4 tabs 2 tabs	Add ritonavir 2 tab

Toxicities of second line drugs

The major toxicities of the second-line drugs are depicted in Table 7 below:

Table 6: Side effects related to the NACO Second Line Regimen:

ARV	Side effect/toxicity	Management
ATV*	Apart from the PI-class specific side-effects like hyperglycaemia, fat maldistribution, hyper lipidaemia (especially with Ritonavir boosting), increased bleeding episodes in haemophiliacs etc., the unique side-effects of Atazanavir include indirect hyper bilirubinaemia (producing yellow discoloration of eyes), skin rash and nephrolithiasis (rare). Unique drug interaction involving Atazanavir: In addition to all the drug interactions involving PI class, Atazanavir has significant drug interaction with antacids, H2 Receptor antagonists and proton pump inhibitors*	The patients need to be counselled that they may appear to be jaundiced with yellow eyes but they should not be afraid as it is only a cosmetic problem (like Gilbert disease). It should not be taken as hepatotoxicity. However, LFT has to be done should someone appear to have jaundice. Also, they should be advised to consume plenty of water Antacid: Give Atazanavir at least 2 hours before or 1 hour after antacids or any buffered medications
ATV: Atazanavir; For other drugs refer to section on ART initiation in children		
CAUTION: We should be cautious in recommending the use of H2 RA & PPIs with ATV/r as most of our patients are ARV-experienced; this is a black box warning for ATV; only systemic antacids can be co-prescribed		
CAUTION: We should be cautious in recommending the use of H2 RA & PPIs with ATV/r as most of our patients are ARV-experienced; this is a black box warning for ATV; only systemic antacids can be co-prescribed		

Drug Interactions:

Avoid concurrent use of the following drugs:

Astemizole, Cisapride, Fluticasone, Indinavir, Lovastatin, Simvastatin, Midazolam, Terfenadine

Unique drug interaction involving Atazanavir:

In addition to all the drug interactions involving PI class, Atazanavir has significant drug interaction with antacids, H2 Receptor antagonists and proton pump inhibitors.

Monitoring children on second line ART

The children on second-line regimen should be monitored for clinical, immunological and virological recovery apart from the adverse effects of drugs. All these children should be clinically screened for OIs especially Tuberculosis and evaluated for nutritional recovery. Routine investigations like complete blood count, lipid profile, renal and liver function tests should be done. CD4 count should be done every 6 months to assess the immunological recovery. Viral load must be repeated every 6 months.

Table 7: Monitoring patients on second line ART

Tests	Months						
	0	1	3	6	12	18	24
Hb, CBC	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Complete LFT	Yes		Yes	Yes	Yes	Yes	Yes
Renal function test	Yes		Yes	Yes	Yes	Yes	Yes
Fasting blood sugar	Yes				Yes		Yes
Fasting lipid profile	Yes				Yes		Yes
Viral Load (VL)	Yes			Yes	Yes	Yes	Yes
CD4	Yes			Yes	Yes	Yes	Yes

Treatment failure in children is usually due to poor adherence to first-line ART. Infants and children are dependent on adult caregivers for timely and correct intake of medicines. The child must be directly observed while swallowing the medicine (sometimes they spit it out or keep in the cheek). Poor adherence can also be due to caregiver issues. Hence, the caregiver must be counselled to see if they have other problems e.g. travel, work, busy, different perceptions on ART ("don't think ART works in children"), poor memory, problem taking ART themselves, etc. Use all the adherence tools to support the child and the caregiver e.g. flip charts, colouring ART calendar, pill-box, favourite TV serials, disclosure to child as appropriate and other innovative options. The options for second-line are limited in children especially when many children are exposed to multiple NNRTI. Hence it is important to ensure optimal adherence in children for the success of first-line ART regimen for a longer duration. When substitution is considered in the event of an adverse effect of the drugs used in first-line ART, it is important to assess the child for treatment failure. If there is evidence of treatment failure, then the ART regimen must be switched rather than substitute a single drug.

19. Issues Related to Paediatric Counselling

Care and support of children living with HIV (CLHIV) pose very different challenges compared with those in adults. Both the child client and his/ her caregivers must be supported through sensitive counselling. While any Person Living with HIV (PLHIV) needs psycho-social support to live with the illness and manage treatment, chronic illness in children presents special challenges. These challenges include the children's abilities to understand the HIV disease and treatment, the challenges of counselling support to cope with side-effects and lifelong treatment and the issues of confidentiality and stigma and discrimination in their immediate environment. Counselling needs are also likely to change as the child grows older, progresses through various stages of child development and demands adaption to these changing needs during counselling. Further, the counsellor and the other members of the clinical team must judiciously decide whether a particular counselling message is better addressed to the primary client (that is the child) and/or to the caregivers.

While the counsellor will carry the major responsibility for counselling both sides, it is also important for other members of the clinical team to develop a child-sensitive attitude and create an atmosphere where children will feel comfortable. The ART team must make efforts to procure the special tools prepared by NACO, such as the ART Adherence Colouring Books (called My ART Calendar), the NACO Snakes and Ladders Health Education games and the Visual Analogue Scale. They must educate themselves in the use of these aids. Further, efforts should be made to create a child-friendly corner using some portion of the contingency funds. Simple and cost-effective items that are also durable could be purchased such as wall cut-outs of Disney characters or a plastic play house. A simple blackboard with a chalk may be placed at the child's eye level in a corner of the waiting area so that he/ she may express his/ her creativity. Simple and cheap chalks or crayons may be purchased for the purpose of counselling and may be placed with the counsellor. A display board may be set up to display drawings and craft work made by the children.

Who Needs Counselling?

The ART counsellor will focus on two types of counselling: counselling the child client himself/ herself and counselling about the child's issues. The latter is directed towards the caregivers.

Child centred counselling

Communication with children is the use of age-appropriate language to facilitate both the passage of information to the child and the expression of their feelings. The basic skills for counselling children and adults are the same. Child-centred counselling includes:

- Development of rapport between the child, caregiver and counsellor
- Focusing on the child's needs and is tailored to the child's physical and psychological development
- Striving to promote the child's potential and abilities
- Building self-esteem and respects the child's identity and emotions

During counselling always respect the child's identity and emotions and protect the "best interest" of the child, including the right to participate in decisions that affect them, non-discrimination and confidentiality of information. Counselling always involves the child and the child's caregiver.

Children are unique and not just tiny adults. Their physical, psycho-social and spiritual needs are different which need different responses than that given to the adults. For the effective and comprehensive care of these children, it requires us to understand these differences. However, basic counselling skills are the same as those used for communicating with the adults.

Communication with children depends on the developmental level and ability to express their feelings and issues themselves. Very young children have difficulty in expressing themselves verbally as they cannot use words to describe their emotions or thoughts. Hence, practical ways must be found to communicate with children and help them express their feelings.

Interactive tools such as drawing, story-telling, plays, drama are media through which a child can be helped to express themselves. These methods also create a non-threatening atmosphere for the child. It is difficult to sustain a young child's attention. Using different methods helps to sustain the child's attention. These methods help to explore sensitive issues and identify solutions.

Barriers for the communication with the children

Communication barriers refer to anything that negatively affects effective communication between two or more people. The consequences arising due to these barriers include miscommunication, misinformation, mistrust, anger and frustration, isolation, blame and denial. These barriers can be classified into

- Language – language barrier is when there is no common language (e.g. when an adult uses non-age appropriate language with the child)
- Cultural barriers
- Due to poor skills – lack of active listening, recipient problem
- Knowledge – wrong message or wrong information
- Age – adult's failure to come to the child's level
    - ➤ The assumption that parents/ guardian will handle communication with the child and therefore there is no need to communicate with the child
    - ➤ The assumption that the child is too young to understand
    - ➤ The assumption that certain medical information might harm the child or that the child is too weak to receive the information

Key Counselling Issues for Child Clients:

Adherence - taking medicine regularly

The key challenge for child clients is to help them develop good habits towards taking medicine on a daily basis. Though the parent or caregiver is primarily responsible for ensuring that children take treatment, it is necessary to make the child client a willing partner in managing his/ her own health through regularly taking treatment. Even the most tractable or obedient child will have days of poor compliance to medicine.

With very small children, it is important to emphasize that taking medicine on time will keep them safe from falling ill (or in case they are ill, to improve quickly) so that they can be free to play.

Freedom to play is not only the right of the child but also the most potent incentive you can offer to a very young client. For slightly older children, the message may be altered to include emphasis on being responsible towards their health and being fit to attend school like other children of their age. As they become cognitively capable of understanding medical facts, they can be introduced to concepts related to viral infection in general initially, and to more specific information on HIV later. It is important to link the medicine to keeping the viral infection in check.

The clinical team can ensure adherence through the use of the ART Adherence Colouring Books such as 'My ART Calendar' published by NACO.

Disclosure - Learning about being infected

Helping a child to understand the nature of his/ her infection is an important issue that affects his/ her willingness to take medicines. A large research literature on disclosure of HIV status to children exists. It is highly recommended that children should be informed about the nature of their illness because knowing one's HIV status is likely to encourage compliance to treatment – even in children. However, the second part of the recommendation is that the timing of disclosure to the child cannot be a universal date or age.

Disclosure counselling in children is not an all-or-none phenomenon. Children should be prepared gradually to accept the full and complete knowledge of having HIV infection. A parallel example in the physical world is how we introduce children to solid foods from an initial, exclusive diet of milk. Initially, soft easily digestible foods are introduced such as small pieces of banana. Later, we graduate to foods that require more effort for chewing and digestion – especially as the number of teeth increase. In a similar manner, disclosing to a child his/ her HIV status should be done against the context of his/ her ability to understand and cope with the news of his/ her HIV status. For young children, it is sufficient to say that there are germs in the body that can make them very sick. Older children will not be satisfied with such a simplistic answer and may demand more details. Counsellors and caregivers should be prepared for such questions. Interactive communication tools like storytelling (Bam-Bam Virus) can be used to communicate with these children.

The understanding and acceptance of a child may wax and wane in response to the individual's stage of development and also in response to changes in his/ her life. For instance, a child of 12 who displays acceptance about his/ her HIV status could display resentment when he/ she reaches the age of 17 if he/ she recognizes the potential of HIV to limit his/ her life choices such as finding a life partner or enjoying sex, free from worry of infecting the sexual partner. Similarly, a child who physically moves from school to college may face challenges in maintaining the monthly visit to the ART centre, or may find it awkward to take medicines in the presence of new friends. Counsellors should be alert to these changes and should support the client when needed.

Coping - Learning to live with a chronic illness

With advances in HIV medicine, this infection has become a chronic manageable illness. For the individual, it introduces the challenge of living with the illness on a daily basis and factoring it into all life decisions. The monthly visit to the ART centre offers the counsellors an opportunity to explore these challenges with the children.

Specific Issues of Adolescents

In addition to all the issues mentioned above, adolescents face the following challenges:

- Developmental delays – that is delayed growth and development, often resulting in late

puberty and in girls, delayed or irregular menstrual cycles. These may be further worsened by progressing HIV illness and malnutrition.

- Transition from paediatric to adult care, including the choice of appropriate ARV regimens; and adherence

Counsellors should prepare their clients for these transitions using appropriate anticipatory guidance. They should also be ready when clients raise these issues, or when they appear to be facing these challenges.

Key Counselling Issues for Parents / Caregivers:

Acceptance of Infection in Child

This is a very emotive topic for family members. In most instances, the transmission has occurred from the parent to the child. So, acceptance of HIV infection in the child is complicated by guilt on the part of the parent and worry about being blamed by the child. Counselling for the parents must help them deal with personal guilt and worry as well as acknowledge that the emotional needs of the parent cannot be a reason to ignore or subsume the needs and rights of the child.

A particularly difficult situation to navigate is that of a child who is going through the recommended tests that are part of the Early Infant Diagnosis programme. The emotions of the caregiver may see-saw between hope and dejection as the test dates approach and recede.

Disclosure Issues

Parents and caregivers must be supported through the process of disclosure of the HIV status to the child client. Counselling is required to enable them to break the news gently to the child. Some caregivers may request counsellor support in terms of having the latter break the news. In such cases, it is strongly recommended to include caregivers in the counselling sessions along with the child. Caregivers' feedback on the preparedness of the child to receive such disclosure counselling should be considered. However, the counsellor should also gently offer his/ her own assessment of the readiness of the child to hear this message.

One common fear of caregivers (and also of counsellors) is that children who learn their status may inadvertently blurt out this fact to other people, and thus increase the chances of being stigmatized. The counsellor and other team members should address this issue by suggesting disclosure in stages based on the capacity of the child to understand the impact of the diagnosis. Further, the team can normalize the situation by comparing HIV to a chronic illness like diabetes that also requires constant personal health promoting behaviours from clients.

Parents may also fear that the child may feel depressed and suicidal. Suicidal thoughts can be minimized through carefully staggering the explanation of the diagnosis – namely partial disclosure first and then full disclosure.

Caregivers and parents may be unwilling to share the child's HIV status with other people. This concern and worry could cause interruptions in treatment because of unwillingness to fill prescriptions locally, hiding or relabelling medicine bottles to maintain secrecy within the family, and missing doses when the parent is unavailable. These issues should also be discussed during counselling. Counsellors can gain a complete picture of the child's adherence and the caregiver's administration of the medicine by asking both the child and the caregiver about the process of taking medicine. Discrepancies in the reports from both sides should be discussed in counselling.

Preparing for Treatment

Before starting ART, it is essential to assess if the client is ready to begin treatment. This includes his/ her ability and commitment to take medicines correctly and consistently for the rest of his/ her life. For infants and young children, the treatment provider should assess the family's / caregiver's' readiness and commitment. For instance, can the family ensure that they will return for regular, reliable follow up visits? Some families may designate an older sibling as the person who ensures that the infected children take medicine. It is critical in such cases to ensure the sibling is capable and willing to handle such a responsibility. If required, the team may recommend an alternative caregiver.

Adolescents should be involved in their own treatment and care. While initiating ART in adolescents, the following issues must be reviewed:

- Simplifying the treatment regimen (to ensure maximum adherence)
- Maturity of the client
- Long term adherence and full psycho-social support

Clients, at ART centre, have a long-term engagement with the centre. While waiting in the waiting area for services, it is common for them to compare notes with fellow patients. The treatment team should start asking potential questions about why one drug is selected over another (e.g., use of LPV/r in a child initiated on ART at <3 years age vs. Efavirenz based regime in an older child). Also, it is important to give advance warning to clients about the minor side-effects of ARV drugs such as nausea, headache, and abdominal discomfort. Explain how long a client may expect these symptoms to persist, whether they will lessen over time, how to manage them, etc.

Supporting treatment

Counselling should enable the caregivers to support treatment of the child. Common complaints are how to help children to take the same medicine day after day, difficulty in consuming adult-size pills, queries from children about why they should take treatment unlike their peers and handling situations like telling other family members. Anticipatory guidance is a counselling technique that prepares clients in advance for common difficulties. Apart from this, counsellors can support parents through organizing parental support groups and offering group counselling. By harmonizing clinic services to ensure that most paediatric patients are seen on a day, which is likely to be the most common school holiday in the region, centres can ensure that child clients are seen mostly on one day of the week. This will provide opportunities for group education sessions during morning OPD hours and smaller group sessions in the quieter hours of the afternoon.

Immunization Advisory

As the GOI is now immunizing children in campaign mode (MR Vaccine) to eliminate various childhood illnesses, newer challenges have emerged among children with HIV infection. The use of live vaccine in these CLHIVs should be carefully monitored. As these vaccines are given in a campaign mode, the reason for refusal of vaccine especially in a symptomatic CLHIV might lead to inadvertent disclosure or stigma and discrimination. Hence the parents of such children should be counselled about this and prepared to refuse vaccination without disclosing HIV status of the child. For example, these parents may refuse vaccination saying that the child is allergic to egg protein etc. Asymptomatic CLHIV with CD4 % above 15 % can be safely immunized even with live vaccines. The SMO/ MO should assess the child for the safety of immunization with live vaccines.

Planning for the future

When caregivers are parents who are on ART themselves, it is important to alert them about the need to plan for the future of the child in case of their own untimely death. This includes financial and legal planning. It is also important to enable the parent to identify who will be the legal guardian and caregiver in such an eventuality.

How to structure counselling:

It is important for the counsellor to see the child from time to time in order to build a rapport with him/ her. This rapport is the basis on which successful disclosure and medication-related counselling can be positioned. In some ART centres, it is observed that the child's caregiver may come to pick up the medicine refill citing that the child is in school and is not facing any health problems. In such circumstances, it is important to schedule follow-up visits for the school weekly holiday for at least some months, or to schedule a clinic visit on non-school hours.

Regular monthly visits are opportunities to take up individual issues for counselling. The counsellor must prioritize what issue he/ she would like to discuss during a particular visit. Introduce the topic by simply saying, "Have you given any thought to the following?" After the topic is initially introduced, the counsellor has the option to explore this further during subsequent visits. Medical decisions (such as following the next EID test) should generally be prioritized over non-medical decisions. Each medical decision should always be explored so that the caregiver understands its rationale. While counselling caregivers about their personal issues, it is appropriate to keep the children occupied so that caregivers have privacy and space to share their concerns.

Building rapport and trust with a child is an endeavour that takes time. Counsellors who are accustomed to working with adults have to unlearn many behaviours and expectations about clients. Counselling children is more effective when interactive methodologies such as drawing, story-telling and puppetry are used. ART counsellors who opt out of using such techniques with children cannot claim to be good counsellors; lack of time is no excuse for non- usage of these techniques.

When following-up children over a period of time, counsellors should also ensure that they raise issues related to the change in developmental status – for instance, child moving from crawling to walking, to puberty.

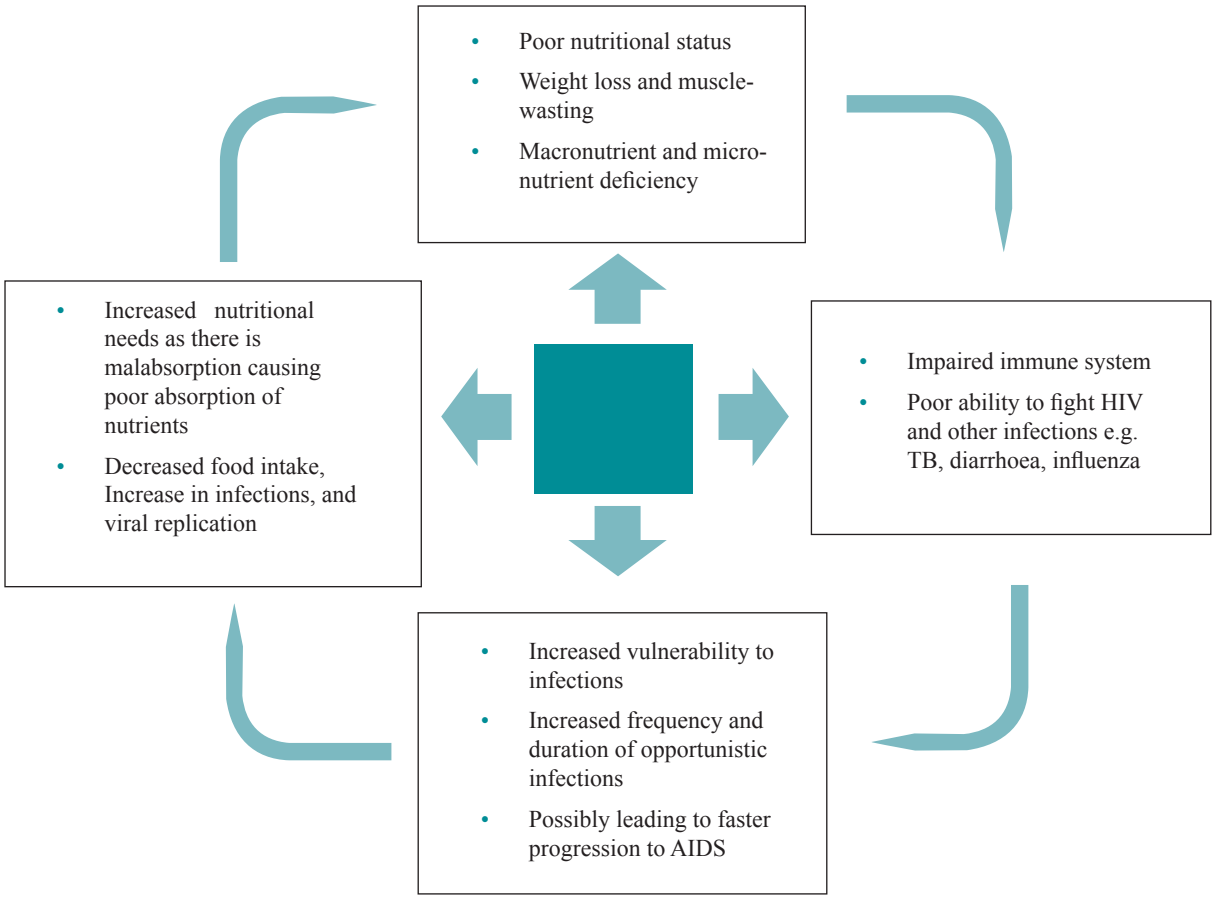
To conclude, every counsellor must have some basic qualities and skills to practice "counselling in children". Counselling skills must be used to help care-givers take decisions regarding testing, nutrition including infant feeding options, ART initiation, treatment adherence, disclosure and adolescent issues. A CLHIV require ongoing psycho-social support, regardless of when one learns his or her HIV status.

20. Nutrition in HIV Infected Infants and Children

1. Introduction

Nutritional care is a crucial part of the continuum of care for HIV infected children. HIV and associated infections increase the need for energy, proteins and micronutrients like iron, zinc, vitamin C. Failure to meet these increased needs may lead to malnutrition and further weakening of the immune system. This makes the child more vulnerable to opportunistic infections like TB, pneumonia, diarrhoea that further increase the nutritional demands of the body, accelerating the decline in nutritional status. Thus, a vicious cycle exists between HIV infection and malnutrition (figure 1).

Figure 1. Malnutrition and HIV: A vicious cycle



Source: Adapted from RCQHC and FANTA 2003a.

Appropriate nutritional support from the early stages of HIV infection can prevent onset of malnutrition and other nutritional deficiencies. It will also help maintain the performance of the immune system. The nutritional care of HIV exposed infants has already been covered in the section on 'Care of HIV exposed infants". The present guidelines are based upon the WHO document

"Guidelines for an integrated approach to the nutritional care of HIV infected children (6 months-14 years), 2009", and the current national recommendations for nutrition of HIV infected children dealt with in detail in the document "Nutrition guidelines for HIV exposed and infected children 0-14 years of age" by NACO and WHO, India.

2. Assessment of nutritional status

Assessing a child's growth provides valuable information about the adequacy of his nutritional status and health. Growth is assessed by measuring weight and height of children (length for children less than 2 years of age) and interpreting these parameters in relation to age, sex of the established reference standards. It is recommended that WHO growth reference standards are used for assessing growth parameters of children upto 5 years of age. These are available as growth charts as well as reference tables for boys and girls separately (Refer to annexures 14, 15 & 18). For children aged beyond 5 years of age, Indian Academy of Paediatrics (IAP) growth charts based on growth reference data from Indian children are recommended (Ref to annexures 16 & 17, Source: http://iapindia.org/Revised-IAP-Growth-Charts-2015.php).

The parameter "weight for age" reflects body weight in relation to the age. While a single reading gives limited information, serial recording of weight plotted on a 'weight for age' chart gives a good idea about the child's growth over a period of time. 'Weight for age' chart is the most commonly used growth chart. 'Height for age' is a measure of linear growth. Plotting length/ height on the "length/ height for age" chart helps in detecting "stunting", a common finding in HIV infected children. The parameter 'weight for length' reflects body weight in relation to linear growth. Evaluating 'weight for length' for children upto 5 years of age helps in early detection of weight faltering. For a child beyond 5 years, BMI [weight (kg)/ height (m)2] is a better indicator than 'weight for length'. Weight for length / BMI is also used as a parameter to identify severe acute malnutrition (SAM) as described later. The reader may refer to WHO charts for weight for length for children upto 5 years of age (Refer to annexures 18, Source: http://www.who.int/childgrowth/standards/en/) and IAP Body Mass Index (BMI) charts for children aged 5- 18 years (Refer to annexures 19 & 20, Source: http://iapindia.org/Revised-IAP-Growth-Charts-2015.php).

A child who is well will have his nutritional parameters (weight for age, length for age, weight for length / BMI) within ± 2 Z scores of the median expected for the age and sex. If the child's weight, length or weight for length / BMI is less than -2 Z score, it indicates the presence of underweight, stunting or wasting respectively. A serial recording of these parameters over time should yield a curve parallel to one of the standard growth curves on the growth chart. When the child's growth parameters falter, serial recordings on a growth chart will no longer be parallel to the standard growth curves. Regular measurement of the weight and height is an essential activity to be undertaken for every HIV infected child. Serial assessment and plotting of weight and height on a growth chart help in early detection of growth faltering. Faltering in growth, especially a weight lower than that expected for child's height often occurs even before opportunistic infections or other symptoms become overt in HIV infection. Early detection of growth faltering allows scope for timely intervention to prevent further deterioration. The weight should be recorded at every visit and height (length for children upto 2 years of age) once in 3 months for all HIV infected children upto 5 years of age. For children beyond 5 years of age, height can be taken at 6 monthly intervals since the rate of growth is slower. Mid-upper arm circumference (MUAC) is also a good indicator of a child's general nutritional status. At places where it may not be feasible to measure the length or height, MUAC is a useful tool for screening of malnutrition and identifying children at high risk of mortality.

Some children are at a very high risk of malnutrition. These high-risk situations include:

- The child's growth curve shows flattening (no weight gain)
- The child's growth curve is dropping downwards (weight loss)
- Change in care-giver or home circumstances
- Caretaker's report of poor appetite or not gaining weight in the child

The growth of these children should be monitored carefully and remedial measures instituted before they become severely malnourished. They should be examined for visible signs of malnutrition like loss of subcutaneous fat and muscles and bipedal oedema. Children without visible signs of malnutrition should be given nutritional support at home, with early follow-up (5- 7 days). They should also be assessed for other medical problems.

Based upon the anthropometric measures and presence of visible signs of malnutrition, the nutritional status of HIV infected children can be classified as given in table 1. Determination of the nutritional status will guide the dietary requirements and further management of these children as described later.

Table 1: Classification of nutritional status of HIV infected children (0-1 4 years):

SIGNS	CLASSIFY AS
Signs of severe visible wasting, or Oedema present in both feet, or Weight-for-height (BMI for children > 5years) less than -3 z-score or MUAC less than: 115 mm in children 6- 60 months 129 mm in children 5- 9 years 160 mm in children 10- 14 years	Severe malnutrition
Reported weight loss, or Very low weight (weight for age less than -3 z-score), or Underweight (weight for age less than -2 z-score) , or Confirmed weight loss (> 5 %) since the last visit, or Growth curve flattening	Poor weight gain
Child is gaining weight (weight for age more than -2SD and gaining weight appropriately)	Growing appropriately
Chronic lung disease or TB or persistent diarrhoea or other chronic OI or malignancy	Conditions with increased nutritional needs
[6]Nurses, counsellors & other paramedical workers may classify a child as "severe malnutrition" based upon presence of visible severe wasting, oedema on both feet or MUAC criteria. However medical officers should also use the additional criterion based on weight for height/ BMI [7] Use BMI for age for children > 10 years	

3. Nutritional needs of HIV infected children 6 months to 14 years of age

Energy and protein needs of HIV infected children depend upon their age, growth pattern and presence of associated complications. These children have higher energy needs as compared to healthy children due to increased metabolic demands placed by HIV infection. Presence of associated

6 Nurses, counsellors & other paramedical workers may classify a child as "severe malnutrition" based upon presence of visible severe wasting, oedema of both feet or MUAC criteria. However medical officers should also use the additional criterion based on weight for height/BMI

7 Use BMI for age for children>10 years

opportunistic infections and other chronic conditions like chronic lung disease, persistent diarrhoea etc. further increases the metabolic demand. Table 2 gives the total energy needs of HIV infected children depending upon their nutritional status. HIV infected children with chronic lung disease, tuberculosis, persistent diarrhoea or other chronic opportunistic infections or malignancy have increased nutritional needs in spite of a good nutritional status. The additional energy requirements for these children are similar to children with poor weight gain (Table 3). Children who are not growing well may require additional medical interventions such as treatment for opportunistic infections or ART. Unless associated complications are appropriately managed, improvement in diet alone may not result in normal growth, weight recovery or improvement in clinical status.

Table 2: Total energy needs of HIV-infected children (kcal/day)

Age of Infant/ child	Daily energy needs of HIV uninfected children*	HIV infected and asymptomatic 10 % additional Energy	HIV infected and poor weight gain or other symptoms 20 % additional energy	Severely malnourished and HIV infected (post-stabilisation) 50-100 % additional energy**
6- 11 mon.	690	760	830	150- 220 kcal/kg/day
12- 23 mon.	900	990	1080	150- 220 kcal/kg/day
2- 5 years	1260	1390	1510	150- 220 kcal/kg/day
6- 9 years	1650	1815	1980	75- 100 kcal/kg/day
10- 14 years	2020	2220	2420	60- 90 kcal/kg/day

**Based on the average of total energy requirements for light and moderate habitual physical activity levels for girls and boys by age group. Joint FAO/WHO/UNU Expert Consultation, October 2001. ftp://ftp.fao.org/docrep/fao/007/y5686e/y5686e00.df*

***Management of Severe Malnutrition: a manual for physicians and other senior health workers. WHO,1999.*

4. Nutritional management of HIV infected children: practical guidelines

In general, feeding guidelines for HIV infected infants and children are same as those for healthy children apart from the need for meeting increased energy needs. If an infant is confirmed to be HIV infected, the mother is strongly encouraged to breast feed exclusively for 6 months and continue breast-feeding upto 2 years or beyond as per the norm for general population. This will ensure optimum growth of the infant and provide protection from infections. All infants diagnosed as HIV infected are started on ART as per the national recommendations. Complementary foods are introduced at 6 months of age as recommended for all infants. The quantity and frequency of food are increased, as the child grows older. The food consistency is also gradually made thicker and variety is introduced adapting to the child's requirement and abilities. The IMNCI guidelines for feeding healthy children of different age groups are given in annexure 22 and the age-related food intake standards for children in annexure 23.

4.1 Nutritional management of a HIV infected child growing well

HIV infected children who are growing well and are asymptomatic need about 10 percent extra energy to maintain normal growth, development and activities as compared to uninfected children of their age. The additional energy is best given as additional household foods as part of a balanced diet.

4.2 Nutritional management of a HIV infected child growing poorly or having conditions with Increased nutritional needs

Children with poor weight gain should have a complete assessment including a detailed dietary history and evaluation for co-morbidities like opportunistic infections that may have an impact upon the nutritional status. These children, along with those with increased energy needs like chronic lung disease, TB, persistent diarrhoea, require extra 20- 30 percent energy each day. These are also best given through additional household foods. If this is not possible, specific nutritional supplements may be given till the underlying condition is effectively managed. The mother or the caretaker should be given dietary counselling about meeting these increased nutritional needs at home.

Table 3 shows the additional energy requirements for children with different nutritional status and examples of dietary modification that would meet these increased needs.

Table 3: Additional energy requirements of HIV infected children and means of providing them

Additional Energy Requirement in HIV Infected Children			
	Asymptomatic with adequate growth (10 % additional energy)	Poor weight gain or increased nutritional needs (20- 30 % additional energy)	Severely malnourished (50- 100 % additional energy)
6- 11 months			
Calories required in addition to usual requirement*	60-70 kcal/day	120-150 kcal/day	-
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Add 2 tsp of edible oil and 1tsp of sugar to porridge in addition to normal diet	Add 2 tsp of edible oil and 1-2 tsp of sugar to porridge or other foods. Aim to add 2 times daily	Therapeutic feeding as per national guidelines to provide 150-220 kcal/kg/ day based upon the actual weight
12- 23 months			
Calories required in additional to usual requirement*	80-90 kcal/day	160-190 kcal/day	-
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Add 2 tsp of edible oil and 2 tsp sugar to porridge, or a medium banana.	Extra cup (200ml) of full cream milk with 1 tsp sugar or 2 big idlis or bread butter (2 slice)	Therapeutic feeding as per national guidelines to provide 150-220 kcal/kg/ day based upon the actual weight
2 - 5 years			
Additional Calories*	100-140 kcal/day	200 – 280 kcal/day	Based on actual weight 150-220 kcal/kg/day
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Extra cup of milk or sweetened curd or 1 extra roti with vegetables or 1 paratha	2 puris with vegetables or 1 cup porridge or chikki 2 pieces	Therapeutic feeding as per national guidelines to provide 150-220 kcal/kg/ day based upon the actual weight

6 – 9 years			
Additional Calories*	130- 190 kcal/day total = 1815 kcal/day	260 – 380 kcal/day	Based on actual weight
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Extra cup (200 ml) of full cream milk or 1 egg omelette or 1 extra roti with vegetables	Extra cup of full cream milk and one vegetable stuffed paratha, or 2 parathas with curd or halwa 100 gm (1/2 cup) or poha11/2 cups	Therapeutic feeding as per national guidelines to provide 75- 100 kcal/kg/ day based upon the actual weight
10-14 years			
Additional Calories*	170- 230 kcal/day	340 – 400 kcal/day	Based on actual weight
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Extra one roti in lunch and dinner with vegetable or one dosa with sambhar or one stuffed paratha	1 Egg omelette with 2 slices of bread or 1 stuffed paratha and 1 cup milk	Therapeutic feeding as per national guidelines to provide 60- 90 kcal/kg/ day based upon the actual weight

* Calories in addition to that recommended for normal children in the same age group

4.3 Management of children with Severe Acute Malnutrition (SAM)

Children with severe acute malnutrition i.e. signs of visible wasting, bilateral oedema or weight for length/ height Z-score <-3, irrespective of whether taking ART or not, must be identified and managed correctly since they are at a very high risk of mortality. Children with SAM require 50- 100 percent extra energy every day after the period for stabilization till nutritional recovery (usual duration 6- 10 weeks). They should be treated with therapeutic feeding. Children with no medical complications may be managed at home if they still have a good appetite. They can receive good supervision at home and therapeutic feeds can be provided. Children who are sick and have associated complications like infections, or a poor appetite or are unable to eat, must be referred for inpatient care by trained staff with experience in nutritional rehabilitation. The nutritional management of HIV-infected severely malnourished children is largely the same as for any other severely malnourished child. For details on management of children with SAM refer to the WHO/NACO nutrition guidelines for HIV infected children. In addition, these children should be evaluated at the ART centre for exclusion of opportunistic infections including TB and assessed for ART if they are not receiving it already. If a child already on ART is found to have SAM, he should be evaluated for treatment adherence, treatment failure or development of new OIs.

4.4 Supportive measures:

The following measures support the improvement of nutritional status and health of HIV infected children and should be provided to all children:

- Micro-nutrient supplements: Micro-nutrient intake at the recommended level should be ensured through a balanced diet. If the child's diet does not contain a variety of fruits, vegetables and food from animal sources give a daily supplement that provides 1 RDA of vitamins and other micro-nutrients. Investigate for the presence of anaemia and give iron supplements if deficiency is confirmed.
- Give vitamin A supplements every 6 months for children upto 5 years of age in the following dose:

- 6- 12 months: 1,00,000 IU orally
- 1- 5 years: 2,00,000 IU orally

- For children beyond 5 years of age vitamin A should be provided through daily micro-nutrient supplements
- De-worm every 6 months (albendazole 400 mg single dose orally every 6 months after 1st year of life)
- Continue co-trimoxazole prophylaxis as indicated
- In patients with recent history of diarrhoea, give zinc 20 mg daily for 2 weeks
- Encourage regular play and age appropriate activities: Play helps maintain appetite and build muscles. Children who play are healthier and happier. Parents or caretakers should be encouraged to participate in age appropriate activities with the children. This promotes child-caretaker interaction and is a source of happiness for both.
- Administer routine childhood immunization

4.5 Feeding a child during illness and recovery period

HIV-infected children commonly experience poor appetite during sickness. It is often difficult to feed such children. During these acute illnesses, they are likely to lose weight. Some of the ways to encourage a child to eat include the following:

- Make the child comfortable
- Be patient and feed slowly
- Feed small amounts frequently. Children may tire easily while eating, making it difficult to eat sufficient food at a sitting. Offering feeds frequently may be needed to increase food intake
- Give food items that the child likes
- Give a variety of foods and extra fluids
- If the child is thirsty give fluids that have some energy e.g. milk. Avoid commercial juices or fizzy drinks that have very little nutritional value
- Pay attention to the child and make feeding a happy time
- For younger infants and children continue breastfeeding. A sick young child may prefer breastfeeding to eating other foods. All sick children should be offered appropriate foods unless there is a medical reason

In the recovery period, it is important to:

- Increase energy and protein consumed in everyday food items by adding extra one meal per day
- Feed the child on demand day and night
- Encourage the child in simple and loving ways

21. Common co-morbidities in children with HIV infection

At the time of diagnosis of HIV infection, CLHIV may have a variety of clinical manifestations depending upon their age and severity of immunodeficiency. These manifestations may involve one or more systems and influence the clinical staging of HIV, ART regimen, as well as the treatment for these conditions per se. This multi-systemic involvement has a direct influence on the health status and mortality and an indirect influence on the ART adherence due to drug interactions and added pill burden. Practically all the systems may be involved either directly by the HIV virus itself or secondary to other opportunistic infections. Common co-morbidities seen in CLHIV are summarized in table 1. This section gives a brief description of these co-morbidities; details of these are in the other relevant sections and in the manual on the management of opportunistic infections.

Table 1: Common co-morbidities seen in CLHIV at time of diagnosis

System	Manifestations
Infections	TB, bacterial, fungal, viral infections: localized or disseminated (sepsis)
Nutrition	Wasting Stunting Vitamin deficiencies
Gastro-intestinal system	Recurrent/persistent diarrhoea, oral /oesophageal candidiasis, recurrent/persistent oral ulcers,
Hepato-biliary system	Hepatitis B, hepatitis C, hepatitis due to other organisms
Haematological system	Anaemia, thrombocytopenia
Central nervous system	Delayed development, developmental regression, meningitis due to various bacterial/ viral agents including TB and cryptococcal, HIV encephalopathy
Respiratory system	Recurrent/persistent pneumonia, bronchiectasis, sinusitis, chronic otitis media, Lymphoid interstitial pneumonitis (LIP)
Skin & soft tissue	Infections: bacterial/ fungal, nutritional dermatosis, scabies, molluscum contagiosum, herpes zoster, pruritic papular eruptions

1. Malnutrition

Malnutrition is extremely common in CLHIV. While infants and young children are more likely to present with wasting, older children who may have an intermediate disease progression, are more likely to present with stunting. Malnutrition is an important cause of mortality in CLHIV, especially in the developing world. Assessment of the nutritional status and management of children with malnutrition is covered in the chapter on nutrition. While children with mild / moderate malnutrition may be managed on an out-patient basis, those with severe acute malnutrition (SAM) will require admission and therapeutic feeding.

2. Anaemia & thrombocytopenia

Anaemia is present in a large proportion of CLHIV at presentation. The causes include:

1. Chronic infection and diseases (including HIV Infection)
2. Poor nutrition: iron, folic acid and B12 deficiencies
3. Autoimmune diseases
4. Virus associated conditions (e.g. parvovirus B 19 red cell aplasia)
5. Adverse drug effects
6. Blood loss, especially chronic blood loss, through intestinal hookworm infection
7. Haemolysis caused by many conditions, including bacterial infections and malaria

Evaluation for the type of anaemia and its correction using appropriate therapy are important components of nutritional rehabilitation in these children.

Thrombocytopenia is also commonly encountered in CLHIV and may be an initial manifestation of HIV infection. Aetiologies include immune mediated platelet destruction, thrombotic thrombocytopenic purpura and impaired haematopoiesis. Bone marrow studies need to be done to exclude other causes of thrombocytopenia. Management is usually the same as in HIV non-infected children.

3. Infections

Opportunistic infections (OIs) are infections caused by pathogens that usually do not cause disease in an individual with a healthy immune system. A compromised immune system, however, presents an opportunity for the pathogen to cause disease. Most OIs occur among children with substantially immune-compromised state i.e. when CD4 < 10%, but serious bacterial infections, herpes zoster and TB can occur across the spectrum of immune categories. Early initiation of ART has dramatically decreased rates of AIDS-related opportunistic complications and deaths in adults and children.

3.1 Tuberculosis: TB is the most common opportunistic infection in HIV infected children as well as a leading cause of death among them. Infection with HIV is a strong risk factor for the progression from latent to active tuberculosis. All CLHIV are actively evaluated for tuberculosis by screening for four symptoms viz., current cough, fever, poor weight gain and contact history of TB, during every visit to a health facility and every contact with a health-care provider. Those with > 1 of these symptoms are further evaluated for TB. Diagnosis of TB in context of HIV and its management are discussed separately.

3.2 Bacterial infections: Serious and recurrent bacterial infections are major causes of morbidity and mortality in HIV-infected children worldwide. Immunologic defects in both cell-mediated (T cell) and humoral (B cell) immunity, functional asplenia, decrease in the neutrophil number and function and defects in the complement components, all contribute to the increased susceptibility to bacterial agents in these children. Bacterial pathogens such as pneumococcus, non-typhoidal salmonellae (NTS) and other gram-negatives are common causes of septicaemia in HIV-infected children that has a high case fatality rate, especially in the young and malnourished. Common bacterial infections in CLHIV include pneumonia, cellulitis, skin and internal organ abscess, otitis media, dysentery, meningitis and sepsis.

HIV-infected children with invasive bacterial infections generally have a clinical presentation similar to children without HIV infection. The classical signs, symptoms and laboratory test abnormalities that usually indicate invasive bacterial infection (fever, elevated white blood cell [WBC] count) are usually present but may be lacking in these immune-compromised children.

3.3 Other infections: In addition to bacteria, various viral, fungal and protozoan infestations are also common in CLHIV. Most common among these are:

3.3.1 Viral infections: Hepatitis B and C, CMV, herpes simplex, varicella / herpes zoster, molluscum contagiosum

3.3.2 Fungal infections: Pneumocystis jiroveci, cryptococcosis (meningitis/ disseminated infection), candidiasis (dermal/ oral/ oesophageal / disseminated), penicilliosis

3.3.3 Protozoan infestations: Toxoplasma, cryptosporidium, kala-azar, malaria, amoebiasis, giardiasis

A detailed description of clinical manifestations and management of these infections is included in the manual on opportunistic infection.

4. Diarrhoea

Diarrhoea is one of the most common complaints in HIV infected children. A child with HIV infection can have acute diarrhoea (liquid stools > 3 episodes /day of, duration < 14 days), dysentery (diarrhoea along with blood in stools), or persistent diarrhoea (diarrhoea lasting for > 14 days). The severity of diarrhoea is influenced by many factors including the aetiological agent and host characteristics such as immunodeficiency, nutritional status and age. A variety of organisms, including bacterial, viral, fungal and protozoa can cause diarrhoea in CLHIV (table 2). HIV enteropathy itself may lead to persistent diarrhoea.

Table 2: Microbes associated with diarrhoea in CLHIV

Persistent or Chronic Diarrhoea	Bloody Diarrhoea
• Enteropathogenic & aggregative E. coli • Nontyphoidal salmonella • Cryptosporidium • Microsporidia • Giardia lamblia • Ascaris lumbricoides • Cytomegalovirus • Cyclospora • Isospora belli	• Shigella • E. coli • Non typhoidal salmonella • Entamoeba histolytica

A child with acute diarrhoea is managed like a non-HIV infected child. The key treatment points include:

- Assessment of the severity of dehydration and its appropriate management using ORS / intravenous fluid (for severe dehydration)
- Continuing feeding
- Explaining the danger signs to the caregiver: feeding poorly, developing lethargy/ convulsions,

persistent vomiting and appearance of blood in stools

HIV-infected children are more prone to persistent diarrhoea. The differential diagnosis of persistent diarrhoea in HIV-infected children includes opportunistic infections (viral, bacterial, protozoan parasites), secondary conditions (allergies, lactose intolerance), HIV-related medication side effects, and nutritional deficiencies. The presence of unexplained persistent diarrhoea places an HIV-infected child into WHO stage 3 disease.

Appropriate management of diarrhoea in the chronically malnourished child is particularly critical; severely malnourished children have more than an 8-fold risk for mortality than normally nourished children.

Evaluation of a child with persistent diarrhoea includes assessment for:

- Dehydration and its severity
- Nutritional status
- Associated vitamin deficiencies
- Rectal prolapse and anal excoriation
- Associated infections, especially urinary tract infection

Important investigations indicated in evaluation of a child with persistent diarrhoea are given in table 3.

Table 3: Investigations in a case of persistent diarrhoea

Investigation	Comment
Stool microscopy for WBCs/ hpf and specific aetiologies	• Stool for WBCs/ hpf >10 suggest Shigella, Entamoeba histolytica, CMV or Invasive E. coli • Stool for WBC/ hpf 0 suggests normal or Cryptosporidium, Cyclospora, Giardia, MAC • Specific organisms may be identified such as Giardia and Entamoeba
Stool for modified ZN stain	Cryptosporidium, Cyclospora
Stool pH and reducing substances	Stool pH < 5.5 and reducing substances positive suggests lactose intolerance
Stool for ova and cysts	Helminthiasis, Entamoeba histolytica
CD4 count / CD4 %	CD4 < 50/cmm: Consider disseminated CMV / MAC CD4 < 100/cmm: Cryptosporidiosis or chronic microsporidiosis

Important points in management of a child with persistent diarrhoea are:

- Give the child more fluids than usual using low osmolarity ORS, to prevent dehydration
- Give supplemental zinc (10- 20 mg) to the child, every day for 10 to 14 days
- Continue to feed the child to prevent malnutrition
- For diarrhoea with blood: give Ciprofloxacin (15 mg/kg/day, in 2 divided doses for 3 days), OR cefixime (15 mg/kg/day, in 2 divided doses for 5 days), and Metronidazole (7.5 mg/kg 3 times a day for 7 days)
- Lactose intolerance is suspected when infants/ young children predominantly on milk feeds continue to pass explosive, watery stools causing perianal erythematous excoriation very

similar to perianal candidiasis. Special diets that are low in lactose or are lactose free may be indicated till the intestinal mucosa recovers

- Persistent diarrhoea may also possibly need specific treatment for giardia and microsporidia
- After an episode, where possible, advise an extra meal per day for two weeks to help regain the weight lost
- Give daily multivitamins and micronutrients for 2 weeks to all HIV exposed and infected children with persistent diarrhoea.
- Teach all the caregivers of children with HIV to pay particular attention to personal hygiene (hand washing with soap, especially after going to the toilet, after handling stools, and before preparing food and eating), drinking boiled water, eating only thoroughly cooked meat, and eating only cooked or thoroughly washed fruits and vegetables.

A child with severe acute malnutrition (SAM) and persistent diarrhoea must be admitted for management, as these children may have associated complications, require specialized care and may suffer from a high mortality if not promptly managed.

5. Hepatitis

Hepatomegaly and mildly elevated liver enzymes are common in children with HIV, though chronic/ progressive liver disease is unusual. The causes include:

1. Co-infection with viruses (hepatitis A-E, CMV, EBV)
2. Co-infection with MAC, cryptosporidium
3. Fatty liver
4. Drug toxicity

The clinical features include:

History: Jaundice, anorexia, nausea/ vomiting, fever, right hypochondriac pain, pruritus and pale-coloured stools.

Examination: Icterus, hepatomegaly or decreasing span of liver size

Additional features indicating hepatic failure include: altered sensorium, irritability, altered sleep patterns, poor feeding, ascites and bleeding manifestations

The investigations indicated in evaluation of a child with hepatitis are:

1. Liver function tests: (Total/ direct serum bilirubin, serum ALT/AST).

   Enzymes- ALT/AST- are usually elevated. Decreasing levels of enzymes, when associated with rising bilirubin, may be an ominous sign, indicating severe hepatic damage and the need for an urgent and thorough clinical management.
2. Peripheral blood smear for malaria
3. HBsAg, HCV, HAV testing
4. Blood glucose
5. Prothrombin time
6. Electrolytes (Na, K)

The presence of jaundice (recently onset) is indicative of an acute hepatitis. It is essential to gauge the severity of the dysfunction – i.e. is there hepatic encephalopathy and coagulopathy?

The treatment is mainly supportive and involves the following:

1. Remove the potentially offending medication(s) as per the ARV adverse event guidelines
2. If the child is on ATT, institution of modified the anti-tubercular regime
3. Supportive care (monitor, nutrition, rest)
4. For hepatic failure: monitor, intestinal decontamination- lactulose and neomycin, low protein intake, vitamin K, fresh frozen plasma, antibiotics, correction of dyselectrolytemia, antacids / H2 blockers, oxygen / ventilation

Presence of hepatitis, its severity and aetiology, influences the initiation of ART as well as the drug regimens; many antiretroviral drugs especially Nevirapine and PIs have associated hepato-toxicity. Hepatitis B and Hepatitis C co-infections with HIV are dealt with separately.

6. Cough / difficulty in breathing

Respiratory morbidity is very common in children with HIV infection. While evaluating CLHIV with cough and/ or difficult breathing, one must remember that OIs are not responsible for the respiratory symptoms in all cases. Respiratory symptoms may be on account of lung conditions other than infections, OIs or some extra/ non-pulmonary conditions.

In HIV-infected children presenting with cough or difficulty in breathing, the following entities should be sought by history, examination and investigations:

1. Pulmonary causes:

- Pulmonary Tuberculosis
- Pneumocystis Pneumonia
- Lymphoid Interstitial Pneumonitis
- Bacterial pneumonia
- Wheezy bronchitis, bronchial asthma

2. Extra-pulmonary causes:

- Severe anaemia
- Malaria
- Sepsis
- Raised intra-cranial pressure: meningitis, encephalitis

Children with symptoms due to pulmonary causes have cough as a prominent symptom while cough is not that significant in those who have non-pulmonary diseases or conditions leading to respiratory distress.

Acute pneumonia and PCP have been discussed elsewhere. Complications of pneumonia such as empyema and pneumothorax can be easily identified by clinical and radiological examination. Both these conditions require urgent medical attention.

TB is suspected in cases with failure to thrive or weight loss in addition to persistent fever and

persistent pneumonia that responds poorly to antibiotics. History of contact with a TB patient can be elicited. TB can be diagnosed by chest radiography, sputum/ gastric aspirate or broncho-alveolar lavage for CBNAAT, and FNAC of enlarged nodes, if present.

Bronchiectasis is a disease characterized by irreversible abnormal dilatation of the bronchial tree, and represents a common end stage of a number of nonspecific and unrelated antecedent events. Bronchiectasis is classified as WHO Stage 3 disease. Persistent cough and fever with productive purulent sputum or haemoptysis should arouse suspicion of bronchiectasis. Clubbing is usually present. Chest examination reveals localized signs, which do not easily resolve with the usual antibiotic treatment. Chest X-ray may show cystic spaces, occasionally with air-fluid levels and honeycombing. However, these findings are seen in more severe forms. Milder cases will show loss of broncho-vascular markings, crowding of bronchi and loss of lung volume.

Bronchiectasis needs careful management. Acute exacerbations need to be treated with adequate antibiotic therapy (2- 4 weeks) and postural drainage of sputum. Antibiotics should be carefully chosen to cover broad spectrum of micro-organisms, including gram negative bacteria. Attempt should be made to isolate the organism by sputum culture or induced sputum, or secretions obtained through bronchoscopy. Tuberculosis and LIP may be frequently underlying and need to be looked for. The treatment involves administration of antibiotics during acute exacerbations and bronchodilators. Surgical treatment may be necessary if the symptoms are severe or refractory to medical management and the disease is limited to one segment or a lobe.

Lymphocytic interstitial pneumonia **(LIP)**, a clinical stage 3 criterion is a lympho-proliferative, non-infectious pulmonary disorder that is characterized by diffuse infiltration of CD4 lymphocytes, plasma cells, and histiocytes in the alveolar septa and along the lymphatics. It is most common in children infected with HIV, especially those aged > 2- 3 years. Disease usually has an insidious onset of mild but persistent cough, with or without exertional dyspnoea, and breathing difficulty. The patients also have associated clubbing. LIP should be suspected if a child does not respond, or if chest X-ray findings persist or worsen despite appropriate anti-bacterial and anti-tuberculosis treatment. Treatment of LIP includes bronchodilators and corticosteroids (short course for mild intermittent symptoms and long course with slow taper in cases with chronic course).

While evaluating a HIV infected child with respiratory symptoms, it should be remembered that the patient may be having more than one clinical entity responsible for their symptoms. It is not infrequent for a patient to have TB and bronchiectasis or TB and LIP or LIP and bronchiectasis.

Pneumonia in children with HIV infection:

HIV-infected/ exposed children are at significantly increased risk of developing pneumonia. Diagnosis and treatment of very severe, severe and non-severe pneumonia is the same in HIV infected/ exposed children as in HIV-negative children. For severe and very severe pneumonia, one should use a combination of Ampicillin or Crystalline Penicillin and Gentamicin as the first line treatment. If this fails, use Ceftriaxone as second-line or Ciprofloxacin and Gentamicin.

Bacterial pneumonia responds fast and improvement is evident within 3- 5 days. In case of poor response, suspect PCP and other disorders (foreign body, complicated bacterial pneumonias, asthma, tuberculosis, inappropriate antibiotics, resistant organisms, underlying LIP, bronchiectasis, etc.); they need to be evaluated as usual

Annexures

NACO – National Technical Guidelines for ART (October 2018)

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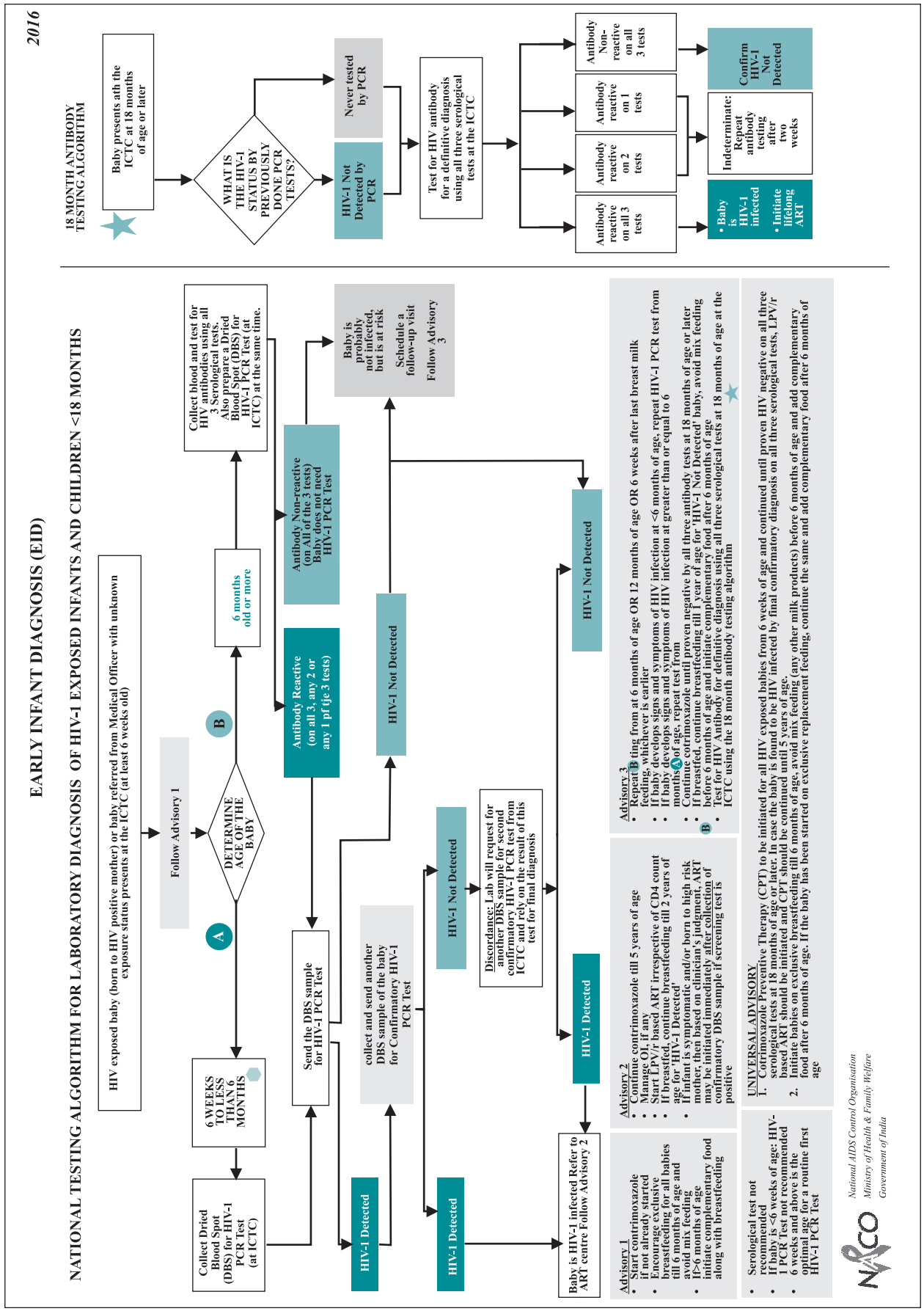
22	IMNCI Guidelines On Feeding Recommendations For Children
23	Age Related Food Intake Standards For Children

Annexure 1: National Testing Algorithm For HIV-1 Exposed Infants And Children Below The Age Of 18 Months



Annexure 2: Paediatric dosing chart

National Pediatric ART Dosing Schedule

Drug	Weight (in kgs)															
	3 to 5.9		6 to 9.9		10 to 13.99		14 to 19.9		20 to 24.9		25 to 29.9		30 to 34.9		>35	
	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening
Ziodvudine + Lamivudine (60/30)	1	1	1.5	1.5	2	2	2.5	2.5	3	3						
Ziodvudine + Lamivudine (300/150)											1	1	1	1	1	1
Abacavir + Lamivudine (60/30)	1	1	1	1.5	2	2	2.5	2.5	3	3.5	4	4				
Abacavir + Lamivudine (600/300)													0	1	0	1
Lopinavir/ ritonavir (80/20)- mg/ml syrup	1 ml	1 ml	1.5 ml	1.5 ml												
Lopinavir/ ritonavir (100/25)					2	1	2	2	3	2	3	3				
Lopinavir/ ritonavir (200/50)													2	2	2	2
Efavirenz (200)					0	1	0	1.5	0	1.5	0	2	0	2		
Efavirenz (600)															0	1
Ziodvudine + Lamivudine + Navirapine (60/30/50)	1	1	1.5	1.5	2	2	2.5	2.5	3	3						
Ziodvudine + Lamivudine + Navirapine (300/150/200)											1	1	1	1	1	1
Navirapine (50)	1	1	1.5	1.5	2	2	2.5	2.5	3	3						
Navirapine (200)											1	1	1	1	1	1
Ritonavir (100) (For super boosting)	0.5	0.5	1	1	1	1	2	1	2	1.5	2	2.5	3	3	3	3
Stavudine + Lamivudine (6/30)	1	1	1.5	1.5	2	2	2.5	2.5	3	3						
Stavudine + Lamivudine (30/150)											0	1	0	1	0	1
Stavudine + Lamivudine + Navirapine (6/30/50)	1	1	1.5	1.5	2	2	2.5	2.5	3	3						
Stavudine + Lamivudine + Navirapine (300/150/200)											1	1	1	1	1	1

Annexure 3: Consent Form For Patients Registering Into HIV Care And Initiating ART

Consent form for patients registering into HIV Care & starting ART

I, (name)……, (address) ……..... ..... CONSENT to share all information pertaining to my/my dependent child's health and HIV/AIDS status with the service providers who will be part of the management of my/my dependent child's condition.

And

I AGREE to receive antiretroviral therapy provided under the national programme.

I fully understand the information that has been provided by the health care staff in the following:

- That the ART is not an emergency and thus will be started as per the decision of the doctor. I shall attend the ART centre as per appointment for timely initiation of ART and regular follow-up.
- That receiving ART involves shared confidentiality with other service providers such as CBO/ NGO/ CSC/ positive network who may support my/my dependent child's treatment and other welfare measures through outreach and home-based care activities at home.
- That ART requires 100 % adherence to drugs and I shall abide by the same.
- That I understand the side effects of ART.
- That I shall not stop the drugs on my own and will return to the centre if there is any problem. In case I stop the drugs on my own accord/do not adhere to the regimen, I shall not hold the health care staff of the ART Centre responsible for any complication arising out of the same.
- In case, I am/my dependent child is on ART from outside on a different regimen, I agree to receive the drugs/ regimen provided under the national programme.
- In case, I/my dependent child want to take ART from other centre or to go other city for livelihood or other reasons, I will inform my ART Centre and get a "transfer out" letter before leaving.

…… ……

Signature of witness date /

Signature of patient with

(Doctor/nurse/counsellor) with date

Signature of Caregiver

(This should be translated in local language &/or explained to patient before taking patients signature)

Annexure 4: Checklist For Adherence Counselling

Checklist for first visit at ART centre:

- Introduce self and ask for the client's introduction
- Find out the purpose of the visit and check the HIV report
- Assess the knowledge of HIV/AIDS, routes of transmission and risk reduction
- Assess if the client is mentally prepared about the result
- Check how you can give emotional and social support
- Find out about his/ her lifestyle and if they are willing to change
- Assess if there are any suicidal ideations and/or frustrations
- Check for prior ART exposure
- Check for any addictions
- Check his/ her living, financial, psychological and social conditions
- Risk assessment
- Check about the HIV status of his/ her family members
- Explain the difference between HIV and AIDS and clarify that it is not necessary that a HIV positive client is an AIDS client
- Check for common OIs
- Conduct 4 symptom TB screening
- Referral and linkages as required
- Provide IEC/ BCC materials and condom
- As per client's need, provide information regarding other district and state ART centres
- It is necessary to take address and ID proof of the client
- Register the client and fill the white card, green book, consent form and also pre-ART register
- Provide space for the clients to ask queries and answer the questions
- Schedule an appointment for a follow-up counselling session

Check list for pre-ART adherence counselling:

- Recall the client's understanding about the previous session/ visit
- Check client's CD4 count, viral load
- Check knowledge of client/ caregiver about HIV/AIDS / CD4 count / ART eligibility and importance of ART
- Inform whether client is eligible for ART and need of ART
- Provide information on the role of ART in HIV treatment
- Explain about importance of regular visit at ART centre and need for regular CD4 testing
- Conduct 4S screening
- Identify potential barriers / factors affecting adherence (treatment related, client related, attitudes and behaviour of providers related, environmental and social related) and suggest possible solutions for these barriers / factors affecting adherence

- Inform that regular clinical follow-up and laboratory investigation is necessary
- Identify the support services required for the client
- Requirement of follow-up visit needs to be explained and decided accordingly

Check list for ART preparedness counselling:

- Review and recap the client's understanding about previous session/ visit
- Check whether client has accepted his/ her HIV status
- Identify caregiver/guardian and check acceptance of child HIV status
- Check caregiver understanding about need of ART
- Check understanding and importance of CD4 count, need of ART and initiation of ART
- Check whether the client has accepted lifelong treatment
- Conduct 4S Screening
- Make the client understand the importance and need of monthly visits
- Check feasibility of monthly drug pick-up
- Check readiness to start ART
- Check preparedness to initiate ART
- Give information about possible ART side effects and its management
- Inform about the importance of regular clinical follow-up and laboratory investigation
- Identify support services required
- Plan for follow-up visit

Check list for adult ART adherence counselling:

- Review the client's adherence to treatment
- Conduct 4S screening
- Physical verification and cross checking of drug (pill counting)
- Check when they missed a dose last time
- Discuss the reasons for not taking/ giving the pills
- Discuss the importance of timing in taking ART
- Check side effects as per the client's experience
- Identify treatment for side effects in a private / Govt. sector
- Explain the importance of adherence and work out fresh strategies for adherence
- Check for psychological symptoms such as depression, anxiety, etc.
- Discuss diet plan, nutrition, exercise, positive living, etc.
- Discuss how treatment has affected other areas of their life
- Check the client's supply of medicine for the coming month and also ensure that they do not have any problems with taking the medicine
- Discuss about ongoing treatment issues
- Monitor the failure of ART treatment
- Fix an appointment for the next visit

Check list for paediatric adherence counselling:

- Review the client's adherence for treatment
- Conduct 4S screening
- Physical verification and cross checking of drugs (pill counting)
- To check when did they missed a dose last time
- Use of colour, drawing, story-telling and role play to maintain adherence
- Discuss the reasons for not taking/giving the pills
- Check whether dose was taken at the correct time and discuss importance of timing
- Explain the importance of adherence and work out fresh strategies for adherence
- Discuss diet plan, nutrition, exercise, positive living, etc.
- Review social and family support at regular basis
- Discuss about ongoing treatment issues
- Monitor failure of ART treatment
- Fix an appointment for the next visit

Annexure 5: National TB Programme: Definitions

Table 1: Classification of TB case

Microbiologically confirmed TB case	TB patient with biological specimen positive for acid fast bacilli (AFB), or positive for Mycobacterium tuberculosis (M. TB) on culture, or through quality assured rapid diagnostic molecular test
Clinically diagnosed TB case	TB patient who is not microbiologically confirmed but has been clinically diagnosed with active TB by a clinician on the basis of radiological abnormalities or clinical signs with a decision to treat the patient with a full course of ATT
Pulmonary TB	Any microbiologically confirmed or clinically diagnosed case of TB involving lung parenchyma or tracheo-bronchial tree
Extra-Pulmonary TB	Any microbiologically confirmed or clinically diagnosed case of TB involving organs other than lungs, such as pleura, lymph node, intestine, joints, bones, etc.

Table 2: Type of TB patient

A	**New**		A TB patient who has never had treatment for TB or has taken anti-TB drugs for less than one month
B	**Previously treated**		A TB patient who has received one month or more of anti-TB drugs in the past
	I	**Recurrent**	A TB patient declared as successfully treated (cured/ treatment completed) and subsequently found to be microbiologically confirmed TB case
	II	**Treatment after failure**	A TB patient who has previously been treated for TB and the treatment failed at the end of their most recent course of treatment
	III	**Treatment after Loss to Follow Up (LFU)**	A TB patient previously treated for TB for one month or more and declared LFU in the end of their most recent course of treatment and subsequently found microbiologically positive
	IV	**Other previously treated patients**	TB patients who have been previously treated for TB but whose outcome after their most recent course of treatment is unknown or documented
C	**Transferred in**		A TB patient who is received for treatment in a TB unit after registering for TB treatment in another TB unit

Annexure 6: National TB Programme: Drug-Resistant TB – MDR-TB and XDR-TB

MDR-TB: A TB patient, whose sputum is culture positive for M. tuberculosis and is resistant in-vitro to Isoniazid and Rifampicin with or without other anti-tubercular drugs based on DST results from an RNTCP-certified culture & DST laboratory

XDR-TB: An MDR TB case, whose recovered M. tuberculosis isolate, is resistant to at least Isoniazid, Rifampicin, a fluoroquinolone (Ofloxacin, Levofloxacin, or Moxifloxacin) and a second-line injectable anti-TB drug (Kanamycin, Amikacin, or Capreomycin) at an RNTCP-certified culture & DST laboratory

MDR-TB: Treatment (Category IV)

- The intensive phase (6-9 months):
  - 6 drugs: Kanamycin, Levofloxacin, Ethionamide, Cycloserine, Pyrazinamide and Ethambutol
- The continuation phase (18 months):
  - 4 drugs: Levofloxacin, Ethionamide, Ethambutol and Cycloserine
- Reserve substitution drugs:
  - PAS, Capreomycin
  - Moxifloxacin

XDR-TB: Treatment (Regimen V)

- The Intensive Phase (6-12 months):
  - 7 drugs: Capreomycin, PAS, Moxifloxacin, High dose-INH, Clofazimine, Linezolid and Amoxyclav
- The Continuation Phase (18 months):
  - 6 drugs: PAS, Moxifloxacin, High dose-INH, Clofazimine, Linezolid and Amoxyclav
- Reserve substitution drugs:
  - Clarithromycin, Thioacetazone* (Thioacetazone is contraindicated for its use in PLHIV)

Annexure 7: Anti-TB drugs –Adverse Drug reactions and Drug-drug interactions

1. Anti TB Drugs -Adverse Drug reactions

Table 1: Symptoms and causative anti-TB drugs

Symptoms	Drug responsible
Upper abdominal pain – Frequent	All oral anti-tubercular drugs
nausea, vomiting	All oral anti-tubercular drugs
Nausea, vomiting with yellowness of skin and dark colour urine; Indication of Jaundice	Mainly by Pyrazinamide, Rifampicin and Isoniazid
Loose motions frequency > 4 times, liquid stools	Poor hygiene and mainly by Isoniazid and Rifampicin
Itching / Rashes	Mainly by Ethambutol, Rifampicin and Streptomycin
Rashes (SJ Syndrome / TEN)	Mainly by Ethambutol, Rifampicin and Streptomycin
Anaemia: Tiredness, lethargy, headache, pale look, palpitations	Mainly Isoniazid, Rifampicin, Pyrazinamide
Ear toxicity: Ringing in the ears, loss of hearing, dizziness and loss of balance leading to recurrent fall	Mainly Streptomycin and other amino glycosides
Kidney toxicity: Swelling of face or legs, less or no urine	
Giddiness, feeling abnormal	Mainly Streptomycin and Isoniazid
Tingling / burning / numbness in the hands and feet	Mainly Isoniazid
Seizure: Convulsions	Isoniazid
Psychiatric disturbances: Seeing abnormal things, change of thoughts, suicidal thoughts	Isoniazid

2. Algorithm for reintroduction of ATT

Adverse drug reaction	Advice on reintroduction
Hepatotoxicity	Can be given after liver enzyme returns to 2x ULN
Ocular toxicity	• The main suspect drug is Ethambutol • Reintroduction of Ethambutol is not recommended
Immune mediated Nephritis	• The main suspect drug is Rifampicin • Reintroduction with Rifampicin is not recommended
Non-serious cutaneous ADRs -No mucous membrane involvement or less than 10 % of BSA	After withholding all drugs re-introduce the drug one at a time
Serious Cutaneous adverse drug reactions - mucous membrane involvement or more than 10 % of BSA	Reintroduction is not recommended (applies for all anti-tubercular drugs)
Immune thrombocytopenia	• The main suspect drug is Rifampicin • Reintroduction with Rifampicin is not recommended
Aplastic Anaemia	• The main suspect drug is INH • Reintroduction with INH is not recommended

Nephrotoxicity	• The main suspect drugs are Aminoglycosides (AGs) • Reintroduction at low doses of AGs can be given after the renal function returns to normal
Ototoxicity	• The main suspect drugs are AGs • Reintroduction with AGs is not recommended
Diarrhoea	• Reintroduction is recommended with one drug at a time every fourth day, once the diarrhoea is resolved

Stepwise increase in the dosage for reintroduction

For key drugs, Isoniazid, Rifampicin, Ethambutol, detailed desensitisation protocol with very small dose and method of dosage preparation is given below:

Drug	Day 1	Day 2	Day 3
Isoniazid	50 mg	Full dose	Full dose
Rifampicin	75 mg	300 mg	Full dose
Pyrazinamide	250 mg	1000 mg	Full dose
Ethambutol	100 mg	500 mg	Full dose

If the test dose of any drug causes a reaction, discontinue this drug, unless it is deemed essential to the regimen. If that is the case, desensitisation can be considered. If rash was particularly severe, dose increment should still be slower.

3. Management of drug induced Hepatitis

- Features that indicate the need to stop medication
  - Transient, asymptomatic increases in serum liver transaminases occur during the early weeks of treatment
  - There is no need to interrupt or change treatment unless there is anorexia, malaise, vomiting or clinically evident jaundice
  - Clinical features of concern include protracted vomiting, mental changes, and signs of bleeding – all of which suggest impending acute liver failure and require immediate discontinuation of anti-tuberculosis medications
- Management of jaundice and other severe features
  - If jaundice or any of the clinical features suggestive of acute liver failure develop, all drugs must be stopped until the jaundice or hepatic symptoms have resolved and the liver enzymes have returned to baseline levels
  - Other causes of hepatitis must be sought
  - It is advisable to wait 2 weeks after the jaundice has disappeared before starting tuberculosis treatment

4. Anti-TB drugs: Dosage adjustment In Renal impairment

- Dose modification for anti-TB drugs:
- Severity of renal impairment is defined by creatinine clearance (CrCl) and renal impairment is considered as:

- Mild (1.5-2 mg/dl serum creatinine)
- Moderate (2-3 mg/dl serum creatinine)
- Severe (> 3 mg/dl serum creatinine)
- Creatinine Clearance calculation by Cockcroft Gault formula

- Required Details:
  - Patient's Age in years
  - Patient's Weight in kg
  - Patient's Serum Creatinine in mg/dl
- Calculating Creatinine Clearance: Cockcroft and Gault Formula
  - $$\text{CrCl (ml/min)} = \frac{(140 - \text{age in years}) \times \text{weight in kg}}{72 \times \text{serum creatinine in mg/dl}}$$
- In female subject, the whole product need to be multiplied by 0.85

Annexure 8: National TB Programme: TB drugs side effects and interactions

Drug	Side effects	Potential drug interactions	Notes
Rifampicin	Gut upset, rash, fever, orange urine / tears / saliva, light sensitivity, liver problems, acute renal failure	PIs, NNRTIs, '-azole' anti-fungal drugs, oral contraceptives, methadone, dapsone	Do not use with PIs or Nevirapine
Rifabutin	Gut upset, rash, eye inflammation, blood cell changes, joint pain, orange urine / tears / saliva, liver function changes, fever	PIs, NNRTIs, fluconazole, oral contraceptives, steroids, methadone	Avoid wearing soft contact lenses as they can become discoloured. Avoid Nevirapine

TB drugs with different Anti-retroviral drugs used in adults

ARV	Rifampicin	Rifabutin	Notes
NRTIs **(Zidovudine, Tenofovir, Lamivudine, Stavudine)**	Use as per weight band	Use	No interactions
Efavirenz	Use as per weight band	Use	Efavirenz usual dose (600 mg daily)
Nevirapine	Drug interaction Do not use	Do not use	High risk of liver toxicity
Boosted PIs	Drug interaction Do not use	Use (150 mg daily)	Rifabutin does not have interaction with PIs Rifabutin: 150 mg daily
Raltegravir	Use as per weight band	-	• Rifampicin has interaction with Raltegravir • In the presence of Rifampicin, Raltegravir dosage has to be 800 mg twice daily
Raltegravir	-	Use (150 mg daily)	When Rifabutin is used in place of Rifampicin, dosage of Raltegravir has to be 400 mg twice daily

Darunavir interactions with Rifabutin

Drug	Dose of Drug	Dose of Rifabutin	Effect on Drug Levels	Effect on Rifabutin Levels	Potential Clinical Effects	Mechanism of Interaction	Management
Darunavir (DRV)	600 mg Q12H	150 mg QOD	Darunavir AUC: increased 57%; Cmin: increased 75%; Cmax: increased 42% Ritonavir AUC: increased 66%; Cmin: increased 31%; Cmax: increased 68%	Rifabutin AUC: no significant change; Cmin: increased 64%; Cmax: decreased 28% 25-O-desacetylrifabutin AUC: increased 881%; Cmin: increased 2610%; Cmax: increased 377%	Increased Darunavir and Rifabutin effects	Inhibition of CYP450 3A4 by Darunavir	Reduce Rifabutin dose to 150 mg QOD when combined with Darunavir/ritonavir

Annexure 9: Additional Guidance on Tenofovir related renal toxicity

Tenofovir (TDF) is now the preferred first-line ART for all new patients to be enrolled in the national programme. It has a good overall safety profile, with fewer metabolic side-effects and mitochondrial toxicities. TDF has a relatively long half-life, allowing once daily dosing and making compliance easier for patients. The major side effects of TDF are:

- Renal toxicity
- Decrease in bone marrow density

However out of these, most significant is TDF related renal toxicity, though overall incidence may by only 3- 5 %. The renal proximal tubule (PT) is the main target of TDF toxicity; however, although the pathogenesis is incompletely elucidated, mitochondria appear to be a major target.

Effect on glomerular function:

In a pooled analysis comparing TDF with Zidovudine a modest but significant decline in eGFR was observed in the TDF-exposed patients. A meta-analysis that included data from 17 studies concluded that TDF exposure is associated with a mean difference in estimated creatinine clearance (CrCl) of −3.9 ml/min over the course of treatment. However, this meta-analysis also found a high degree of statistical heterogeneity in the published data, due to variability in parameters such as follow-up time, previous anti-retroviral therapy (ART) exposure and concomitant usage of protease inhibitors (PIs).

Effect on tubular function:

Serum creatinine and eGFR are predominantly measurements of glomerular function. However, the main target of TDF nephrotoxicity is the PT; in severe cases TDF leads to a breakdown of solute transport in this nephron segment (renal Fanconi syndrome—FS) or acute kidney injury (AKI). Fanconi syndrome includes aminoaciduria, glycosuria, tubular proteinuria, uricosuria and also bone demineralization due to phosphate wasting. This may lead to acute renal failure and this renal toxicity can usually present after 20 weeks or more of Tenofovir therapy; resolution typically takes place within 10 weeks after the discontinuation of the therapy.

Numerous case reports and case series have described FS or AKI in HIV-infected patients taking TDF. The exact incidence of TDF-induced FS is unknown, and attempts at accurate estimates are hampered by underreporting and a lack of clear diagnostic criteria, but based on the available data it is probably < 1 %. Renal biopsy specimens from patients with TDF toxicity typically show acute tubular damage, with misshapen and swollen mitochondria in the PT on electron microscopy. While cases of FS and AKI are relatively infrequent in patients taking TDF, these represent the most severe end of the scale of PT toxicity. Studies have demonstrated that generally it is mild or sub-clinical PT dysfunction in patients on TDF. The reported prevalence varies among studies, partly because of a lack of standardized definitions, but may be greater than 20 %. It is currently unknown whether mild PT toxicity will lead to progressive CKD over time in these patients, but one credible concern is that chronic phosphate wasting might cause a decrease in bone mineral density.

Effect on tubular secretion of creatinine:

Serum creatinine is widely used to calculate CrCl/eGFR. However, in addition to glomerular filtration, about 10- 40 % of creatinine clearance occurs by secretion across the PT epithelium. Decline in CrCl/eGFR within the first 2–3 months of commencing therapy, with very little further

change over time, has been seen in many studies. Therefore, given the pattern of CrCl/eGFR changes reported in patients taking TDF, it is plausible that they might be due to impaired PT creatinine secretion, rather than alterations in the actual GFR. To explore this hypothesis, a recent small study of 19 HIV-infected patients, either remaining on Zidovudine therapy or switching to TDF, looked in detail at changes over time in actual GFR, calculated CrCl, and urine excretion of tubular. In the patients switching to TDF, mean CrCl was significantly decreased, while urine excretion of tubular protein was significantly increased after 48 weeks; however, there was no corresponding change in the actual GFR, and no changes in any of the three parameters were observed in the Zidovudine group. This helps to conclude that the decrease in CrCl in TDF patients was more likely to be due to impaired PT creatinine secretion rather than a change in the glomerular function.

Guidance for treatment:

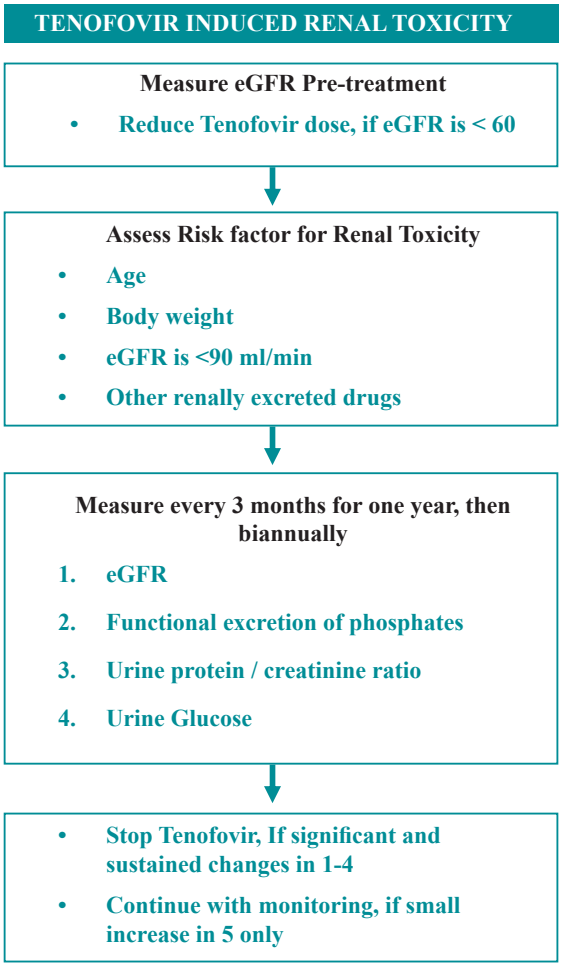
The main target of TDF toxicity is the proximal tubule. Hence, to suspect renal toxicity, the presence of tubular proteinuria is thought to be the most sensitive test of proximal tubule dysfunction. For monitoring renal tubular dysfunction, which often results in Fanconi Syndrome, urine routine showing pH as acidic along with glycosuria and albuminuria will be sufficient for the diagnosis, though a 24-hour urine sample for phosphate, (hypophosphatemia and hypokalaemia) protein and calcium are confirmatory. If feasible, the creatinine clearance may also be calculated and any adverse raise in the level of serum creatinine should raise suspicion about early signs of renal damage.

For initiating on TDF-containing regimens, creatinine clearance calculation is recommended, if feasible, before initiation and every 6 months. Especially in patients of high risk situations like underlying renal disease, Age > 40 years, BMI < 18.5 (or body weight < 50 kg), diabetes mellitus, hypertension, concomitant use of nephrotoxic drugs, doing a creatinine clearance is strongly recommended for this population before opting for TDF. The inability to perform creatinine clearance is not a barrier to TDF use. Hence in a resource limited setting, TDF can even be started without a creatinine clearance level; however, the above-mentioned risk factors should be assessed. TDF dose should be reduced in patients with pre-existing decreased kidney function

Cockcroft- Gault (CG) formula: eGFR = (140 – age) X (Weight in kg) X 0.85 (if female) / (72 X Cr in mg %)

Do not continue TDF when the estimated glomerular filtration rate is < 50 ml/min. In patients suspected with Fanconi syndrome, treatment should be stopped and resolution typically occurs within 10 weeks after discontinuation of the therapy. Patients receiving TDF and meeting any one of the four below mentioned criteria should have kidney function (eGFR) and serum phosphate measured every 6 months and be analyzed for proteinuria and glycosuria.

1. GFR < 90 ml/min
2. Use of other medications eliminated through renal secretion (e.g., adefovir, acyclovir, ganciclovir, or cidofovir)
3. Other co-morbid diseases (e.g., diabetes or hypertension)
4. Following a ritonavir-boosted protease inhibitor regimen



ARV Drugs: Dosage Adjustment in relation to Creatinine Clearance values			
Creatinine Clearance	Tenofovir Dose	Creatinine Clearance	Lamivudine Dose
30-49	300 mg q48h	30-49	150 mg QD
10-29	300 mg twice a week	15-29	150 mg 1st dose and then 100 mg QD
< 10*	Not recommended		
HD	Every 7 days, after dialysis	5-14	150 mg 1st dose and then 50 mg QD
		Less than 5 or on Haemodialysis	50 mg 1st dose and then 25 mg QD

*Note: The pharmacokinetics of Tenofovir have not been evaluated in non-HD patients with CrCl < 10ml/min; therefore, no dosing recommendation is available for those patients

Annexure 10: Grading of selected clinical and laboratory toxicities

Estimating severity of grade	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life-threatening Grade 4
Clinical adverse events NOT identified elsewhere in the table	Symptoms causing minimal or no interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care OR medical or operative intervention indicated to prevent permanent impairment, permanent disability or death
Haemoglobin	8.0 – 9.4 g/dl	7.0 – 7.9 g/dl	6.5 – 6.9 g/dl	<6.5 g/dl
Absolute neutrophil count	1000 – 1500/ cmm	750 – 999/cmm	500 – 749/cmm	<500/cmm
Platelets	75000 – 99000/ cmm	50000 – 74999/ cmm	20000 – 49999/ cmm	<20000/cmm
hyper bilirubinaemia	>1.0 – 1.5 X ULN	>1.5 – 2.5 X ULN	>2.5 – 5 X ULN	>5 X ULN
Glucose (Fasting)	110 – 125 mg/dl	126 – 250 mg/dl	251 – 500 mg/dl	>500 mg/dl
Hypoglycaemia	55 – 64 mg/dl	40 – 54 mg/dl	30 – 39 mg/dl	<30 mg/dl
Hyperglycaemia (non-fasting no prior diabetes)	116 – 160 mg/dl	161 – 250 mg/dl	251 – 500 mg/dl	>500 mg/dl
Triglycerides	-	400 - 750 mg/dl	750 - 1200 mg/dl	> 1200 mg/dl
Creatinine	>1.0 – 1.5 X ULN	>1.5 – 3.0 X ULN	>.0 – 6.0 X ULN	>6.0 X ULN
AST (SGOT)	1.25 – 2.5 X ULN	>2.25 – 5.0 X ULN	>5.0 – 10.0 X ULN	>10.0 X ULN
ALT (SGPT)	1.25 – 2.5 X ULN	>2.25 – 5.0 X ULN	>5.0 – 10.0 X ULN	>10.0 X ULN
GGT	1.25 – 2.5 X ULN	>2.25 – 5.0 X ULN	>5.0 – 10.0 X ULN	>10.0 X ULN
Alkaline Phosphatase	1.25 – 2.5 X ULN	>2.25 – 5.0 X ULN	>5.0 – 10.0 X ULN	>10.0 X ULN
Bilirubin	1.1 – 1.5 X ULN	1.6 – 2.5 X ULN	2.6 – 5.0 X ULN	>5.0 X ULN
Amylase	>1.0 – 1.5 X ULN	>1.5 – 2.5 X ULN	>2.0 – 5.0 X ULN	>5.0 X ULN
Pancreatic amylase	>1.0 – 1.5 X ULN	>1.5 – 2.5 X ULN	>2.0 – 5.0 X ULN	>5.0 X ULN
Lactate	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life threatening consequences	Increased lactate with pH < 7.3 with life threatening consequences

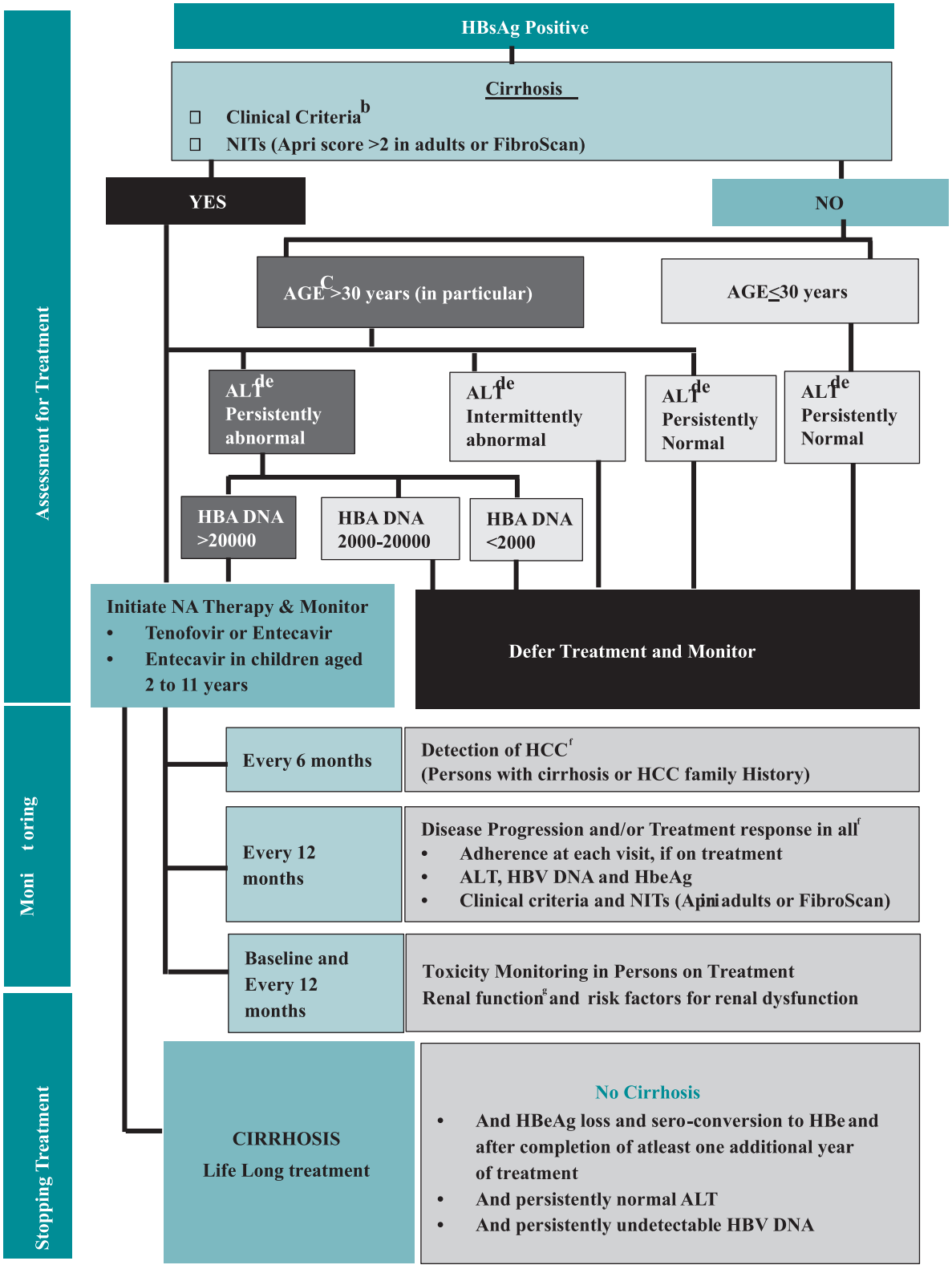
Gastrointestinal	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life-threatening
Nausea	Mild OR transient; reasonable intake maintained	Moderate discomfort OR intake decreased for < 3 days	Severe discomfort OR minimal intake for > 3 days	Hospitalization required
Vomiting	Mild OR transient; 2-3 episodes per day OR mild vomiting lasting < 1 week	Moderate OR persistent; 4-5 episodes per day OR vomiting lasting > 1 week	Severe vomiting of all foods/ fluids in 24 hours OR orthostatic hypotension OR intravenous treatment required	Hypertensive shock OR Hospitalization for intravenous treatment required
Diarrhoea	Mild OR transient; 3-4 loose stools per day OR mild diarrhoea lasting < 1 week	Moderate OR persistent; 5-7 loose stools per day OR diarrhoea lasting > 1 week	Bloody diarrhoea OR orthostatic hypotension OR > 7 loose stools/day OR intravenous treatment required	Hypertensive shock OR Hospitalization required
Respiratory	**Mild Grade 1**	**Moderate Grade 2**	**Severe Grade 3**	**Potentially life-threatening**
Dyspnoea	Dyspnoea on exertion	Dyspnoea with normal activity	Dyspnoea at rest	Dyspnoea requiring Oxygen therapy
Urine analysis	**Mild Grade 1**	**Moderate Grade 2**	**Severe Grade 3**	**Potentially life-threatening**
Proteinuria				
Spot urine	1+	2+ or 3+	4+	Nephrotic Syndrome
24 hours urine	200 mg to 1 g loss/day OR < 0.3% OR < 3 g/L	1 g to 2 g loss/day OR 0.3% to 1% OR 3 g to 10 g/L	2 g to 3.5 g loss/ day OR > 1% OR > 10 g/L	Nephrotic Syndrome OR > 3.5 g loss/day
Gross Haematuria	Microscopic only	Gross, no clots	Gross plus clots	Obstructive
Miscellaneous	**Mild Grade 1**	**Moderate Grade 2**	**Severe Grade 3**	**Potentially life-threatening**
Fever (Oral, >12 hours)	37.7-38.5^{0}C OR 100.0-101.5^{0}F	38.6-39.5^{0}C OR 101.6-102.9^{0}F	39.6-40.50C OR 103-105^{0}F	> 40.5^{0}C OR > 1050F for > 12 continuous hours
Headache	Mild; No treatment required	Moderate OR non-narcotic analgesia treatment	Severe OR responds to initial narcotic treatment	Intractable
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized Urticaria, angioedema	Anaphylaxis

Rash Hypersensitivity	Erythema, pruritus	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	ANY ONE OF: Mucous membrane involvement, suspected Stevens-Johnson syndrome, Toxic Epidermal Necrolysis (TEN), Erythema Multiforme, Exfoliative Dermatitis
Fatigue	Normal activity reduced by < 25%	Normal activity reduced by 25-50%	Normal activity reduced by > 50%; cannot work	Unable to care for self

Source: Division of AIDS, National Institute of Allergy and Infectious Diseases. Version 1.0 December 2004 clarification August 2009

Note: This clarification includes addition of Grade 5 toxicity, which is death

Annexure 11: Algorithm of WHO Recommendations on the Management of Persons with Chronic Hepatitis B infection[a]



NITs non-invasive tests, ALT alanine aminotransferase, APRI aspartase aminotransferase-to-platelet ratio index

a Defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more. The algorithm does not capture all potential scenarios, but the main categories for treatment or monitoring. Recommendations for settings without access to HBV DNA testing are provided in the relevant chapters.

b *Clinical features of decompensated cirrhosis: Portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy, or liver insufficiency (jaundice). Other clinical features of advanced liver disease/ cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema, and oedema.*

c *The age cut-off of > 30 years is not absolute, and some persons with CHB less than 30 years may also meet criteria for antiviral treatment.*

d *ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, though local laboratory normal ranges should be applied. Persistently normal/abnormal may be defined as three ALT determinations below or above the upper limit of normal, made at unspecified intervals during a 6-12-month period or pre-defined intervals during 12-month period.*

e *Where HBV DNA testing is not available, treatment may be considered based on persistently abnormal ALT levels, but other common causes of persistently raised ALT levels such as impaired glucose tolerance, dyslipidaemia and fatty liver should be excluded.*

f *All persons with CHB should be monitored regularly for disease activity/progression and detection of HCC, and after stopping treatment for evidence of reactivation. More frequent monitoring maybe required in those with more advanced liver disease, during the first year of treatment or where adherence is a concern, and in those with abnormal ALT and HBV DNA levels > 2000 IU/ml, not yet on treatment.*

g *Before initiation, assessment should be done of renal function (serum creatinine level, estimated glomerular filtration rate, urine dipsticks for proteinuria and glycosuria, and risk factors for renal dysfunction (decompensated cirrhosis, CrCl < 50 ml/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs, solid organ transplantation, older age, BMI < 18.5 kg/m^2 (or body weight < 50 kg), concomitant use of nephrotoxic drugs or a boosted protease inhibitor (PI) for HIV). Monitoring should be more frequent in those at higher risk of renal dysfunction.*

Annexure 12: Atazanavir induced Unconjugated Hyperbilirubinemia

Background

The recommended prescribed dose of Atazanavir (ATV) is ATV 300 mg + Ritonavir (RTV) 100 mg once daily. No dosage adjustment is required for patients with renal dysfunction unless they are on haemodialysis. Considering the widespread use of Atazanavir, clinicians caring for HIV-infected patients should have familiarity with the entity of protease inhibitor-associated hyper bilirubinaemia.

Isolated unconjugated hyper bilirubinaemia is the most common laboratory abnormality associated with the use of Atazanavir and this is not associated with hepatocellular injury. Although not considered a serious adverse effect, the higher levels of unconjugated hyper bilirubinaemia associated with this drug can manifest as jaundice with high coloured urine. The onset of Atazanavir associated hyper bilirubinaemia typically occurs within several months, and bilirubin levels generally peak within 4 months (range 1 to 8 months); the subsequent natural history on therapy is notable for a non-progressive course, with bilirubin levels remaining generally stable in patients on further follow-up. Routine monitoring of bilirubin is acceptable.

An isolated elevation in total bilirubin should be confirmed as predominantly unconjugated by testing the indirect fraction of bilirubin. The presence of elevated conjugated bilirubin or changes in serum hepatic aminotransferases or alkaline phosphatase warrant further investigation for other causes of hyper bilirubinaemia, such as other drug hepatotoxicity, viral hepatitis, alcoholic hepatitis or cholestasis. It is important to recognize that patients who are on Atazanavir but with acute haemolysis will also develop increased indirect bilirubin levels.

Management

For patients who develop clinically evident jaundice, the decision whether to discontinue the offending protease inhibitor (Atazanavir) usually depends on how severe and noticeable the jaundice is, and whether the patient is willing to tolerate it. Additional work-up is not required if liver enzymes are not raised and are consistent with baseline values. The patient requires proper counselling on the development of yellowish discolouration of eye, which is not associated with liver damage. It must be re-emphasized that the discolouration was physiological and he/ she need not be alarmed.

Dose reduction of Atazanavir is not recommended in this setting. In most cases, a change to an alternative regimen is necessary only for patients who develop an unacceptable level of jaundice with Grade 3 (5-10 times of ULN) and 4 (> 10 times of ULN) elevation of serum ALT and AST.

In case of hepatic insufficiency, dosage adjustment is recommended. Child-Pugh score is utilized to assess the severity and prognosis of chronic liver disease and to identify patients who require liver transplantation. This score is to be used only in those HIV infected subjects who have concomitant chronic liver disease e.g. chronic hepatitis B and C, alcoholic liver disease, NASH and other chronic liver diseases.

ATV/r (300/100 mg) can only be used in patients with chronic liver disease in Child Pugh Class A. It should not be used on second-line patients with Child Pugh Class B or C. Please refer the following tables for the scores and classifications.

Component	Child-Pugh Score		
	Points 1	**Points 2**	**Points 3**
Encephalopathy	none	Grade 1–2	Grade 3–4
Ascites	none	Mild or controlled by diuretics	Moderate or refractory despite Diuretic
Albumin	> 3.5 g/dl	2.8–3.5 g/dl	< 2.8 g/dl
Total bilirubin or	< 2 mg/dl (< 34 µmol/L)	2–3 mg/dl (34 µmol/L to 50 µmol/L)	> 3 mg/dl (> 50 µmol/L)
Modified total bilirubin (for patients of Gilbert Disease and patients on Atazanavir & Indinavir)	< 4 mg/dl	4–7 mg/dl	> 7 mg/dl
Prothrombin time (seconds prolonged)	< 4	4–6	> 6
International normalized ratio (INR)	< 1.7	1.7–2.3	> 2.3

Encephalopathy Grades

- **Grade 1:** Mild confusion, anxiety, restlessness, fine tremor, slowed coordination
- **Grade 2:** Drowsiness, disorientation, asterixis
- **Grade 3:** Somnolent but arousable, marked confusion, incomprehensible speech, incontinence, and hyperventilation
- **Grade 4:** Coma, decerebrate posturing, flaccidity

Child-Pugh Classification

Child-Pugh Classification	**Total Score**
Class A	5-6 points
Class B	7-9 points
Class C	> 9 points

Annexure 13: Risk Assessment guide for the Source Patient

The following points need to be covered when questioning and examining the source patient. These need to take into consideration the local HIV epidemiology, clinical and cultural conditions. There is no such thing as a "score" in this regard—it is up to the doctor to interpret the results of the clinical assessment.

It is important that questioning be conducted in a way that reveals relevant events that may have occurred several years ago:

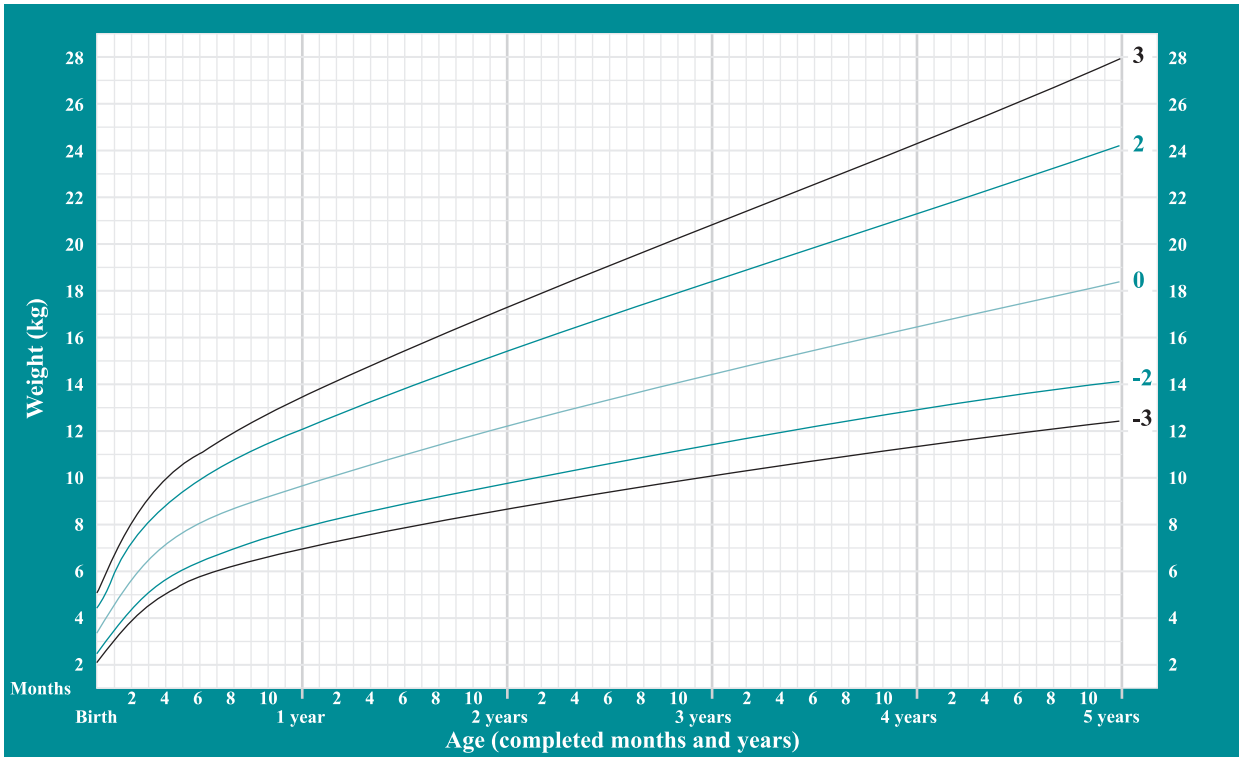
1. Family history: Have any family members recently been ill or died. What was the cause?
2. Recent personal history of HIV acute infection symptoms (generally appear 3 to 6 weeks after infection): general lymphadenopathy (predominantly in the cervical and axillary areas); fever of unknown origin; muscular cramps, joint pain; skin rash, urticaria; oral and genital ulcers.
3. Individual's personal "risk history" of HIV
    - Has the source person ever had a blood transfusion? If so, under which conditions?
    - Has the source person had injections or surgical procedures (including any traditional scarification) with non-sterile/reusable clinical material?
    - Is the source person an injecting drug user (IDU) and does s/he possess injection material?
    - Does the source person belong to a population group considered at risk? For example: sex worker, truck driver; migrant worker; soldier, men who have sex with men
    - Is the source person involved in high-risk sexual activities? Example: practicing unsafe sex with multiple partners; already treated or undergoing treatment for a sexually transmitted disease; having sexual partners of a person in any of the above categories.
4. Suspicion or actual presence of symptoms and/or HIV infection within the previous six months or more: tuberculosis; continuous or intermittent fever; chronic diarrhoea; weight loss; chronic cough lasting longer than a month; skin infections (severe and/or recurrent); oral thrush; night sweats
5. Clinical examination findings
    - Cardinal signs: Pneumocystis Jiroveci pneumonia (PCP); cerebral toxoplasma; oesophageal candidiasis; cytomegalovirus retinitis
    - Characteristic signs: oral thrush; hairy leucoplakia of the tongue; Cryptococcal meningitis; pulmonary or extra-pulmonary tuberculosis; herpes zoster - particularly multi-dermatomal; severe prurigo; high-grade B-cell extra-nodal lymphoma
    - Associated signs: weight loss (recent, unexplained) of more than 10 % of initial body weight; fever (continuous or intermittent) for longer than a month; diarrhoea (continuous or intermittent) for longer than a month; ulcers (genital or perianal) for more than a month; cough lasting longer than a month; neurological complaints or findings; generalised lymphadenopathy (except extra-inguinal) reactions to drugs (not previously observed); skin infections (severe and/or recurrent): e.g. warts, dermatophytes, folliculitis, lymphopenia (known)
6. Past history of any long term medical treatment (e.g. anti-TB treatment, antiretroviral therapy)

Annexure 14: WHO Weight-for-age Chart (Birth-5 years of age)

Weight-for-age BOYS

World Health Organization

Birth to 5 years (z-scores)

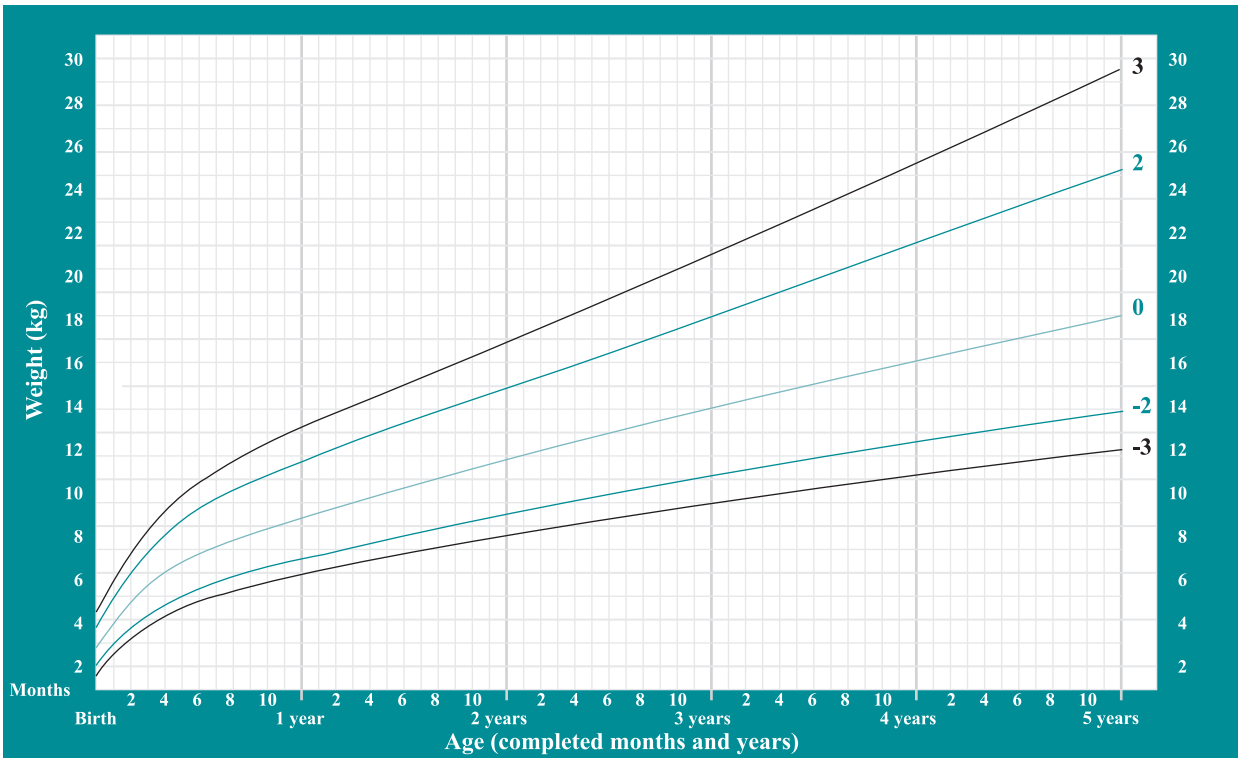


WHO Child Growth Standards

Weight-for-age GIRLS

World Health Organization

Birth to 5 years (z-scores)



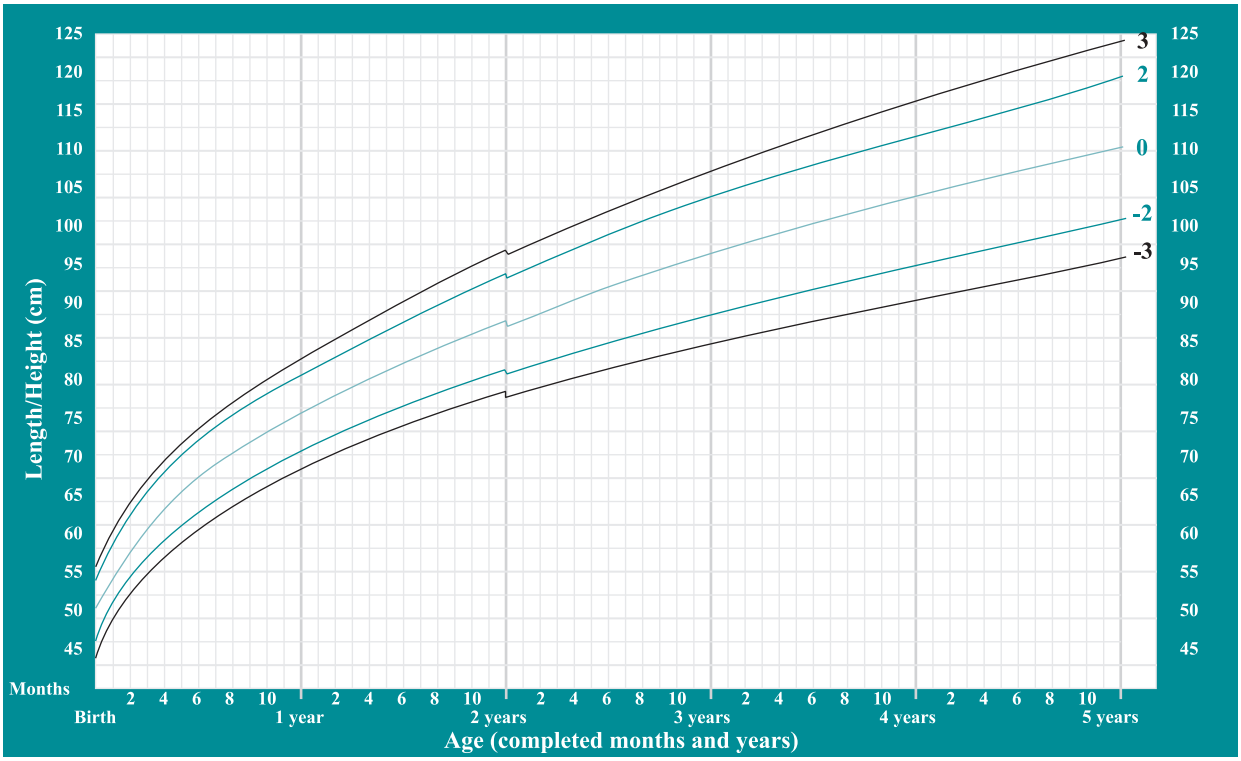
WHO Child Growth Standards

Annexure 15: WHO Length/Height-for-age Chart (Birth to 5 years of age)

Length/Height-for-age BOYS

Birth to 5 years (z-scores)

World Health Organization

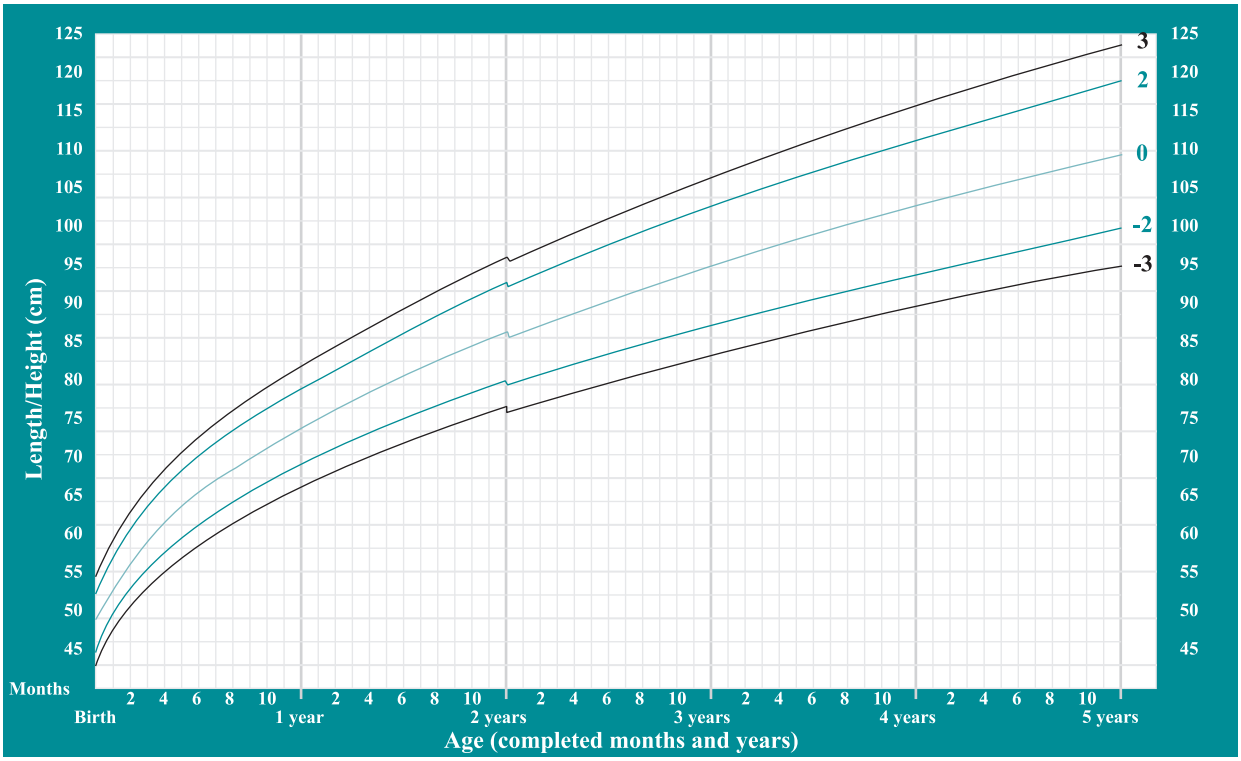


WHO Child Growth Standards

Length/Height-for-age GIRLS

Birth to 5 years (z-scores)

World Health Organization

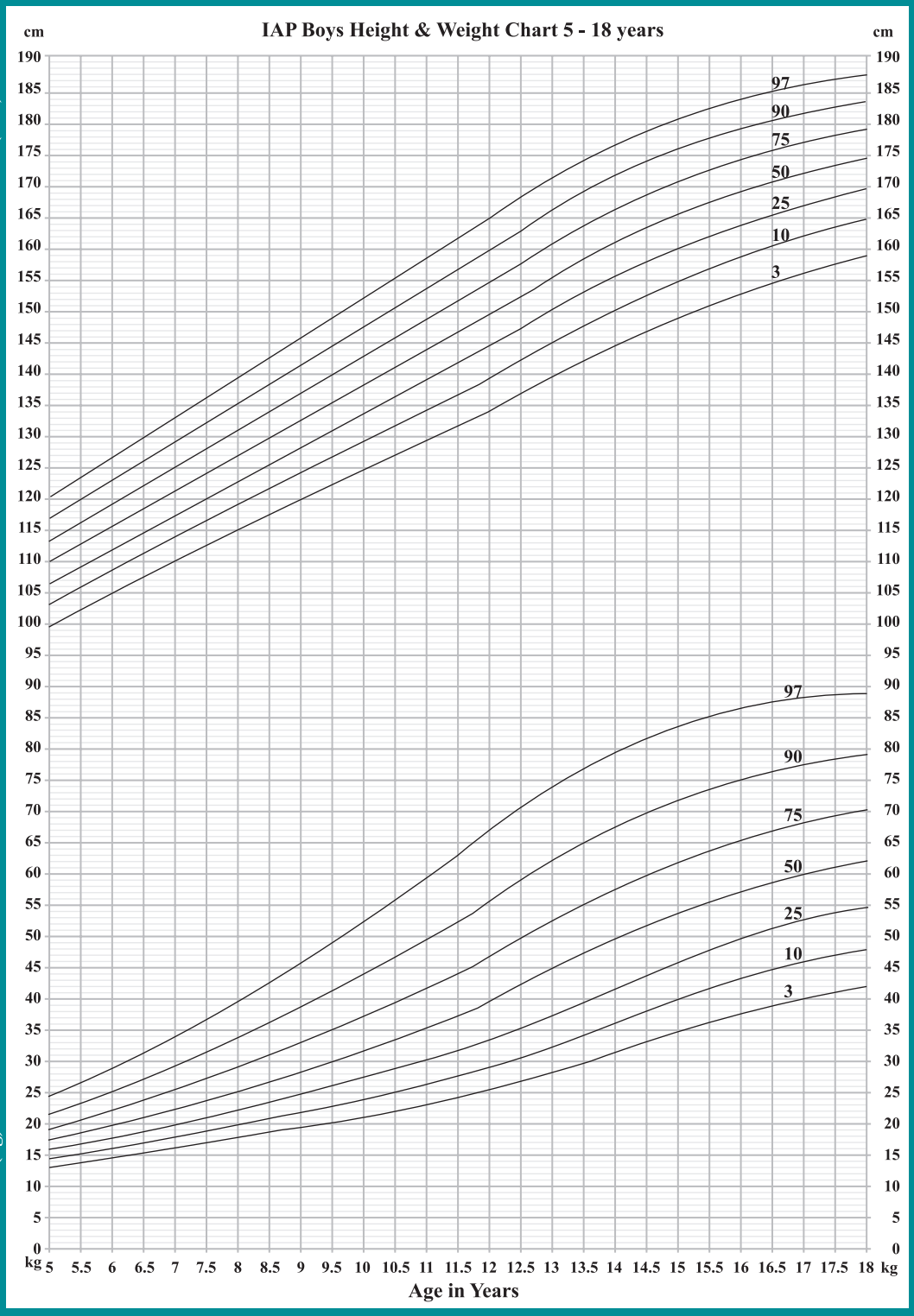


WHO Child Growth Standards

Annexure 16: IAP Boys Height and Weight chart: 5-18 years

5 to 18 Years : IAP Boys Height and Weight Charts

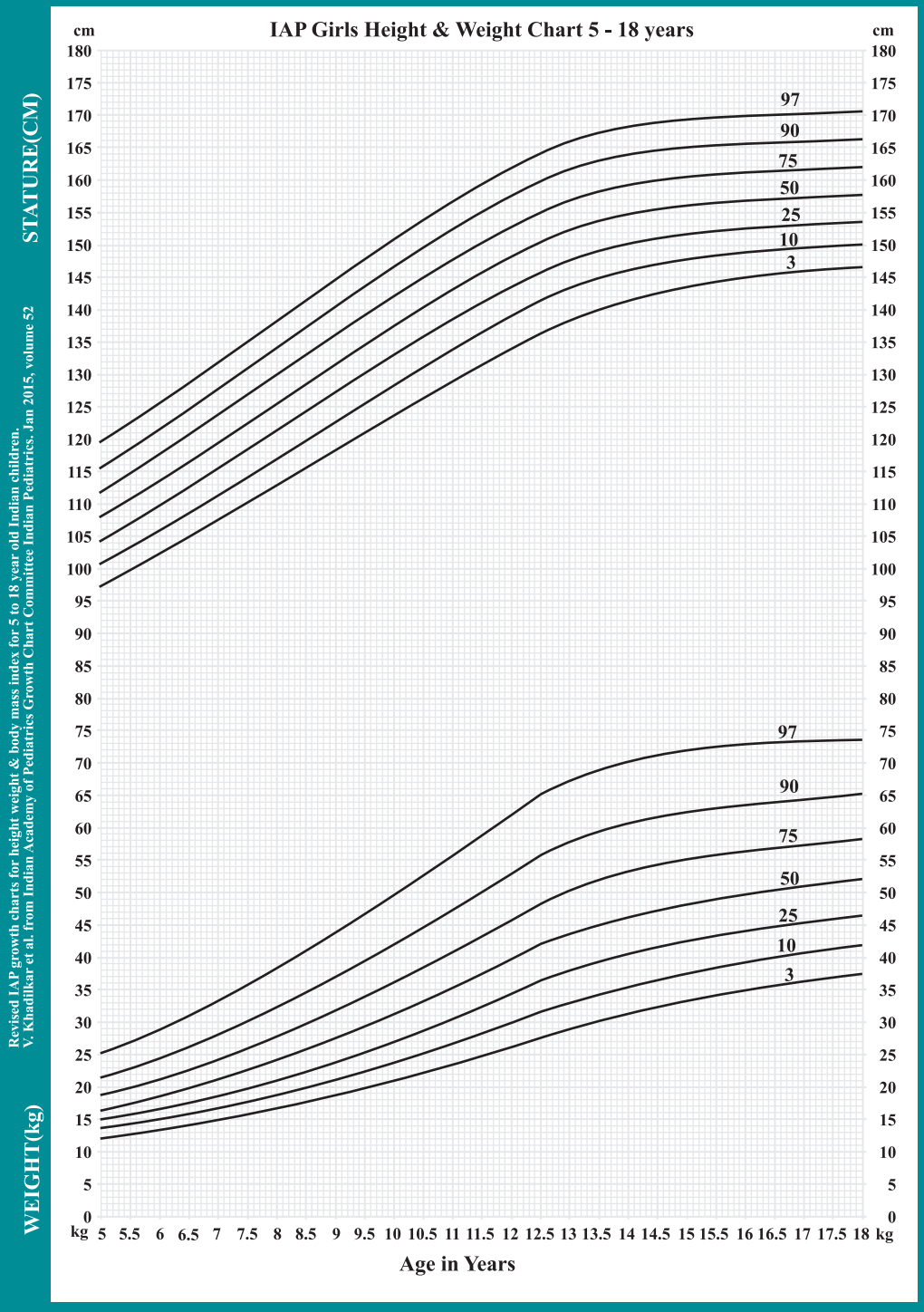
Father's Height_____, Mother's Height_____, Target Height_____



Annexure 17: IAP Girls Height and Weight chart: 5-18 years

5 to 18 Years : IAP Girls Height and Weight Charts

Father's Height_____, Mother's Height_____, Target Height_____

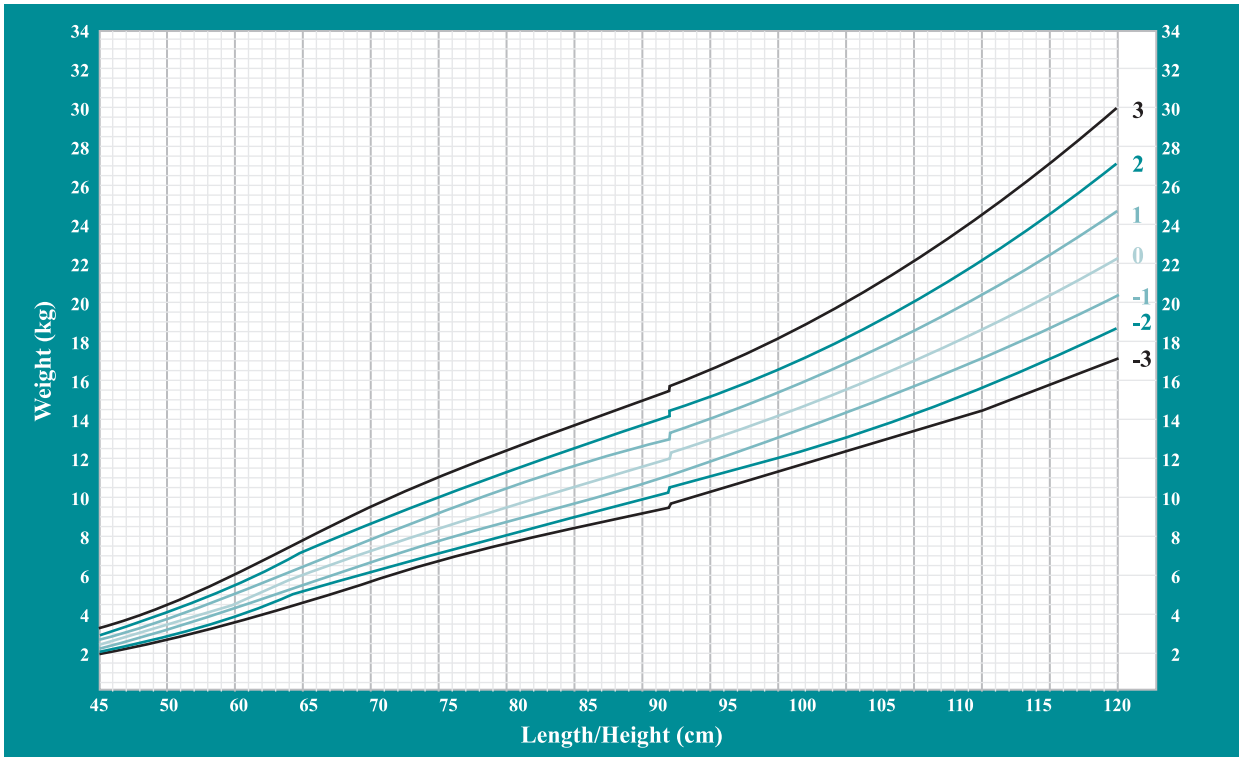


Annexure 18: WHO Weight for Length/Height chart: 0-5 years

Weight-for-length/height BOYS

Birth to 5 years (z-scores)

World Health Organization

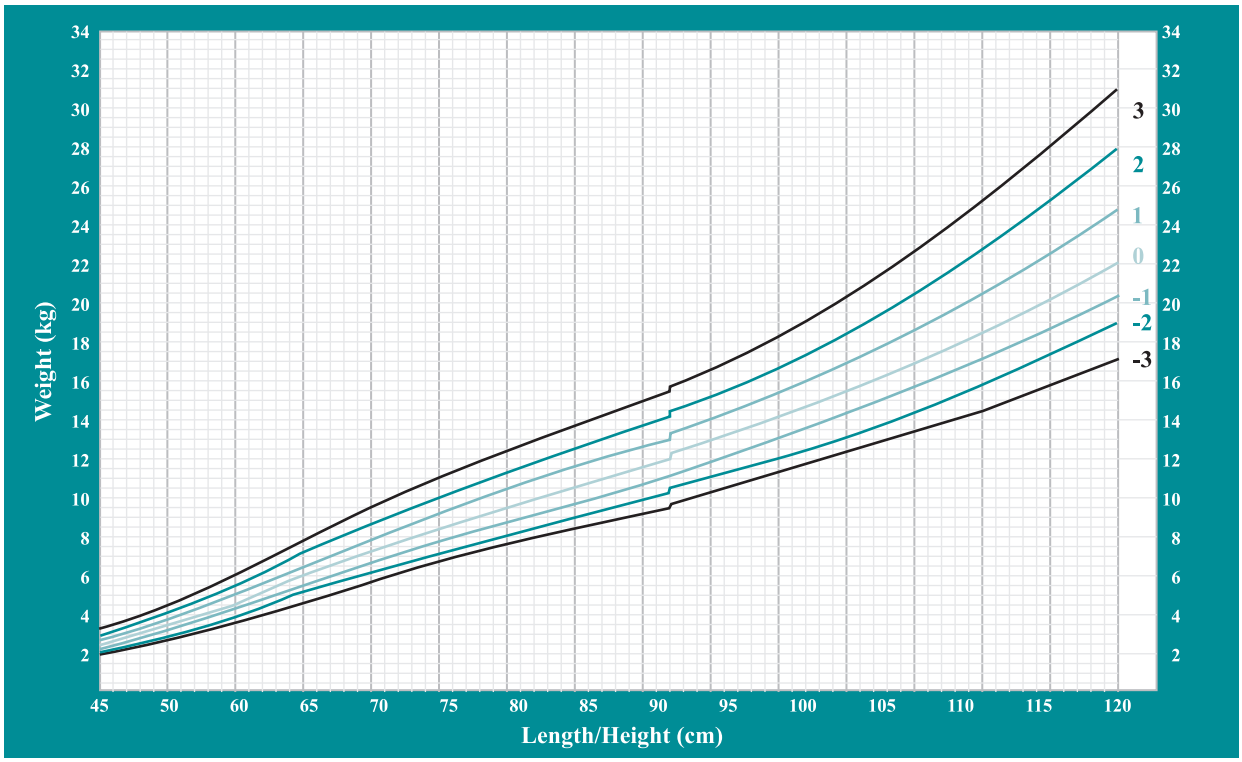


WHO Child Growth Standards

Weight-for-length/height GIRLS

Birth to 5 years (z-scores)

World Health Organization



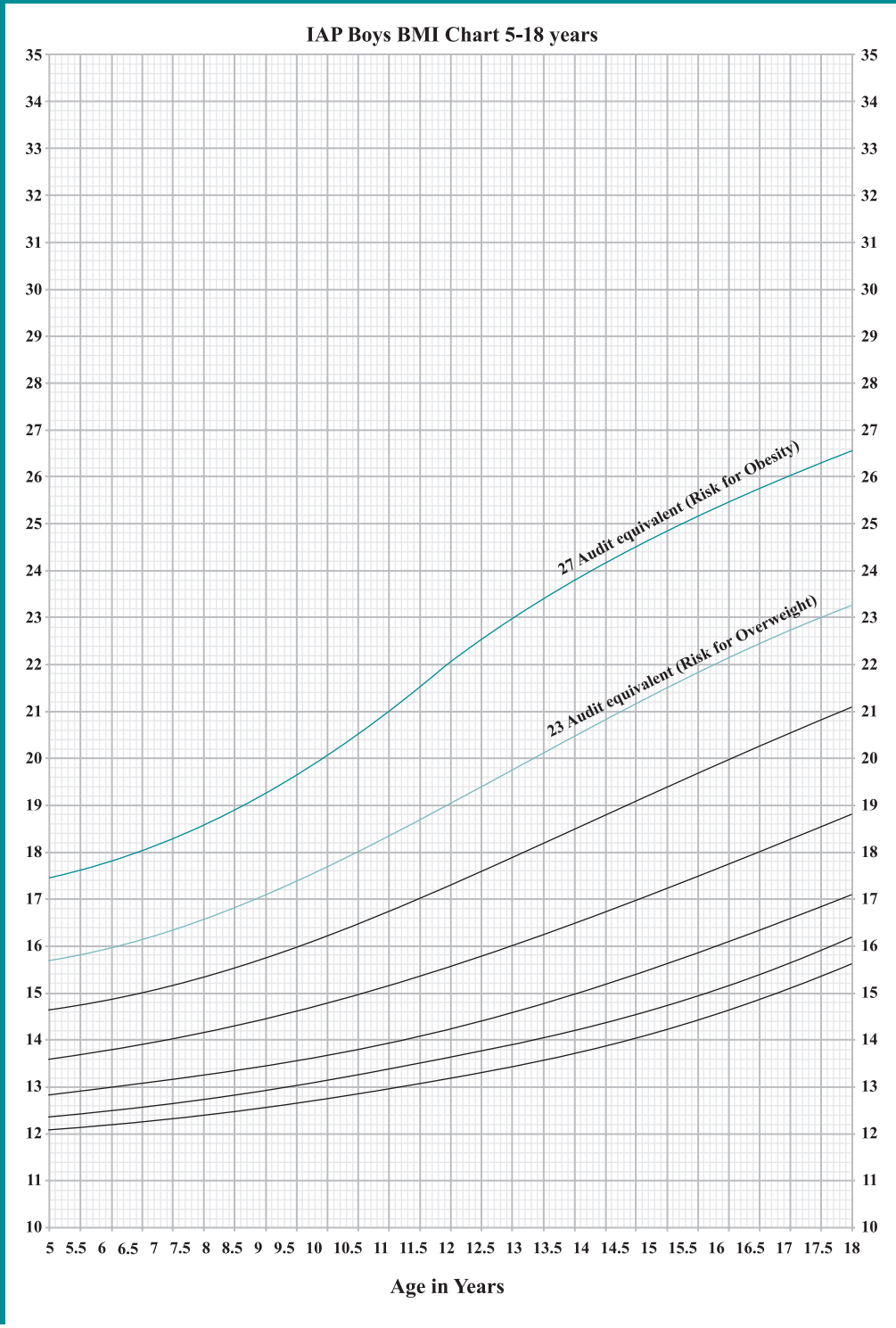
WHO Child Growth Standards

Annexure 19: IAP Boys BMI chart 5-18 years

5 to 18 Years : IAP Boys Body Mass Index Charts

Name _____

DOB _____



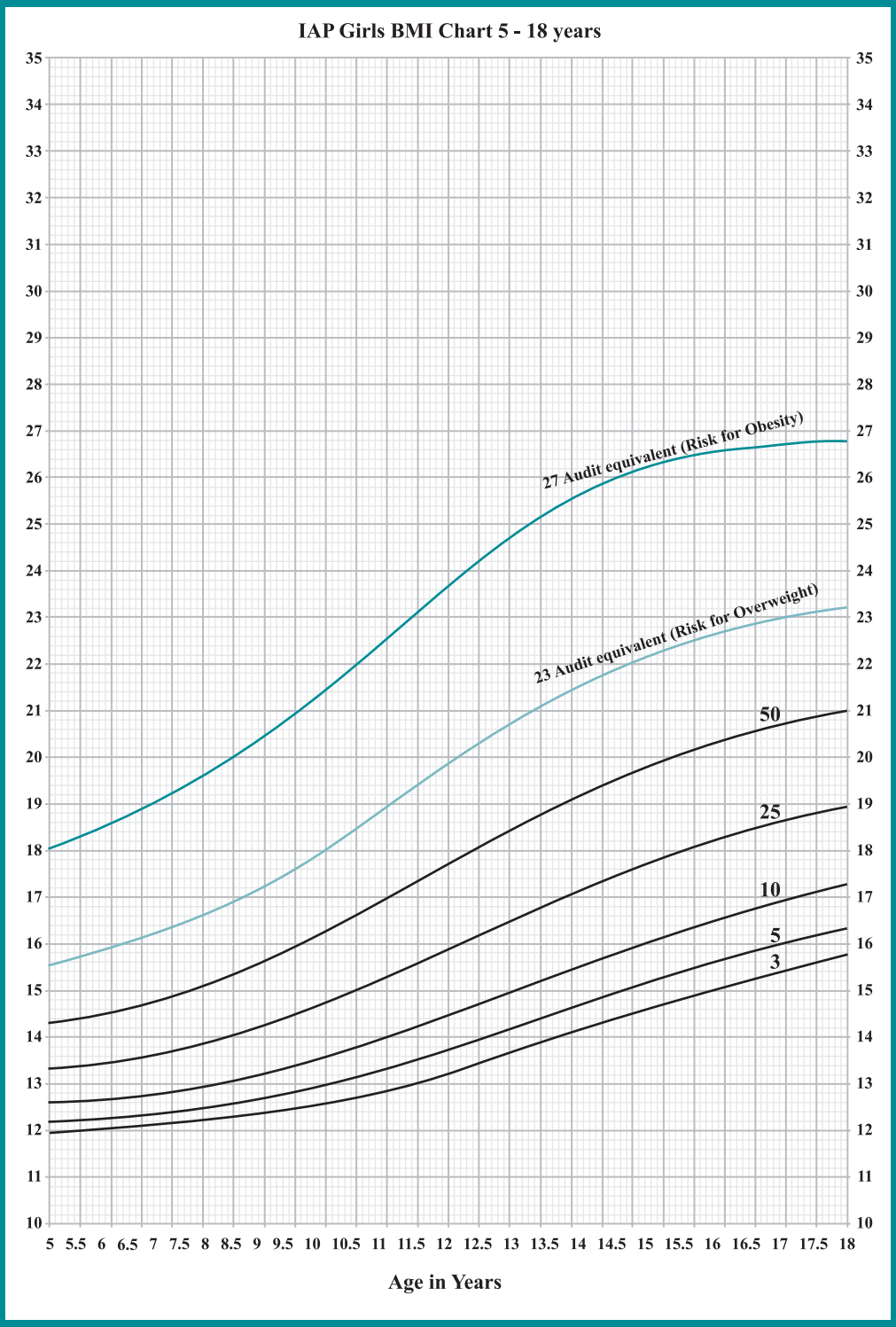
Revised IAP growth charts for height weight & body mass index for 5 to 18 year old Indian children.
V. Khadilkar et al. from Indian Academy of Pediatrics Growth Chart Committee Indian Pediatrics. Jan 2015, volume 52

Annexure 20: IAP Girls BMI chart 5-18 years

5 to 18 Years : IAP Girls Body Mass Index Charts

Name _____

DOB _____



Revised IAP growth charts for height weight & body mass index for 5 to 18 year old Indian children.
V. Khadilkar et al. from Indian Academy of Pediatrics Growth Chart Committee Indian Pediatrics. Jan 2015, volume 52

Annexure 21: Safe Preparation of Formula / Animal Milk and the amount of milk the child will need at different ages

- Wash your hands with soap and water before preparing a feed.
- Use clean utensils for preparation of feed.
- Use suitable infant formula reconstituted as per manufacturers recommendations/ undiluted animal milk with a cup (katori or katori and spoon). Remember cup or spoon feeding is safer than bottle-feeding. (Evidence suggests formula feed is nutritionally more suitable)
- Wash the utensils with soap and water

Animal milk feed	**Formula Feed**
• To prepare milk feed mix 1 level teaspoon of sugar in 1 cup boiled whole cow's milk. Give plain water (preferably boiled and cooled) to the infant between feeds	• Always use the marked cup or glass to measure water and the scoop to measure the formula powder as per manufacturer's recommendation • Measure the exact amount of powder that you will need for one feed. • Boil enough water vigorously for 1 or 2 seconds • Add the hot water to the powdered formula. The water should be added while it is still hot and not after it has cooled down. Stir well • Only make enough formula for one feed at a time. Do not keep milk in a thermos flask because it will become contaminated quickly • Demonstrate and let the mother show mixing of correct amounts of water and formula powder

Table showing the amount of milk the child will need at different ages:

Age	**Approximate amount of milk in 24 hours**	**Approximate number of feeds**
0-4 weeks	200-500 mL	8 x 60 mL
1 up to 2 months	650 mL	7 x 90 mL
2 up to 3 months	750 mL	6 x 120 mL
3 up to 4 months	750 mL	6 x 120 mL
4 up to 5 months	900 mL	6 x 150 mL
5 up to 6 months	900 mL	6 x 150 mL

Annexure 22: IMNCI guidelines on feeding recommendations for children

Table showing the amount of milk the child will need at different ages:

Up to 6 months	6 to 12 months	12 months – 2 years	2 years and older
Breast feed as often as the child wants, day and night, at least 8 times in 24 hours Do not give any other foods or fluids not even water	Breast feed as often as the child wants Give at least one Katori serving* at a time: Mashed roti / rice / bread / biscuit mixed in sweetened undiluted milk OR Mashed roti / rice / bread mixed in thick dal with added ghee / oil or khichri with added oil / ghee. Add cooked vegetables also in the servings OR Sevian / dalia / halwa / kheer prepared in milk or any cereal porridge cooked in milk OR Mashed boiled/fried potatoes *3 times per day if breast fed; 5 times per day if not breast fed	Breast feed as often as the child wants Offer food from the family pot Give at least 1½ Katori serving* at a time of: Mashed roti / rice / bread mixed in thick dal with added ghee / oil or khichri with added oil / ghee. Add cooked vegetables also in the servings OR Mashed roti / rice / bread / biscuit mixed in sweetened undiluted milk OR Sevian / dalia / halwa / kheer prepared in milk or any cereal porridge cooked in milk OR Mashed boiled/fried potatoes Also give nutritious food between meals, such as: banana/ biscuit/ cheeko/ mango/papaya as snacks *5 times per day	Give family foods at 3 meals each day. Also, twice daily, give nutritious food between meals, such as: banana / biscuit cheeko / mango / papaya as snacks
Remember Continue breastfeeding if the child is sick	Remember Keep the child in your lap and feed with your own hands Wash you own and child's hands with soap and water every time before feeding	Remember Ensure that the child finishes the serving Wash your child's hands with soap and water every time before feeding	Remember Ensure that the child finishes the serving Teach your child wash his hands with soap and water every time before feeding

Annexure 23: Age related food intake standards for children

Age Related Milk and Food Standards	Milk Toned (ml)	Food Cooked	Approximate Calories
6 – 11 Months	If BF, then frequently or on demand If not BF, then 500 mL Milk	If BF, give ½ K Cereals 3 times/day If not BF, give½ K Cereals 5 times/ day +½ K Vegetable +½ K Dal + ½ Egg*	645 Kcal (If not BF)
12 - 23 Months	500 mL	1 K Cereals 3 – 4 times/day +3/4 K Vegetable + 3/4 K Dal + 1 Egg*	925 - 1000 Kcal
2 – 5 Years	500 – 750 mL	6 – 8 Cereal Exchanges/day +1 K Vegetable +1 K Dal + 1 Egg*	1100 – 1250 Kcal
5 – 9 Years	500 – 750 mL	8 – 10 Cereal Exchanges / day +2 K Vegetable +2 K Dal + 1 Egg*	1350 – 1650 Kcal
10 – 14 Years	500 – 750 mL	12–14 Cereal Exchanges / day +3 K Vegetable +2 K Dal + 2 Eggs*	2000 – 2200 Kcal

BF: Breastfeeding

1 K = 1 Medium Size Katori = 150 mL

1 Egg = 2 pcs (30g) Non-Veg or 3O g Paneer or 100 g curd

Cereal Exchange List	
Exchange of Cereal	1 Chapatti (20gm), 1 Bread Slice, ½ K khichri, ½ K Suji Kheer ½ K Rice, ½ K Upma, ½ K Poha, ½ K Dalia, ½ K Vermicelli 1 medium Idli, 8 ml Oil, 100 gm Fruit, ½ small potato 2 Sweet biscuits, 3 Salty Biscuits

*If Vegetarian then substitute egg with milk product

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India's Voice Against HIV

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