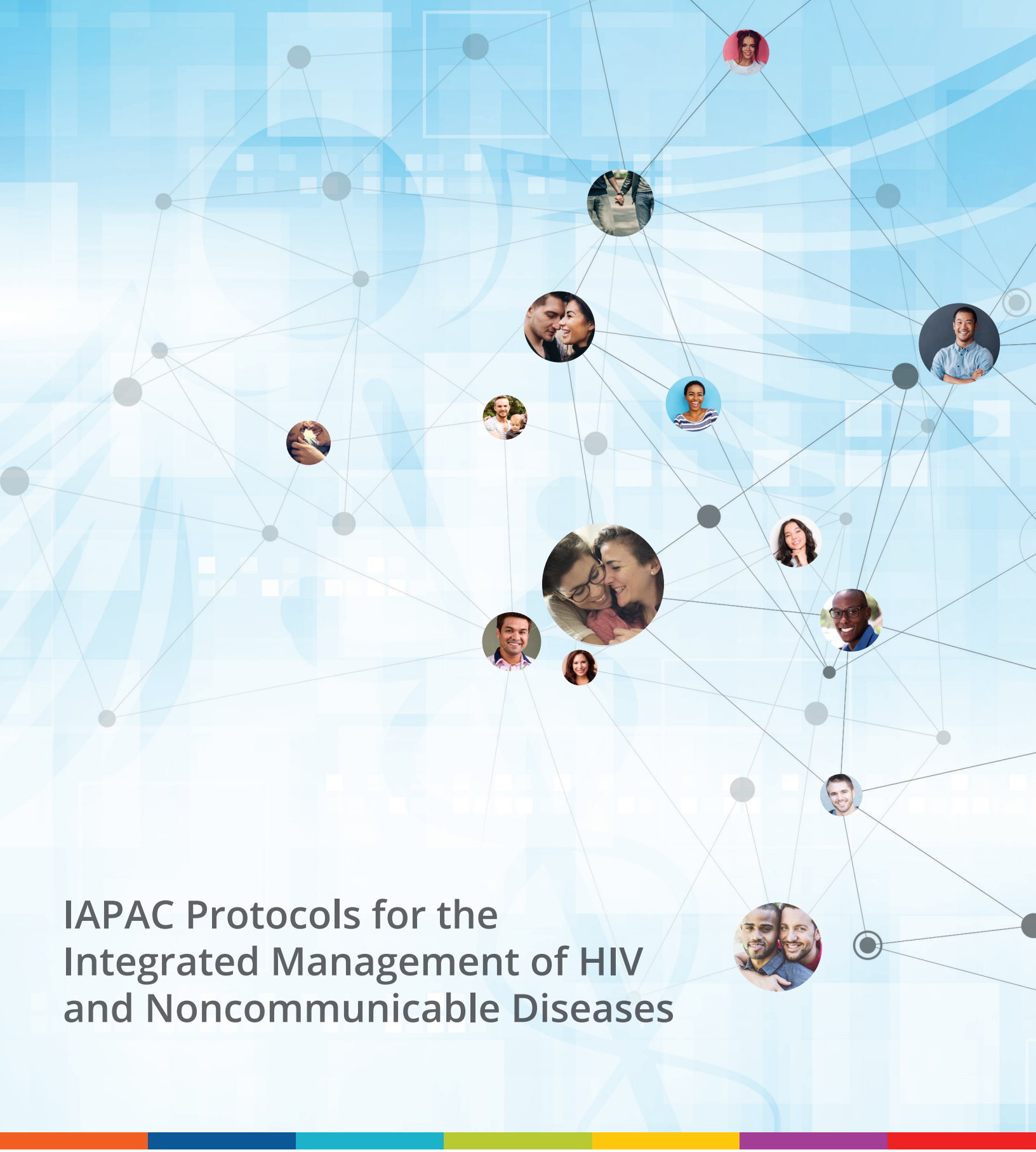


IAPAC Protocols for the Integrated Management of HIV and Noncommunicable Diseases

IAPAC
INTERNATIONAL ASSOCIATION OF PROVIDERS OF AIDS CARE

JULY 2018

CONTENTS

ABBREVIATIONS

ACE-inhibitor angiotensin converting enzyme-inhibitor
ARB angiotensin receptor blocker
AIDS acquired immunodeficiency syndrome
ART antiretroviral therapy
ARV antiretroviral
ATV atazanavir
AZT azidothymidine
BMI body mass index
BP blood pressure
CCB calcium channel blocker
CDC United States Centers for Disease Control and Prevention
CIN cervical intraepithelial neoplasia
CKC cold knife conization
CKD chronic kidney disease
CNS central nervous system
COPD chronic obstructive pulmonary disease
CVD cardiovascular disease
d4T stavudine
DRV darunavir
DTG dolutegravir
EFV efavirenz
eGFR estimated glomerular filtration rate
FDC fixed-dose combination
FEV1 forced expiratory volume in 1 second
FPG fasting plasma glucose
FTC emtricitabine
HbA1c (A1c) glycated hemoglobin
HDL high-density lipoprotein
HIV human immunodeficiency virus
HPV human papillomavirus
IDF International Diabetes Federation
LDL low density lipoprotein
LEEP loop electrosurgical excision procedure (also LLETZ)
LLETZ large loop excision of the transformation zone (also LEEP)
LMICs Low- and middle-income countries
LPV lopinavir
MG Methods Group
mhGAP WHO Mental Health Gap Action Program
MNCH maternal, newborn and child health
NCD noncommunicable disease
NNRTI non-nucleoside reverse-transcriptase inhibitor
NRTI nucleoside reverse-transcriptase inhibitor
NVP nevirapine
OI opportunistic infection
Pap test Papanicolaou test (cytology-based method for cervical cancer screening)
PCP Pneumocystis jirovecii pneumonia
PEF peak expiratory flow
PEFR peak expiratory flow rate
PEN Package of Essential NCD interventions
PEPFAR (President's Emergency Fund for AIDS Relief)
PI protease inhibitor
PLHIV people living with HIV
PHCW primary care health workers
RCT randomized controlled trial
RTV ritonavir
STI sexually transmitted infection
TAF tenofovir alafenamide
TB tuberculosis
TDF tenofovir disoproxil fumarate
UNAIDS Joint United Nations Program on HIV/AIDS
US FDA United States Food and Drug Administration
VIA visual inspection with acetic acid
WHO World Health Organization

INTRODUCTION

Non-communicable diseases (NCDs), including hypertension, cardiovascular disease, renal disease, cancer, chronic respiratory disease, diabetes, and mental health disorders account for 63% of global deaths.[1] Low- and middle-income countries (LMICs) bear 86% of the NCD burden.[1] In many of these countries, access to NCD care and treatment remains limited due to a lack of prevention and treatment guidelines, few trained providers at the primary care level and lack of access to essential diagnostics and medications to treat NCDs. [2, 3] However, some countries, such as Kenya, have produced comprehensive guidelines for the pharmacological and non-pharmacological management of NCDs in their National HIV guidelines. [15]

WHY PROVIDE INTEGRATED HIV/NCD SERVICES

Widespread access to combination antiretroviral therapy means that people living with HIV (PLHIV) can now live near-normal life spans and are facing different health challenges. Non-communicable diseases in PLHIV result from a mix of chronic immune activation, medication side effects, coinfections, and the aging process itself. [15] Although traditional risk factors for cardiovascular disease ([CVD]; diabetes, hypertension, hyperlipidemia, and smoking) exist in PLHIV, evidence from epidemiological studies suggests a 50-100% increase in risk for CVD even after controlling for these factors. [16] Cardiovascular disease is now one of the leading causes of non-AIDS related morbidity and mortality in PLHIV. [16] The US President's Emergency Plan for AIDS Relief (PEPFAR) has called for the integration of HIV treatment into a health center and wellness approach, where PLHIV benefit from medical care that goes beyond HIV alone. [4] New differentiated service delivery models mean that up to 80% of PLHIV can be followed with fewer visits [4], potentially decongesting clinics and allowing more time for the management of more complex heath issues.

TARGET AUDIENCE

The *IAPAC Protocols for the Integrated Management of HIV and Noncommunicable Diseases* manual addresses the screening, prevention and control of common NCDs among PLHIV in resource-limited settings. The protocols' target audiences are healthcare workers and facility managers providing prevention, care and treatment services for PLHIV through HIV clinics and primary healthcare clinics. Additional guidance is provided for settings where more resources are available.

GUIDE FOR IMPLEMENTATION

This manual is intended to be read in conjunction with the accompanying *Integrated Management of HIV and Noncommunicable Diseases: IAPAC Guide for Implementation in Low-Resource Settings*, which provides information on the assessment of facility capacity, essential diagnostics and drugs, training, healthcare worker core competencies, and budget planning.

HOW TO USE THIS MANUAL

This manual uses a public health approach and employs evidence-based, simplified, algorithms, and a core set of medicines and essential technologies, contextualized for PLHIV. The algorithms are cross-referenced to tables and text in the protocols which refer the reader to more information. There are five protocols covering the integrated management of HIV and:

1. Hypertension and cardiovascular risk
2. Diabetes
3. Depression
4. Asthma and chronic obstructive pulmonary disease (COPD)
5. Cervical cancer

NOTE ON CERVICAL CANCER

While cervical cancer is caused by the human papillomavirus (HPV) and therefore has an infectious cause, the cancer is included in NCD guidelines produced by the World Health Organization (WHO) and is a priority NCD within PEPFAR's HIV/NCD project. [5, 6] Cervical cancer is included here for consistency with the WHO and PEPFAR, and because of the significant morbidity and mortality associated with cervical cancer in women and adolescent girls living with HIV and the critical need to link HIV and cervical cancer screening programs.

MEDICINES AND TECHNOLOGIES FOR INTEGRATED HIV/NCD MANAGEMENT

All medicines in the protocols are included in the WHO Model Essential Medicines list 2017. [7, 8] (Table 1) The essential technologies are included in the WHO *Prevention and Control of Noncommunicable Diseases: Guidelines for Primary Health Care in Low-Resource Settings*. [8] (Table 2)

TABLE 1: ESSENTIAL DIAGNOSTICS

Thermometer	
Stethoscope	
Sphygmomanometer	**Add when resources permit**
Measurement tape	Nebulizer
Weighing machine	Pulse oximeter
Peak flow meter	Lipid profile assay
Glucometer	Serum creatinine assay
Blood glucose test strips	Tuning fork
Urine protein test strips	Electrocardiograph
Urine ketone test strips	

TABLE 2: ESSENTIAL MEDICINES	
CLASS	**Included in the WHO Essential Medicines list (2017)**
Thiazide diuretic	Hydrochlorothiazide
Calcium channel blocker	Amlodipine
Beta-blocker	Bisoprolol (includes atenolol, metoprolol and carvedilol as alternatives)
Angiotensin converting enzyme inhibitor	Enalapril
Antidepressants	Amitriptyline Fluoxetine
Statin	Simvastatin
Oral hypoglycemic	Metformin Glibenclamide
Inhalations	Salbutamol Beclomethasone Ipatropium bromide
Steroids	Prednisolone
Xanthine	Theophylline

EVIDENCE SOURCES

The primary sources of evidence used in the preparation of these protocols are guidelines produced by the WHO for the management of NCDs in settings with limited resources. For the most part, these WHO guidelines are not contextualized for PLHIV. Exceptions are the WHO *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*, which provide some guidance on HIV/NCDs and the WHO guidelines for the screening and control of cervical cancer, which provide specific guidance for women and adolescent girls living with HIV. Table 3 summarizes the recommendations included in WHO *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*. [9] Other sources of evidence are listed in Table 4 and in the reference list of peer reviewed publications.

TABLE 3: RECOMMENDATIONS INCLUDED IN WHO CONSOLIDATED GUIDELINES	
HIV diagnosis	Assessment for major noncommunicable chronic diseases and comorbidities Screening for and managing mental health problems and substance use Nutritional assessment and counselling
Enrollment into care	Screening for and managing mental health problems and substance use Nutritional assessment and counselling Screening for cervical cancer
ART Initiation	Blood pressure measurement Serum creatinine and estimated and eGFR if starting tenofovir Screening for and managing mental health problems and substance use Nutritional assessment and counselling Screening for cervical cancer

Table 3: *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach - Second Edition [9]*

TABLE 3: RECOMMENDATIONS INCLUDED IN WHO CONSOLIDATED GUIDELINES	
Receiving ART	Serum creatinine and eGFR if taking tenofovir Screening for and managing mental health problems and substance use Nutritional assessment and counselling Screening for cervical cancer
Suspected treatment failure	Screening and management of mental health problems and substance use Nutritional assessment and counselling Screening for cervical cancer

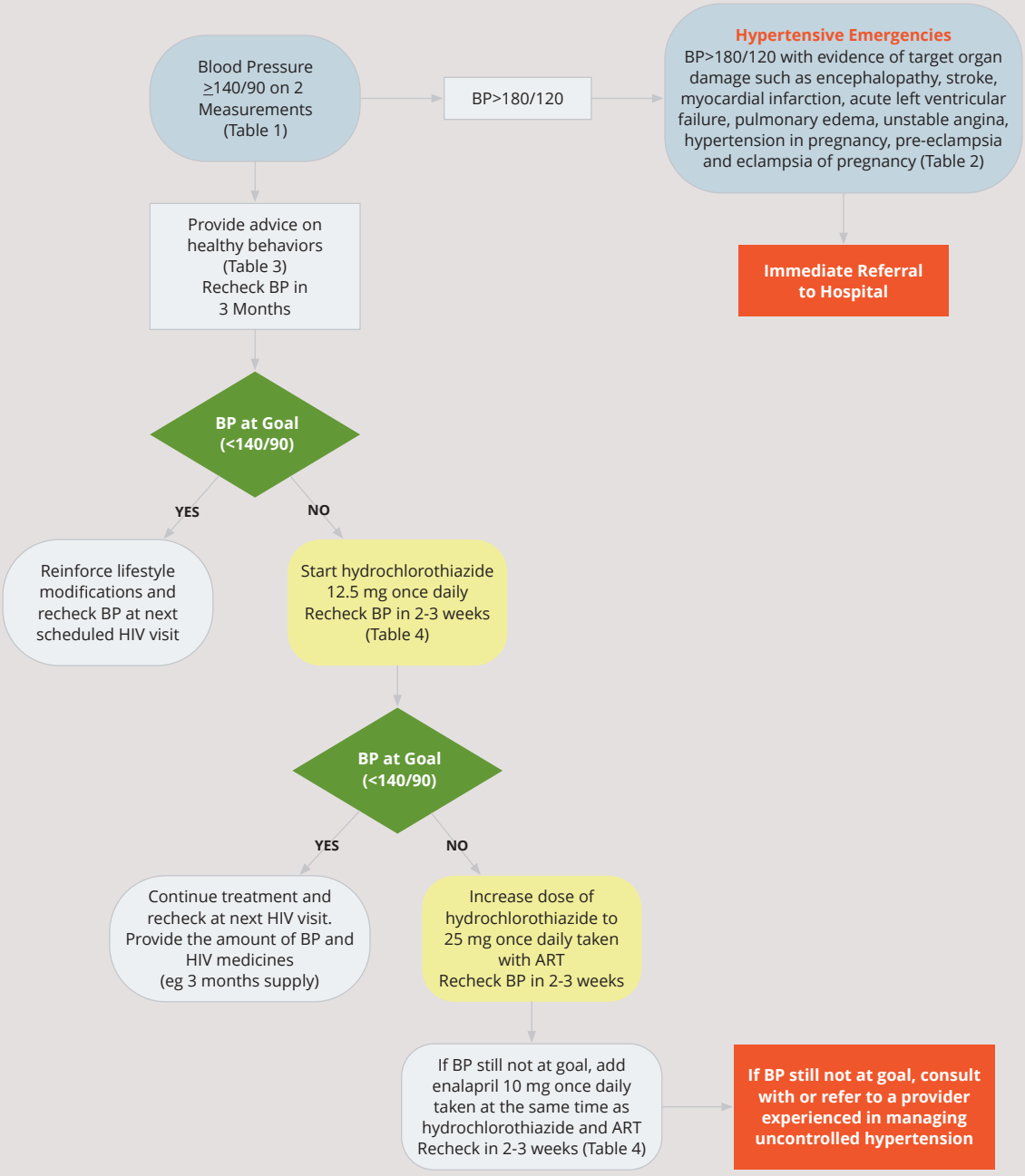
Table 3: *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach - Second Edition [9]*

TABLE 4: REFERENCE DOCUMENTS USED IN THE DEVELOPMENT OF THESE PROTOCOLS
Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach, 2nd Edition. 2016; World Health Organization
Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings. 2010; World Health Organization
Prevention and Control of Noncommunicable Diseases: Guidelines for Primary Health Care in Low-Resource Settings. 2012; World Health Organization
myHIVclinic.org. 2018; International Association of Providers of AIDS Care
Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya. 2016; National AIDS & STI Control Program
South African Hypertension Practice Guideline 2014; The Hypertension Guideline Working Group
Protocol for the Identification and Management of Hypertension in Adults in Primary Care. 2015; Ministry of Health, Kenya, and Healthy Heart Africa
Global Guideline for Type 2 Diabetes. 2012; International Diabetes Federation
Guideline for the Management of Type 2 Diabetes; Chapter 25 HIV and Diabetes: The Society for Endocrinology, Metabolism and Diabetes of South Africa 2017
Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention. 2013; World Health Organization
Comprehensive Cervical Cancer Control: A Guide to Essential Practice, Second Edition. 2014; World Health Organization
A Practical Manual on Visual Screening for Cervical Neoplasia: Testing and Reporting the Results of Visual Inspection with 5% Acetic Acid (VIA). 2018; World Health Organization
mhGAP Intervention Guide for Mental, Neurological, and Substance Use Disorders in Non-Specialized Health Settings, Version 2.0. 2016; World Health Organization Mental Health Gap Action Program (mhGAP)
Priority Interventions HIV/AIDS Prevention, Treatment, and Care in the Health Sector. 2010; World Health Organization
hiv-druginteractions.org. 2017; University of Liverpool
The Peak Flow Meter and its Use in Clinical Practice. 2011; *African Journal of Respiratory Medicine*

PROTOCOL 1:

INTEGRATED MANAGEMENT OF HIV, HYPERTENSION, AND CARDIOVASCULAR RISK

ALGORITHM FOR DIAGNOSIS AND MANAGEMENT OF HYPERTENSION

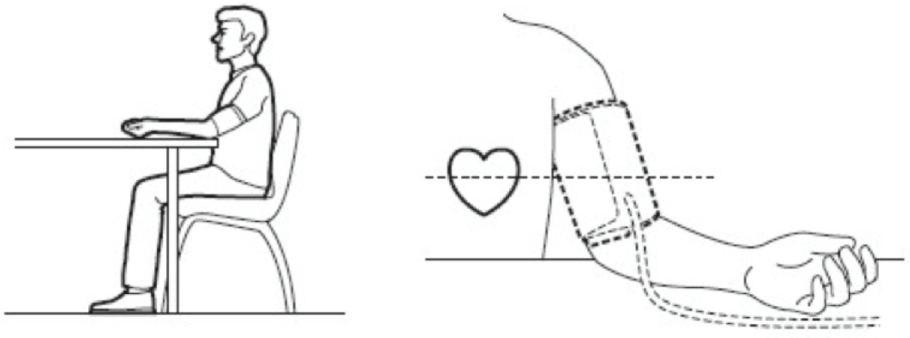


DEFINITION

Hypertension is defined by the WHO as a systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg on two measurements.[10]

MEASUREMENT OF BLOOD PRESSURE

TABLE 1: TECHNIQUE



- Patient should be seated, back supported, arm bared, and arm supported at the heart level
- Allow patient to sit quietly for 3-5 minutes before commencing measurement
- Patients should not have smoked or ingested caffeine beverages in the previous 30 minutes
- Use correct size cuff
- Lower edge of the cuff should be placed 3 cm above the inner crease of the elbow
- Cuff bladder should be centered over the brachial artery (approximately midway between the shoulder and the elbow crease)
- Take two readings 1-2 minutes apart. If consecutive readings differ by >5 mm, take additional readings

HYPERTENSION AND HIV

Infection with HIV and some antiretrovirals (ARVs) are risk factors for hypertension and CVD.[11] There is no association between hypertension and HIV disease severity or duration of HIV infection.[12] All PLHIV should be screened for other risk factors for hypertension such as tobacco smoking, obesity, physical inactivity, and unhealthy diet. People with any risk factor identified should be advised to modify their lifestyle. Screening for hypertension should form part of the regular assessment for all PLHIV who should have their blood pressure assessed at HIV diagnosis, before beginning antiretroviral therapy (ART) and every year after ART initiation.[11, 13] The clinical management of hypertension in PLHIV is similar to the general population with the exception of clinically important drug interactions between antihypertensives and ARVs. (table 6)

SCREENING

The WHO recommends assessment for major NCDs and comorbidities, including hypertension, at HIV diagnosis or initiation of ART. [9] There are no WHO recommendations on the frequency of repeat blood pressure testing in PLHIV. The US Prevention Services Task Force recommends annual screening for adults aged 40 years or older and for those who are at increased risk for high blood pressure including smokers, those with obesity, physical inactivity, excessive alcohol intake, family history, or high-risk ethnicity. [14] Data from the Framingham Heart Study in the general population support an annual blood pressure check.[15]

HYPERTENSIVE CRISES

TABLE 2: HYPERTENSIVE EMERGENCIES AND URGENCIES [16]	
Hypertensive emergencies	• BP >180/120 mm Hg with evidence target organ damage such as: ◦ hypertensive encephalopathy, intracranial hemorrhage, stroke, acute myocardial infarction, acute left ventricular failure with pulmonary edema, unstable angina pectoris, acute renal failure, pre-eclampsia or eclampsia of pregnancy • Requires immediate reduction of BP to limit target organ damage • Refer immediately for intravenous therapy
Hypertensive urgency	• BP >180/120 mm in an otherwise stable patients without acute or impending change in target organ damage or dysfunction. • Manage according to treatment algorithm

HEALTH EDUCATION AND COUNSELING ON HEALTHY BEHAVIORS

PRACTICE POINT

Low-dose thiazide has no drug interactions with any ARVs, are taken once daily, and are readily available and inexpensive and included in the WHO Essential Medicines list. ACE inhibitors also do not interact with ARVs. Calcium channel blockers and beta-blockers have interactions with ARVs.

Risk factors for hypertension include tobacco smoking, diabetes, obesity, sedentary lifestyle, family history of hypertension, and older age.[17] Lifestyle modifications are the first step in the prevention and control of hypertension. (Table 3) These are also recommended for all patients to prevent cardiovascular disease and should be integrated into routine HIV care and treatment.[18]

TABLE 3: HEALTHY BEHAVIORS	
Behavior	**Advice**
Educate	• Engage in regular physical activity • Eat a heart healthy diet, low in saturated fat • Stop tobacco use and avoid harmful use of alcohol • Attend regular medical follow-up
Physical activity	• Engage in moderate levels of physical activity (e.g., walking at least 150 minutes per week) • Reduce and control body weight by reducing high calorie food intake
Tobacco	• Encourage all non-smokers not to start smoking • Strongly advise all smokers to quit smoking and support them in their efforts
Harmful use of alcohol	• See Figure 1 below
Eat a heart healthy diet	• Restrict salt to less than 5 grams (1 teaspoon) per day • Fatty food: Limit fatty meat, dairy fat, and cooking oil • Eat a diet high in fruits and vegetables

TABLE 3: HEALTHY BEHAVIORS	
Behavior	**Advice**
Adherence counselling	If the person is prescribed medication: • Explain the difference between medicines for long- term control (e.g., blood pressure) and medicines for quick relief (e.g., headache) • Explain the dose and how many times a day to take the medication • Explain how to take with ARVs • Label and package the medication • Explain the importance of keeping an adequate supply of medications and the need to take the medicines regularly as advised even if there are no symptoms

Figure 1: *Low-Risk Drinking Limits (Source: US National Institutes of Health) [19]*

ANTIHYPERTENSIVE THERAPY

Antihypertensive therapy for uncomplicated hypertension and irrespective of HIV status is either mono- or combination therapy with a low-dose thiazide diuretic (12.5 mg hydrochlorothiazide or equivalent), a calcium channel blocker (CCB) an angiotensin converting enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB), or beta-blocker.[20] These different classes of antihypertensives produce similar reductions in blood pressure, can be combined and their antihypertensive effect is additive. [21] Diuretics are as effective as newer antihypertensive agents.[22] Higher doses of hydrochlorothiazide (>25mg per day) do not result in further reductions in blood pressure.[23] There is no difference in efficacy between hydrochlorothiazide and other thiazides. [24] Introduce one drug at a time, starting at the lowest dose, and allow 2-3 weeks to achieve maximal effect before titrating dosage up. Titrate to maximum dosage before adding an additional drug. If inadequate response (goal BP <140/90) once dose has been titrated, add a second drug starting at the lowest dose and titrate to the maximum dose. Fixed-dose combinations (FDCs) improve adherence. If there is inadequate response to two agents, consider consultation with or referral to a provider experienced in the management of refractory hypertension.[25] Evaluate and control cardiovascular risk factors and provide patient education and advice on lifestyle modification.

TABLE 4: ANTIHYPERTENSIVE DRUGS
Source: *Prevention and Control of NCDs: Guidelines for Primary Health Care in Low-Resource Settings* WHO and US Food and Drug Administration (FDA) Pregnancy Classification

Class	Drug	Daily dose (mg)	Side effects	Pregnancy class.[2]
Thiazide diuretics	Hydrochlorothiazide EML	12.5-25	Gout Muscle cramps	B
	chlorothiazide	500-1000		
	trichloromethiazide	1-4		
Thiazide-like diuretics[1]	chlorthalidone	25-100		B
ACE inhibitors	Enalapril EML	5-40	Dry cough	D (Do not use)
	lisinopril	10-20		
	ramipril	2.5-20		
	captopril	50-100		
	perindopril	2-4		
Calcium Channel blockers	Amlodipine EML	5-40	Edema Flushing Palpitations	D
Beta blockers	atenolol	50-100	Asthma Heart block	D (Do not use)
	Bisoprolol EML	5-20		C
	propranolol (long acting)	80-120		C

1. A thiazide-like diuretic is a sulfonamide diuretic that has similar properties to a thiazide diuretic
2. A. No known risk B. No known risk in humans C. Insufficient evidence D. Known risk and do not use

EML: Included in the WHO Model Essential Medicines list, 2017

TREATMENT IN SPECIAL POPULATIONS

In people living with diabetes, the WHO recommends thiazides or ACE inhibitors as first-line therapy.[26] Beta-blockers are not recommended for initial management of hypertension in diabetic patients.[26]

INTERACTIONS BETWEEN ANTIHYPERTENSIVES AND ARVS

There are no interactions between thiazide diuretics and ACE inhibitors and ARVs. (Table 4) Drug levels of calcium channel blockers and beta-blockers are increased in the presence of protease inhibitors (PIs) and decreased in the presence of non-nucleoside reverse transcriptase inhibitors (NNRTIs). Dose adjustment of the antihypertensive agent may be required. Drug levels of ARVs are not affected by calcium channel blockers or beta-blockers and no dose adjustment is required.

TABLE 5: DRUG INTERACTION TABLE
Source: University of Liverpool, hiv-druginteractions.org

Antihypertensive	TDF/ TAF	AZT	3TC	FTC	EFV	NVP	DTG	LPV/r	ATV/r	DRV/r
Hydrochlorothiazide										
amlodipine					⬇	⬇		⬆	⬆	⬆
enalapril										
bisoprolol*					⬇	⬇		⬆	⬆	⬆

*WHO Essential Medicines list includes atenolol, metoprolol, carvedilol as alternatives

No interaction

Potential interaction with increased or decrease levels of antihypertensives which may require dose adjustment. Drug levels of ARVs are not affected by calcium channel blockers or beta-blockers and no dose adjustment is required.

Caution should also be exercised when administering B blockers and PIs due to the risk of QT prolongation. **ECG monitoring is recommended.**

⬆ Increase in antihypertensive drug level ⬇ Decrease in antihypertensive drug level

WHO CAN SCREEN FOR, DIAGNOSE, AND TREAT HYPERTENSION?

Any trained healthcare worker can screen for, diagnose, and treat uncomplicated hypertension. In addition to training, simple algorithm-based guidelines, a limited choice of standardized antihypertensives, and clear referral criteria form the basis of management at the primary care level.

WHO NEEDS ROUTINE CONSULTATION WITH OR REFERRAL TO AN EXPERIENCED PROVIDER?

Patients with severe hypertension (BP ≥180/110 mmHg) should be managed at the appropriate level of care and caregiver in accordance with local resources. Patients with blood pressure not at goal following the initiation and dose increases of two antihypertensive medications to the maximum recommended dose should be referred to a provider experienced in the management of refractory hypertension.[27]

WHO NEEDS IMMEDIATE REFERRAL

Patients with BP >180/120 with evidence of target organ damage such as encephalopathy, stroke, myocardial infarction, acute left ventricular failure or pulmonary edema [28]; unstable angina; or pre-eclampsia and eclampsia of pregnancy need immediate referral.

IF RESOURCES PERMIT

TABLE 6: ADDITIONAL INVESTIGATIONS AS INDICATED BY CLINICAL HISTORY AND PHYSICAL EXAMINATION
These investigations are not essential to treat hypertension and should not delay treatment if they are not available [27, 29]

Test	Comment
Fasting glucose	Assessment for diabetes Normal fasting glucose (6.1–7.1 mmol/l) Consider HBA1c or GTT if impaired
Lipids	Assessment of other CVD risk factors to guide interventions
Electrolytes	Low potassium may indicate primary aldosteronism or effects of diuretics
Urinalysis	Microalbuminuria is an early indication of diabetic nephropathy and a marker for a higher risk of cardiovascular morbidity and mortality
Thyroid stimulating hormone (TSH)	Excludes hypothyroidism or hyperthyroidism as a cause of hypertension
Echocardiography (ECG)	Evaluation for end-organ damage such as left ventricular hypertrophy

CARDIOVASCULAR RISK

In addition to hypertension, other risk factors for CVD are obesity, increased waist circumference, smoking, diabetes, and a history of premature CVD in a first-degree relative.

TABLE 7: BMI AND WAIST CIRCUMFERENCE

Height, weight BMI (weight divided by height)	Ideal BMI <25 kg/m^2, overweight 25-30 kg/m^2, obese >30 kg/m^2
Waist circumference	Ideal: Men <102 cm; women <88 cm

TABLE 8: CVD RISK ASSESSMENT

Ask about	• Previously diagnosed heart disease, stroke, diabetes, kidney disease • Any angina, breathlessness on exertion and lying flat, numbness or weakness of limbs, loss of weight, increased thirst, polyuria, puffiness of face, swelling of feet, passing blood in urine • Medicines that the patient is taking • Current tobacco use • Alcohol consumption (Figure 1) • Occupation (sedentary or active) • Any physical activity • History of premature heart disease or stroke in first degree relatives
Assess	• Waist circumference • Measure blood pressure • Examine for pitting edema • Auscultate heart (rhythm and murmurs) • Auscultate lungs (basal crepitations) • Examine abdomen (tender liver) • In diabetic patients examine feet; sensations, pulses, and ulcers • Urine ketones (in those newly diagnosed with diabetes mellitus) and protein • Fasting or random blood glucose (diabetes = fasting blood glucose ≥7 mmol/l (126 mg/dl)) or random blood glucose ≥11.i mmol/l (200 mg/dl) • Total cholesterol (if available)

TABLE 9: CVD RISK MANAGEMENT	
Advice	• Healthy behaviors; diet, physical activity, smoking cessation, and avoiding harmful use of alcohol (Table 3)
Treat	• Hypertension (Protocol 1) • Diabetes (Protocol 2) • Treatment with statins is recommended for all patients with established CVD • Simvastatin is the only statin on the WHO Essential Medicines list but is contraindicated with protease inhibitors; see Table 10 for alternatives • Treatment should be continued in the long term, probably lifelong • Monitoring of blood cholesterol levels is not mandatory • Goals ◦ Total cholesterol <4.0 mmol/l (152 mg/dl) and ◦ LDL-cholesterol <2.0 mmol/l (77 mg/dl) • Lipid-lowering agents other than statins are not recommended • Patients with established coronary heart disease or transient ischemic attack should be treated with regular low dose (81 mg) aspirin in the absence of clear contraindications • Treatment should be lifelong

TABLE 10: DRUG INTERACTION TABLE
Source: University of Liverpool, hiv-druginteractions.org

Antihypertensive	TDF/ TAF	AZT	3TC	FTC	EFV	NVP	DTG	LPV/r	ATV/r	DRV/r
Simvastatin					⬇	⬇				
Lovastatin					⬇	⬇				
Fluvastatin					⬇				⬆	
Pravastatin					⬇	⬇			⬆	⬆
Atorvastatin					⬇	⬇		⬆	⬆	⬆
Pitavasatin									⬆	

*WHO Essential Medicines list includes atenolol, metoprolol, carvedilol as alternatives

No interaction

Potential interaction

Co-administration is contraindicated due to potential for serious reactions such as risk of myopathy including rhabdomyolysis.

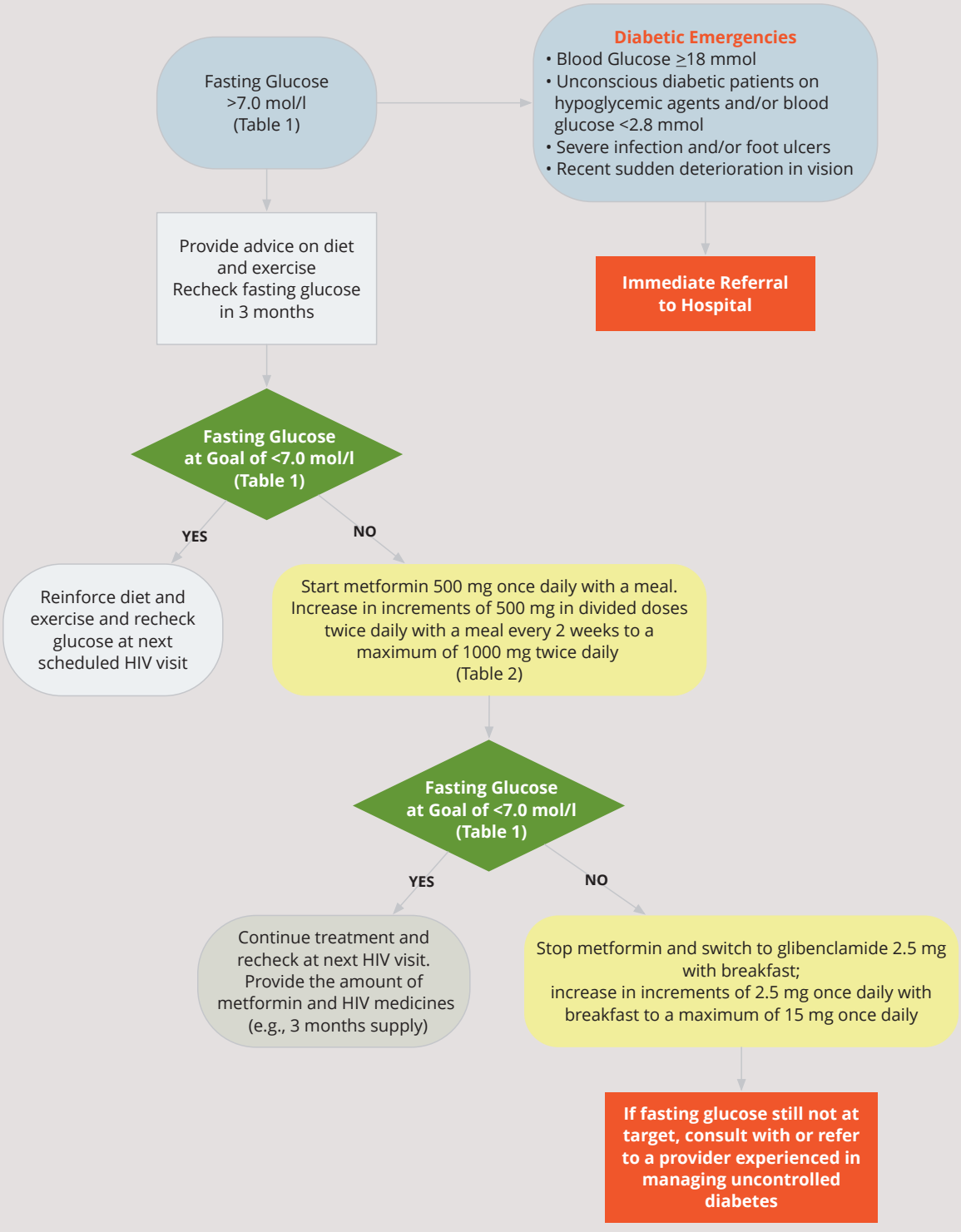
⬆ Potential decrease in statin drug level which may require an increased dose adjustment of statin

⬇ Titrate dose of statin carefully and use lowest dose necessary

PROTOCOL 2:

INTEGRATED MANAGEMENT OF HIV AND TYPE 2 DIABETES

ALGORITHM FOR THE DIAGNOSIS AND MANAGEMENT OF TYPE 2 DIABETES



CLASSIFICATION OF DIABETES

- Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (progressive insulin secretory defect on the background of insulin resistance)
- Diabetes diagnosed in pregnancy (overt or gestational diabetes)
- Diabetes due to other causes (genetic defects, cystic fibrosis, some ARVs, post-organ transplantation) [30]

SYMPTOMS OF DIABETES

- Unusual thirst
- Frequent urination
- Extreme hunger
- Unusual weight loss or weight gain
- Extreme fatigue
- Frequent infections
- Blurred vision
- Tingling or numbness in the hands and feet
- Slow healing of cuts or bruises
- People with type 2 diabetes may have no symptoms for many years [31]

INTERNATIONAL AND NATIONAL GUIDELINES

The WHO has produced has produced guidelines for the integration of the management of type 2 diabetes into the primary care setting. The International Diabetes Federation's *Global Guideline for Type 2 Diabetes* (2012) provides guidance stratified according to the three levels of care; standard of care, care limited by resource constraints, and comprehensive and complete range of health technologies. Neither of these guidelines are HIV-specific. The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMSDA) has produced *Guidelines for the Management of Type 2 Diabetes* (2017) that contains a chapter dedicated to HIV and diabetes.[32]

DIABETES AND HIV

PREVALENCE

The prevalence of diabetes in PLHIV has been reported as 2-14%, with data coming from European, North American, and African cohorts. [33-36] Variations are related to how diabetes was diagnosed and the ethnic composition of the cohort. There is conflicting evidence on whether HIV is an independent risk factor for diabetes with some studies reporting an increased risk of diabetes in PLHIV and some showing no association.[37]

RISK FACTORS

As in the general population, traditional risk factors such as age, BMI, and genetic predisposition play a role in the development of diabetes in PLHIV. Associations between some ARVs and type 2 diabetes have been reported.[38, 39] Associations are more common with older ARVs such as stavudine (d4T), didanosine (ddI), zidovudine (ZDV), indinavir (IDV), and lopinavir (LPV) and less common with tenofovir (TDF), emtricitabine (FTC), and lamivudine (3TC), darunavir (DRV), and atazanavir (ATZ). [32, 40] HIV infection, through inflammatory mediators, can induce a state of insulin resistance. Coinfection with hepatitis C virus (HCV) increases the risk of type 2 diabetes in PLHIV. [32]

DIAGNOSIS

The diagnosis and management of diabetes is included in the WHO list of priority interventions for HIV prevention, treatment, and care in the health sector. [3] The criteria for the diagnosis of diabetes in PLHIV are the same as the general population with one caveat. It has been reported that HbA1c levels underestimate glycemic levels by 10% to 15% in PLHIV. [41-43] HbA1c is the percentage of glycated hemoglobin and reflects long-term glucose status.

TREATMENT AND TREATMENT OUTCOMES

In the absence of treatment strategies specific to PLHIV, current international and national guidelines for the general population serve as the guiding tool for treatment of diabetes in PLHIV. [2] Recommendations specific to PLHIV relate to drug interactions between ARVs and anti-diabetes medication and the use of HbA1c for screening and diagnosis of diabetes. People living with HIV have the same response to treatment as their HIV non-infected counterparts. [8, 9]

SCREENING AND DIAGNOSIS

TABLE 1: SCREENING AND DIAGNOSIS
Diabetes can be diagnosed on any of the following WHO criteria

- Fasting plasma glucose (FPG) ≥7.0 mmol/l (126 mg/dl)
- Random plasma glucose ≥11.1 mmol/l (200 mg/dl) in the presence of classical diabetes symptoms
- 75 g oral glucose tolerance test (OGTT) with FPG ≥7.0 mmol/l (126 mg/dl) and/or 2-hour plasma glucose ≥11.1 mmol/l (200 mg/dl)
- Glycated hemoglobin (HbA1c) ≥6.5%

Type 2 diabetes has a long asymptomatic phase which frequently goes undetected.[44] Screening, early detection, and intervention is one strategy for reducing the complications of type 2 diabetes which result in reduced quality of life and premature mortality. [44]

Diabetes is diagnosed by measurement of plasma glucose in a blood sample with a fasting plasma glucose level of ≥7.0mol/l (126 mg/dl). [8, 45] Diabetes can also be diagnosed by a HBA1C level ≥6.5%, a 2-hour post-oral glucose tolerance test glucose level 2-hour plasma glucose ≥11.1 mmol/l (200 mg/dl) or a random plasma glucose ≥11.1 mmol/l (200 mg/dl) in the presence of classical diabetes symptoms. [44]

Fasting capillary glucose (finger prick) is likely to be the most feasible measurement in low-resource settings. [46] Fasting values for venous and capillary plasma glucose are identical. Point-of-care blood glucose meters can be used in diagnosing diabetes if laboratory services are not available. [8]

The International Diabetes Federation (IDF) *Global Guidance for Type 2 Diabetes* recommends that visually read glucose test strips have a role in limited care situations where blood glucose meters are not available.[44] The IDF further recommends that, if blood glucose testing is not available in limited care settings, the presence of glycosuria, especially with classical symptoms, may be used to diagnose diabetes. [44]

SCREENING FOR DIABETES IN PLHIV

Screening to detect type 2 diabetes and assess risk for future diabetes is the same for those with and without HIV infection, with the exception of the caveat around the use of HbA1C (see above). Screening should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m^2) and who have one or more additional risk factors for diabetes: physical inactivity, family history, high-risk ethnicity, hypertension, and women with a history of gestational diabetes or the delivery of a baby weighing >4kg. [30, 47] In those without these risk factors, testing

should begin at age 45 years. [30] HIV-positive patients should be screened at HIV diagnosis or before initiating ART and annually after that if initial screening was normal.[9, 32] Generally, people with type 1 diabetes present with acute symptoms of diabetes and markedly elevated blood glucose levels, and most cases are diagnosed soon after the onset of hyperglycemia. [30]

COLLECTION AND PROCESSING

Glucose should be measured immediately after collection of capillary blood by point-of-care testing, or if a blood sample is collected, plasma should be immediately separated, or the sample should be collected into a container with glycolytic inhibitors and placed in ice-water until separated prior to analysis.

DIET AND PHYSICAL ACTIVITY

The majority of persons with type 2 diabetes are overweight or obese, which further increases their risk of hyperglycemia, hyperlipidemia and hypertension.[48] Being overweight or obese is the main modifiable risk factor for type 2 diabetes. [49] Type 2 diabetes can also be prevented or delayed in persons at high risk by weight loss and increasing physical activity.[50] Overweight people should receive advice to reduce weight by reducing their food intake. Calorie guidelines for weight loss are 1,200-1,500 calories/day for women or 1,500-1,800 calories/ day for men or an energy deficit of 500 or 750 calories per day, based on the individual. Everyone should receive advice on regular daily physical activity appropriate for their physical capabilities (e.g., walking 30 minutes at least 5 days a week)

ORAL HYPOGLYCEMIC AGENTS

If glucose control is not achieved with lifestyle modification alone, oral hypoglycemic therapy should be initiated. Biguanides and sulfonylureas are recommended in resource-limited settings. [8, 46]

TABLE 2: ORAL HYPOGLYCEMIC AGENTS
Source: WHO mhGAP Intervention Guide Version 2.0 and US FDA full prescribing information

Class	Drug	Dose	Side effects	Pregnancy class.[1]
Biguanides	Metformin EML (standard release)	Start with 500 once daily, given with a meal; (breakfast or dinner) [51] Responses are generally not seen at doses <1,500 mg per day Dosage increases should be made in increments of 500 mg weekly every 2 weeks to achieve glycemic target of <7.0mol/l (126 mg/dl) or side effects lead to the interruption of therapy, up to a total of 1,000 mg per twice daily.[51] **(See warning below on the maximum recommended dose of metformin in PLHIV taking dolutegravir)**. A longer-acting formulation is available in some countries and can be given once per day.	Diarrhea Nausea/ Vomiting Flatulence Asthenia Indigestion Abdominal Discomfort Headache Lactic acidosis	B
Sulfonylureas	Glibenclamide EML	2.5-15	Hypoglycemia Weight gain	C
	Glipizide	2.5-20		
	Gliquidone	15-180		
	Gliclazide	40-320		
	Glimepiride	1-6		

A. No known risk B. No known risk in humans C. Insufficient evidence D. Known risk and do not use
EML: Included in the WHO Model Essential Medicines List 2017

BIGUANIDES

Type 2 diabetes is a progressive illness and the introduction of oral hypoglycemic agents will often be necessary in patients on diet treatment only, and the dosage further increased to improve glycemic control.[8]

Metformin, a biguanide, is the most commonly prescribed oral antihyperglycemic medication globally and is considered first-line therapy for persons with newly diagnosed type 2 diabetes, including PLHIV. [25, 32, 44, 52, 53] Metformin should be used with caution in PLHIV with renal insufficiency, liver disease, active infection including tuberculosis (TB), and those with cachexia (wasting) or congestive cardiac failure due to the risk of lactic acidosis induced by metformin. [54, 55] Metformin should not be used in conjunction with thymidine based NRTIs (d4T, ddI) as the risk of lactic acidosis is increased due to mitochondrial toxicity. Metformin should be co-administered with dolutegravir (DTG) with caution. (see *DTG and Metformin* below and Table 5)

Metformin should be discontinued during acute severe illness such as pneumonia, other severe infection, dehydration, or myocardial infarction.[8]

DTG AND METFORMIN

Coadministration of metformin (500 mg twice daily) with once-daily DTG increases metformin C_{max} and AUC by 66% and 79%, and coadministration with twice-daily DTG increases metformin C_{max} and AUC by 111% and 145%. [56] A dose adjustment of metformin should be considered when co-administering DTG with metformin in order to maintain glycemic control. [56] The US Prescribing Information recommends limiting the total daily dose of metformin to 1,000 mg when co-administered with DTG. [57] Monitoring renal function and blood glucose is recommended when metformin and DTG are coadministration. As metformin is eliminated renally, patients with moderate renal impairment may be at increased risk for lactic acidosis due to increased metformin concentrations.[57] (See table 5)

SULFONYLUREAS

Sulfonylureas should be prescribed to individuals who have contraindications to metformin, or in whom metformin does not improve glycemic control at the maximum tolerated metformin dose.[58] Glibenclamide is a second-generation sulfonylurea and the only sulfonylurea on the 2017 WHO Essential Medicine list. It is most likely to be available in low-resource settings. [8] As a precaution against severe hypoglycemia, glibenclamide should be started at a low dose of 2.5-5 mg once daily with breakfast and adjusted according to response to a maximum of 15 mg daily (46). The Society for Endocrinology, Metabolism, and Diabetes of South Africa (SEMSDA) guidelines recommend that glibenclamide should not be used at primary care level and that the sulphonylurea of choice should be gliclazide modified-release because it has equivalent efficacy compared to other sulphonylureas, consistently associated with lower rates of hypoglycemia and better cardiovascular and renal safety relative to other sulphonylureas.[32]

SWITCHING ART

A patient who develops diabetes while taking ARVs that is potentially diabetogenic, especially if on thymidine-based NRTIs (zidovudine, didanosine) and first-generation PIs (LPV, IDV), should be switched to a different ART regimen, if possible, comprised of ARVs with a safer metabolic profile such as DTG, TDF, ATZ, and DRV.

TABLE 3: DRUG INTERACTION TABLE
Source: University of Liverpool, hiv-druginteractions.org

Antihypertensive	TDF/ TAF	AZT	3TC	FTC	EFV	NVP	DTG	LPV/r	ATV/r	DRV/r
Metformin							⬆			
Glibenclamide					⬇	⬇		⬇	⬇	⬇
Glipizide					⬆			⬇	⬇	⬇
Gliquidone					⬆			⬇	⬇	⬇
Gliclazide					⬆			⬇	⬇	⬇
Glimepiride					⬆			⬇	⬇	⬇

*Essential medicines list includes atenolol, metoprolol, carvedilol as alternatives

No interaction

Potential interaction with increased or decrease levels of the sulfonylurea which may require dose adjustment of the sulfonylurea. Monitor blood glucose and adjust the sulfonylurea dosage as needed.

Caution should be exercised when coadministering metformin with DTG as metformin levels are increased and dose reduction of metformin should be considered. The US Prescribing Information recommends limiting the total daily dose of metformin to 1,000 mg when co-administered with DTG. **Renal monitoring is recommended as PLHIV with renal impairment are at increased risk of lactic acidosis due to increased metformin levels in the presence of DTG.**

⬆ Increase in antidiabetic agent level

⬇ Decrease in antidiabetic agent level

TABLE 4: MANAGEMENT STEPS Source: WHO PEN Protocol 1 [46]	
Step	**Key messages**
Lifestyle modification	• Advise overweight patients to reduce weight by reducing their food and calorie intake • Advise all patients to practice regular daily physical activity appropriate for their physical capabilities such as walking 30 minutes at least 5 days a week
Oral hypoglycemics	• Give metformin for type 2 diabetes if not controlled by diet and exercise • Titrate metformin to target glucose value (Fasting blood glucose <7 mmol/l) • Give a sulfonylurea to patients who have contraindications to metformin or if metformin does not improve glycemic control
Cardiovascular care	• Give an antihypertensive for those with BP ≥130/80 mmHg • If resources permit, give a statin to all with type 2 diabetes aged ≥ 40 years • Cease smoking
Foot care	• Give advice on foot hygiene, nail cutting, treatment of calluses, appropriate protective footwear: ◦ Avoid walking barefoot or without socks ◦ Wash feet in lukewarm water and dry well especially between toes ◦ Do not cut calluses or corns ◦ Look at your feet every day and if you see a problem or an injury, go to your healthcare worker • Assess feet using simple methods (inspection, pin-prick sensation, and peripheral circulation assessment by palpation of pedal pulses)
Eye care	• Check visual acuity annually • If possible, use direct fundoscopy through dilated pupils to assess retinopathy • Referral as needed
Referral	• Fasting plasma glucose or >14 mmol/l despite maximal doses of metformin and sulfonylurea • Individuals with newly diagnosed diabetes and urine ketones 2+ • Severe infection and/or foot ulcers • Recent deterioration in vision • Gestational diabetes • Blood pressure >130/80 mmHg despite treatment with 2 blood pressure lowering agents
Followup	• At visit coinciding with HIV care

ANTIHYPERTENSIVE TREATMENT

The target blood pressure in diabetic patients with and without HIV is ≤130/80mmHg.[8] It is ≤140/90mmHg in non-diabetic individuals. [59] Low-dose thiazides (12.5 mg hydrochlorothiazide or equivalent) or ACE inhibitors are recommended as first-line treatment of hypertension in diabetic patients. They can be combined. Beta-blockers are not recommended for initial management of hypertension in diabetic patients but can be used if thiazides or ACE inhibitors are unavailable or contraindicated.

GESTATIONAL DIABETES

Hyperglycemia first detected during pregnancy is classified as either diabetes in pregnancy/overt diabetes (fasting plasm glucose ≥7.0 mmol/l) or gestational diabetes (fasting plasm glucose ≥5.1-6.9 mmol/l). [60] Overt diabetes during pregnancy, whether symptomatic or not, is associated with significant risk of adverse perinatal outcomes. [60] Diabetes in pregnancy in an HIV-positive woman should be managed by an experienced provider.

SEVERE HYPOGLYCEMIA

Hypoglycemia (low blood glucose) is a frequent complication in diabetic patients receiving medication to lower blood glucose, particularly sulfonylureas. Severe hypoglycemia is defined as hypoglycemia where the patient is unable to self-treat [61]. It is corrected by oral ingestion of carbohydrates, if that is feasible, or parenteral glucose if not feasible. Unconscious diabetic patients on hypoglycemic agents and/or blood glucose ≤2.8 should be given intravenously 20-50ml of 50% glucose (dextrose) over 1- to 3-minute hypertonic glucose intravenously. Food should be provided as soon as the patient can ingest food safely.

HYPERGLYCEMIC EMERGENCIES

Diabetic ketoacidosis and hyperosmolar hyperglycemic state are life-threatening conditions that require treatment in hospital by experienced providers.

WHO CAN SCREEN FOR, DIAGNOSE, AND TREAT TYPE 2 DIABETES?

A provider trained in the use of urine dipsticks, finger prick or venous blood draw, the use of a glucometer and interpretation of the urine or blood results can screen for and diagnose type 2 diabetes. Counselling and education on healthy lifestyle choices, diet and weight reduction can be provided by any appropriately trained provider. Oral hypoglycemic therapy should be Initiation by a provider experienced in the use of oral hypoglycemic agents in PLHIV and the potential interactions between ARVs and oral hyperglycemic agents. Any trained provider can re-prescribe oral hypoglycemic agents to PLHIV who are stable on their anti-diabetic treatment.

WHO NEEDS ROUTINE CONSULTATION WITH OR REFERRAL TO AN EXPERIENCED PROVIDER?

Consultation with or referral to an experienced provider is recommended by the WHO in the following circumstances: [8]

- Fasting plasma glucose or >14 mmol/l despite maximal doses of metformin and sulfonylurea
- Individuals with newly diagnosed diabetes and urine ketones 2+
- Severe infection and/or foot ulcers
- Recent deterioration in vision
- Gestational diabetes
- Blood pressure ≥130/80 mmHg despite treatment with 2 blood pressure-lowering agents

WHO NEEDS IMMEDIATE REFERRAL

- Blood glucose >18 mmol
- Unconscious diabetic patients on hypoglycemic agents and/or blood glucose <2.8
- Severe infection and/or foot ulcers
- Recent sudden deterioration in vision

IF RESOURCES PERMIT

STATINS

The WHO recommends that a statin should be given to all patients with type 2 diabetes aged ≥40 years conditional on the availability of resources for statins, after complete coverage by metformin, sulfonylureas and antihypertensive medications, all of which have priority over statins when resources are limited. [62] Choices of statin are lovastatin, simvastatin, pravastatin, or atorvastatin.

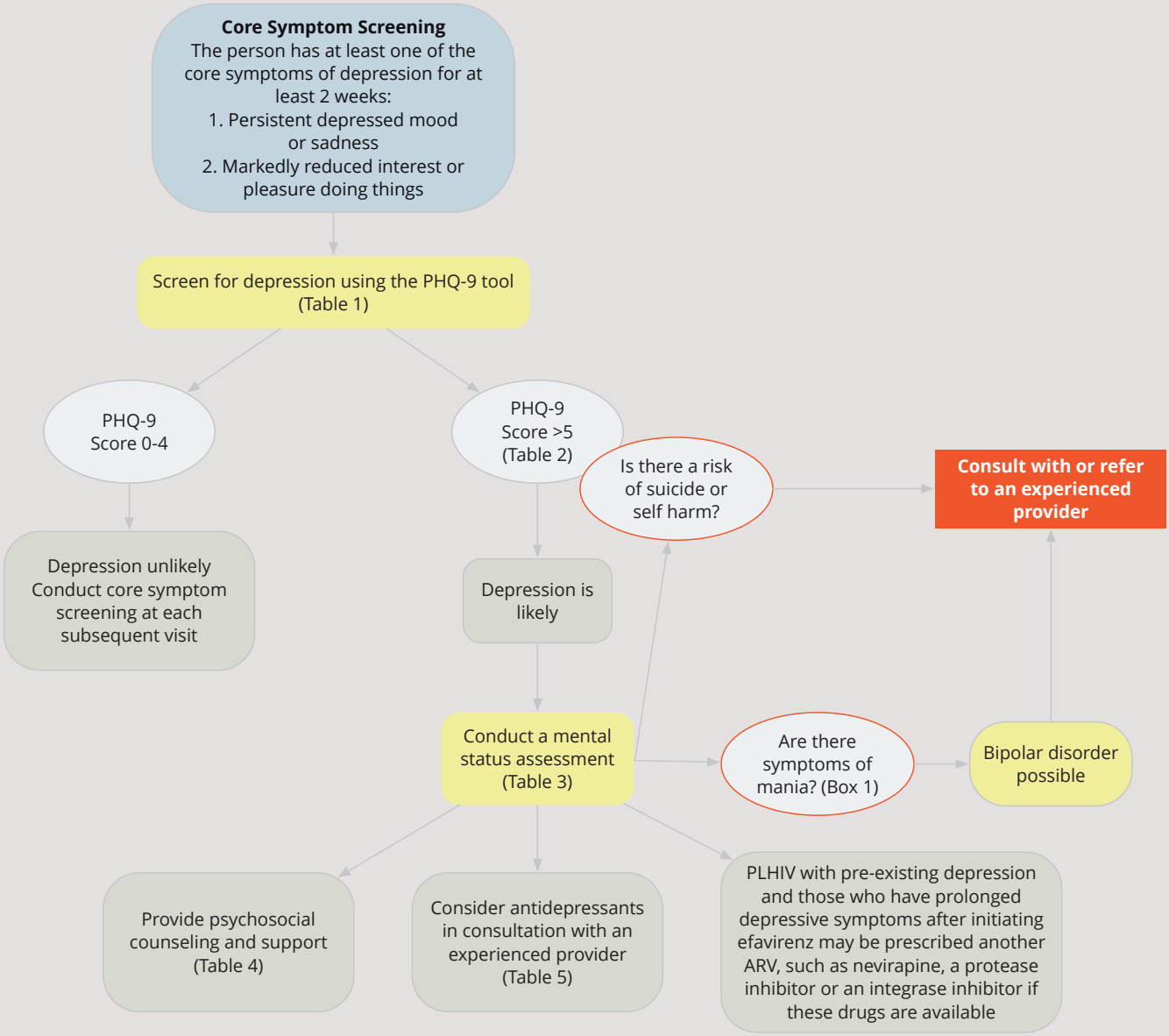
SCREENING FOR DIABETIC RETINOPATHY

The WHO recommends that people with type 2 diabetes should be screened for diabetic retinopathy by an ophthalmologist when diabetes is diagnosed, and every two years thereafter, or as recommended by the ophthalmologist. This recommendation is based on data from developed world countries which show that a substantial proportion of newly diagnosed diabetic patients already have diabetic retinopathy but acknowledges that many low-resource settings do not have the laser equipment for photocoagulation of retinal/macular lesions for treating sight-threatening retinopathy. [63]

PROTOCOL 3:

INTEGRATED MANAGEMENT OF DEPRESSION AND HIV

ALGORITHM FOR THE SCREENING, DIAGNOSIS, AND MANAGEMENT OF DEPRESSION



DEFINITION

Depression is a common mental disorder, which presents as persistent sadness or loss of interest or pleasure in daily living accompanied by disturbed sleep or appetite, feelings of guilt or low self-worth, tiredness, poor concentration, difficulty making decisions, agitation, hopelessness, and suicidal and self-harm thoughts or acts.[64]

DEPRESSION IN PLHIV

Depression is 2-3 times more prevalent in PLHIV than in the general population in both well-resourced and resource-limited settings.[65, 66] Depression is a significant contributing factor to poor adherence to ART and poor HIV treatment outcomes including treatment failure.[67-70] The WHO has identified mental health assessment and treatment as an essential care intervention for PLHIV in resource-limited settings.[62] Both psychotherapy and antidepressant medication and combinations of the two have demonstrated benefit in alleviating the symptoms of depression in PLHIV. [67, 71]

EFAVIRENZ AND DEPRESSION

Efavirenz (EFV) is a component of first-line ART in current WHO HIV treatment guidelines [76]. The central nervous system (CNS) side effects of EFV, which include dizziness, irritability, headache, diminished concentration, euphoria, vertigo, dreams and nightmares, and depression, are common but generally mild and transient.[72] Dosing on an empty stomach as well as at bedtime improves tolerability.[73] The incidence of EFV-associated CNS side effects has been reported as 40-60%.[74] Approximately 2% of subjects report more serious neurological effects, including delusion, paranoia, depersonalization, hallucinations, anxiety, mania, and severe depression. [74] The majority of EFV-induced CNS effects appear early, even after the first dose, and resolve within 1 month. In some cases, they can persist for months or not resolve at all.[9] It is important to explain the side effects, and their usual mild and transient nature, to people before they start EFV. People living with HIV with pre-existing depression and those who have prolonged depressive symptoms after initiating EFV may be prescribed another ARV, such as DTG, NVP, or a PI, if these drugs are available.

DEPRESSION AS PART OF BIPOLAR DISORDER

Bipolar disorder, also known as manic-depressive illness, is a disorder characterized by unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. People with bipolar disorder are more likely to seek help when they are depressed than when experiencing mania. (BOX 1) Bipolar disorder is associated with increased HIV transmission risk behavior among PLHIV. [75] A careful medical history is needed to ensure that bipolar disorder is not mistakenly diagnosed as depression. Unlike people with bipolar disorder, people who have depression only do not experience mania. Bipolar disorder needs to be managed by an experienced provider. Medications used to treat bipolar disorder include mood stabilizers, antipsychotics and antidepressants.

SCREENING FOR DEPRESSION IN PLHIV

Screening for depression is a simple and efficient way to find undetected cases and improve diagnostic accuracy in non-specialized primary care settings. [76] All PLHIV should receive basic screening for and management of mental health problems and substance use, including depression, before initiating ART, and at each contact with a healthcare worker or peer adherence supporter in the setting of a community adherence group or club.[9] Screening is especially critical at any time treatment failure is suspected or if viral load is detectable after 6 months on ART whether or not viral suppression was achieved in the past. [72] All PLHIV should receive

basic screening for depression using the WHO core symptom screening question: *Has the person had at least one of the core symptoms of depression, persistent depressed mood or sadness or markedly reduced interest or pleasure doing things for at least 2 weeks?* [77] People who answer "yes" to either of these questions and those with suspected treatment failure or a detectable viral load should undergo a more thorough screening for depression using the PHQ-9 screening tool.

PATIENT HEALTH QUESTIONNAIRE 9 (PHQ-9)

Several tools are available to facilitate depression screening.[78] The Patient Health Questionnaire 9 (PHQ-9) is a self-administered diagnostic instrument which has been shown to be a reliable and valid tool in making a symptom-based diagnosis of depression and measuring depression severity.[69, 76, 79] It has been used to screen for depression in PLHIV in both well-resourced and resource-limited settings.[69, 80-84] The PHQ-9 tool forms only part of depression assessment, which must also include history taking, physical examination and mental health status assessment (Table 3), of PLHIV in whom depression is suspected. Depressive symptoms can be confused with those of other medical illnesses which can be detected by physical examination. (i.e., weight loss and fatigue may be associated with diabetes, cancer or thyroid disease). Depressive symptoms can be confused with normal distress following severe stress (e.g., domestic violence, death of a loved one, disaster) as revealed by history-taking.

TABLE 1: PHQ-9 FOR DEPRESSION SCREENING

Name Date

Instructions

There are 9 questions. For each question, ask the person to circle the number which best applies to them. (0=not at all; 1=several days; 2=more than half the days; 3=nearly every day)
The health care worker can also ask the person each question and circle the answers
The depression score is the sum of all the numbers circled
Interpretation and management recommendations are provided at the bottom of the table

Question: Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself, or that you are a failure, or that you have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things (linked with person's usual activities, such as reading the newspaper or listening to a radio program)	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Add all the circled numbers in each column	A =	B =	C =	D =

Depression Score = A+B+C=D

TABLE 2: INTERPRETATION OF PHQ-9 SCORE AND MANAGEMENT			
Total Score	**Provisional Diagnosis**	**Management**	
0-4	Depression unlikely	Repeat screening at subsequent visits if new concerns that depression has developed	
5-9	Mild depression	Provide psychosocial counselling and support. If taking efavirenz, provide counselling on the CNS side-effects of EFV	
10-14	Moderate depression	Provide psychosocial counselling and support	Consider antidepressants medication If unfamiliar with the use of antidepressants consult with or refer to an experienced provider
15-19	Moderately severe depression		
20-27	Severe depression		

TABLE 3: CONDUCTING A MENTAL HEALTH STATUS ASSESSMENT	
Component of the assessment	**Details**
Essential care and practice	• Take a full medical history • Conduct a physical examination • Conduct a mental health status assessment • Identify and manage the mental health condition
Presenting complaint	• What is the main symptom or reason that the person is seeking care • Ask when, why, and how it started
Mental health history ASK ABOUT	• Similar problems in the past, any psychiatric hospitalizations • Current and past medications prescribed for mental conditions • Current and past thoughts of self-harm or suicide, or history • Tobacco, alcohol and substance use • Family history of mental health issues
Mental health status examination ASK ABOUT	Observe the persons appearance and behavior • Mood and content of thoughts • Sleep disturbances • Any perceptual disturbances (e.g., hearing voices) • Any manic behavior (e.g., increased activity, energy or agitation, euphoria, increased talkativeness, racing thoughts)
Symptoms of depression ASK ABOUT	• Multiple persistent physical symptoms with no clear cause • Low energy, fatigue, sleep problems • Persistent sadness or depressed mood, anxiety • Loss of interest or pleasure in activities that are normally pleasurable • Suicidal/ self-harm thoughts or actions

TABLE 4: MANAGEMENT STEPS	
Step	**Key messages**
Psychosocial support and education	• What the condition is and its expected course and outcome • Available treatments for the condition and their expected benefits • Duration of treatment • Importance of adhering to treatment • Potential side-effects (short and long term) • Potential involvement of community health workers (CHWs) or other trusted members in the community
Self-management skills	• Continue ART as prescribed • Continuing activities that they used to find interesting and pleasurable • Maintaining a regular sleep cycle • Keep physically active • Participate in community and social events • Return if any thoughts of self-harm
Reduce stress and strengthen social support	• Assess for and try to reduce stressors • (Re)activate the person's social network • Identify and discuss stressors such as health issues, family and relationship problems, gender based violence, finances, stigma and discrimination • Identify and discuss problem solving techniques • Identify supportive family members and involve them as appropriate • Teach stress management such as relaxation techniques
Promote functioning in daily activities	• Provide support to continue regular social, educational and occupational activities as much as possible. • Identify social activities that may provide psychosocial support (e.g., family gatherings, visiting neighbors and community activities) • Offer life skills training and/or social skills training if needed
Pharmacological Interventions	• Use pharmacological interventions when available and when indicated in the management algorithm and table provided • In selecting the appropriate medication, consider the side effect profile, drug-drug interactions, or drug-disease interactions • Educate the person about risks and benefits of treatment • potential side effects, duration of treatment, and importance of adherence
Followup	• Arrange a follow-up visit after the initial assessment • Schedule follow-up visits more frequently until the symptoms begin to respond to treatment • Once symptoms start improving, schedule less frequency and coinciding with regular HIV visit • At each visit, assess for response to treatment, medication side-effects, and adherence to medications and psychosocial interventions • Explain that the person can return to the clinic at any time in between follow-up visits, if needed • Have a plan of action for when the person does not show up for appointments • Use family and community resources to contact people who have not returned for regular follow-up • Consult a specialist if the person does not improve or worsens

BASIC PRINCIPLES OF PRESCRIBING ANTIDEPRESSANTS

Depression can effectively be managed by a combination of pharmacological and non-pharmacological interventions. Healthcare providers should not consider medications as their only therapeutic strategy. Antidepressant treatment should be for a pre-planned period of time, typically 6-9 months. Doses should start with the minimum recommended dose and increased gradually. It takes 2-4 weeks for maximum therapeutic benefit and improvement in symptoms to be achieved. [85] Antidepressants should not be stopped abruptly but the dose gradually reduced by 25% per week and then stopped. Polypharmacy (two or more antidepressants) should be avoided. There are two main classes of antidepressants, tricyclic antidepressants (TCA) and selective serotonin re-uptake inhibitors (SSRI). The efficacy of the two classes is comparable. [86, 87] Up to 50 % of patients receiving antidepressant treatment experienced side effects during the first 6-8 weeks of treatment.[88] The proportion of patients with side effects is lower in those taking an SSRI compared to those taking a TCA.[88, 89]

TABLE 5: ANTIDEPRESSANT DRUGS
Source: WHO *mhGAP Intervention Guide Version 2.0* and US FDA Full Prescribing Information

Class	Drug	Dose (mg)	Side effects	Pregnancy class.[1]
Tricyclic antidepressant (TCA)	Amitriptyline EML	• Start 25 mg at bedtime • Increase by 25-50 mg per week to maximum 150 mg daily **NOTE:** Minimum effective dose in adults is 75 mg • Elderly: Start 25 mg once daily at bedtime • Increase to maximum 100 mg once daily at bedtime • Children/Adolescents: Do not use	Sedation Orthostatic hypotension (risk of fall), blurred vision, difficulty urinating, nausea, weight gain, Sexual dysfunction. ECG changes (e.g. QT prolongation), cardiac Arrhythmia Increased risk of seizure	C
Selective serotonin re-uptake inhibitor (SSRI)	Fluoxetine EML	• Start 20 mg daily in the morning **NOTE:** 20 mg/day is sufficient to obtain a satisfactory response in most cases • If insufficient clinical response after 6 weeks, increase to 40 mg once daily in the morning	Sedation, insomnia, headache, dizziness, gastrointestinal disturbances, changes in appetite, sexual dysfunction. bleeding abnormalities in those who use aspirin or other non-steroidal anti-inflammatory drugs, low sodium levels	C

1. A. No known risk B. No known risk in humans C. Insufficient evidence D. Known risk and do not use

EML: Included in the WHO Model Essential Medicines List 2017

WHO CAN SCREEN FOR, DIAGNOSE, AND TREAT DEPRESSION?

All providers, including lay HCWs can, and should, ask people the core depression screening question: *Have you had persistent depressed mood or sadness or markedly reduced interest or pleasure doing things for more than 2 weeks*? The PHQ-9 can be self-administered or facilitated by a HCW trained in its use and interpretation of the result. Non-pharmacological interventions for depression, such as mobilizing social support and stress reduction may be administered by a trained HCW, including lay HCWs. Antidepressant medications should be initiated by a healthcare provider experienced in their use. Refills for stable PLHIV can be prescribed by a HCW who is familiar with and understands the patient's treatment plan.

WHO NEEDS ROUTINE CONSULTATION WITH OR REFERRAL TO AN EXPERIENCED PROVIDER

Consult with or refer to a provider with expertise in the management of depression, as needed, if there are signs or symptoms of mania and depression is thought to be part of bipolar disorder, there is no response to treatment or drug side effects are experienced, or if a switch from EFV to another ARV may not be available at the primary facility.

WHO NEEDS IMMEDIATE REFERRAL

A patient at risk of self-harm or suicide needs an immediate referral.

DRUG INTERACTIONS

There are no drug interactions between first line ARVs (NRTIs, NNRTIs, or integrase inhibitors) and amitriptyline or fluoxetine. Protease inhibitors increase drug levels of amitriptyline or fluoxetine, but no adjustment of dose amitriptyline or fluoxetine is needed. Amitriptyline and PIs should be administered with caution as both prolong the cardiac QT interval and ECG monition is recommended. Amitriptyline or fluoxetine do not effect ARV drug levels.

TABLE 6: DRUG INTERACTION TABLE
Source: University of Liverpool, hiv-druginteractions.org

Antihypertensive	TDF/ TAF	AZT	3TC	FTC	EFV	NVP	DTG	LPV/r	ATV/r	DRV/r
Amitriptyline								⬆	⬆	⬆
Fluoxetine								⬆	⬆	⬆

*Essential medicines list includes atenolol, metoprolol, carvedilol as alternatives

No interaction

Potentially increased amitriptyline concentrations although to a moderate extent. No dosage adjustment of amitriptyline is recommended. **Caution should also be exercised when administering amitriptyline and PIs due to the risk of QT prolongation. ECG monitoring is recommended.** Drug levels of ARVs are not affected

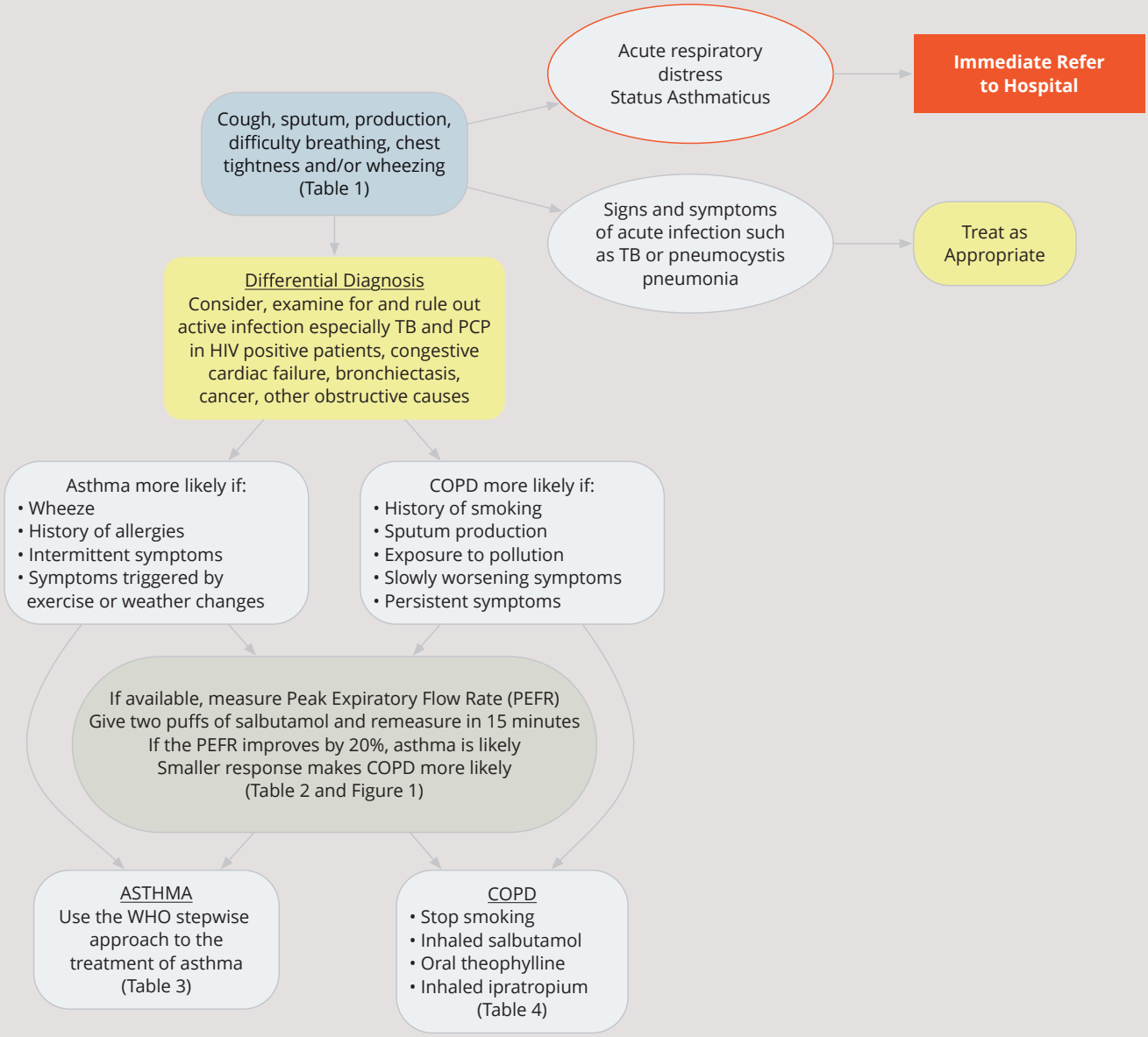
Potentially increased fluoxetine concentrations although to a moderate extent. No dosage adjustment of fluoxetine is recommended. **Drug levels of ARVs are not affected**

⬆ Increase in antidepressant agent level

⬇ Decrease in antidepressant agent level

PROTOCOL 4:
INTEGRATED MANAGEMENT OF ASTHMA, COPD, AND HIV

ALGORITHM FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA AND COPD



DEFINITIONS

1. Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent respiratory symptoms and chronic airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.
2. Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These symptoms are typically reversible and responsive to bronchodilator therapy.

LUNG DISEASE AND HIV

Pulmonary disease remains a primary source of morbidity and mortality in PLHIV, although the advent of potent combination ART has resulted in a shift from predominantly infectious to noninfectious pulmonary complications.[90, 91] People living with HIV are at higher risk for COPD, asthma, pulmonary hypertension, and lung cancer compared to non-HIV infected individuals. [91, 92] The prevalence of COPD in PLHIV in varies by study and by definition, but, by spirometry, 7-9% of PLHIV have clinical obstruction, while one-third have respiratory symptoms.[93] The US-based Lung HIV Consortium reported that spirometry among PLHIV showed that 27% and 10% had obstructed and restricted airflow patterns, respectively.[94] The incidence of lung cancer is 2.7 times higher in PLHIV than in the general population. [95] Risk factors for lung cancers among PLHIV include ageing, tobacco use, prior lung infections, and inflammation caused by HIV itself. [96]

DIAGNOSIS AND MANAGEMENT OF ASTHMA AND COPD

TABLE 1: DIAGNOSIS

Risk factors	• Atopy (allergy) • Tabaco smoking • Respiratory tract infections • Beta-blockers • HIV	
History	**Favoring a diagnosis of asthma**	**Favoring a diagnosis of COPD**
	• Wheeze • Previous diagnosis of asthma • History of allergies • Intermittent symptoms • Worse at night or early morning • Symptoms triggered by exercise or weather changes • Response to salbutamol	• Previous diagnosis of COPD • History of heavy tobacco smoking • Sputum production • Prolonged exposure to indoor or outdoor pollution • Slowly worsening symptoms • Persistent symptoms with little day-to-day variation
Physical examination	• Normal examination between exacerbations • Wheeze • Rhonchi • Prolonged expiration • In severe exacerbations (status asthmaticus): use of accessory muscles, tachypnea, tachycardia	• Hyperinflation (barrel chest) • Wheezing • Diffusely decreased breath sounds • Hyper-resonance on percussion • Prolonged expiration • Coarse crackles beginning with inspiration

TABLE 1: DIAGNOSIS		
Imaging	• Chest X-ray usually normal; may show hyperinflation in severe disease	
Pulmonary function tests	• See below	
Differential diagnosis	• Bronchiectasis • Aspergillosis • Constrictive bronchiolitis • Eosinophilic bronchitis	• Post-viral bronchiolitis • Upper airway obstruction (tumors) • Congestive heart failure

PEAK FLOW METER

Peak flow meters are inexpensive, point-of-care, hand-held devices that provide objective, reproducible assessments of airflow.[8] They measure the peak expiratory flow rate (PEFR) and can be used for diagnosing asthma, monitoring response to treatment and are a useful tool in patient self-management of asthma. Normal peak flow rates vary according to age, height, and gender. A normal score should be within 20% of a person of the same age, gender, and height who does not have asthma. [8]

TABLE 2: HOW TO USE A PEAK FLOW METER [97]
1. Set the cursor to zero (0)
2. Stand up or sit straight and hold the peak flow meter horizontally in front of the mouth
3. Take a deep breath in and close the lips firmly around the mouthpiece
4. Breathe out as hard and as fast as possible
5. Note the number indicated by the cursor
6. Return cursor to zero and repeat this sequence twice more, obtaining three readings. The highest or best reading of all three measurements is the peak flow at that time
7. The highest reading should be recorded in the patient's daily asthma diary or recorded on a peak flow chart

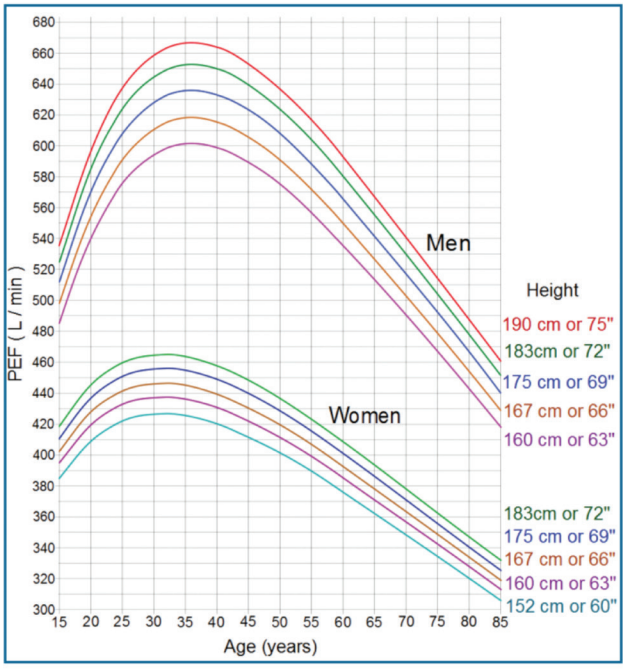


Figure 1: Normal Peak Expiratory Flow Rates (PEFR)

TABLE 3: MANAGEMENT OF ASTHMA		
Management of stable asthma	Use the WHO stepwise approach to treatment (Steps 1-5 below) At each point it is important to check adherence to their medications and that their inhaler technique is correct	
	Step 1.	Inhaled salbutamol (salbutamol) as required (prn)
	Step 2.	Continue inhaled salbutamol prn and add inhaled beclomethasone 100ug or 200ug twice daily, which may take several day to be fully effective
	Step 3.	Continue inhaled salbutamol prn and increase the dose of beclomethasone to 200ug to 400ug twice daily
	Step 4.	Add low-dose oral theophylline or increase dose of inhaled beclomethasone; the recommended adult dose of theophylline is 100 mg twice daily
	Step 5.	Add oral prednisolone in the lowest dose possible to control symptoms; for PLHIV requiring regular prednisolone, refer to an experienced provider
Management of exacerbations of asthma	• Salbutamol by continuous nebulization at 5-10mg per hour, if nebulizer available • Prednisolone 30-40mg per day for 5 days • Oxygen, if available, and if oxygen saturation levels are low (<90%)	
Assessment of asthma control	Asthma is well controlled if the patient has: • Peak expiratory flow rate, if available, above 80% of predicted for age and gender (Figure 1) • No more than 2 occasions a week when asthma symptoms occur and require inhaled salbutamol • Asthma symptoms on no more than 2 nights a month • No or minimal limitation of daily activities • No severe exacerbation (i.e., requiring oral steroids or admission to hospital) within a month	
Review	Patients with other than very mild asthma should have regular reviews every 3 or 6 months, at the same time and place and by the same provider as regular HIV care visits, and more frequently when treatment has been changed or asthma is not well controlled; this should always include observation of inhaler technique	

TABLE 4: MANAGEMENT OF COPD	
Management of stable COPD	• Inhaled salbutamol, two puffs as required, up to four times daily • If symptoms persist, add low-dose oral theophylline (200-400 mg per day) • If available, ipratropium inhalers can be used instead of, or added to, salbutamol, but they are more expensive • Stop smoking • Avoid indoor and outdoor pollution
Management of exacerbations of COPD	• The same as above for asthma • Antibiotics should be given if there is evidence of infection
Review	• Review every 3 or 6 months, at the same time and place and by the same provider as regular HIV care visits, and more frequently when treatment has been changed or symptoms are not well controlled; this should always include observation of inhaler technique
Consultation or referral	Consultation with or referral to an expert provider should be considered if: • COPD remains poorly controlled • Diagnosis of COPD is uncertain • Regular oral prednisolone is required to maintain control

TABLE 5: ASTHMA AND COPD DRUGS
Sources: US FDA Full Prescribing Information

Drug	Daily dose (mg)	Side effects	Pregnancy class.[1]
Inhaled Salbutamol EML	Two puffs as required up to 4 times per day	Tremor	C
Inhaled Beclomethasone EML	100-400ug (1-2 puffs) twice daily. If used with salbutamol, inhale salbutamol first, wait 5 minutes and then inhale beclomethasone	Pharyngitis Oral candida	C
Inhaled Ipatropium bromide EML	Two puffs 4 times per day	Paradoxical bronchospasm Increase intraocular pressure Urinary retention	B
Prednisolone EML	Dosing is variable and should be individualized based on asthma severity and the response of the patient Typically 30-40 mg per day for 5 days (WHO)	Multi-organ including: increase susceptibility to infections, sodium retention, fluid retention, hypertension muscle weakness osteoporosis peptic ulcer, thin fragile skin menstrual irregularities, cushingoid state, glaucoma	C
Theophylline EML	200-400 mg per day	Nausea Abdominal pain Tremors	C

1. A. No known risk B. No known risk in humans C. Insufficient evidence D. Known risk and do not use

EML: Included in the WHO Model Essential Medicines List 2017

NOTE ON THEOPHYLLINE

Theophylline is included in the WHO Essential Medicines list and recommended by the WHO as adjunctive therapy for asthma and COPD. Multiple studies have demonstrated the inferiority of theophylline to inhaled salbutamol, beclomethasone, and ipratropium bromide in the management of asthma and COPD and theophylline is not recommended as first-line therapy for either asthma or COPD. Theophylline should be used with caution in PLHIV taking PI-containing ART.

TABLE 6: DRUG INTERACTION TABLE
Source: University of Liverpool, hiv-druginteractions.org

Antihypertensive	TDF/ TAF	AZT	3TC	FTC	EFV	NVP	DTG	LPV/r	ATV/r	DRV/r
Inhaled Salbutamol										
Inhaled Beclomethasone										
Inhaled Ipatropium										
Prednisolone					↓	↓		↑	↑	↑
Theophylline								↓	↓	↓

*Essential medicines list includes atenolol, metoprolol, carvedilol as alternatives

No interaction

Potential interaction with increased or decrease levels of prednisolone. No prednisolone dose adjustment required. Drug levels of ARVs are not affected by prednisone/prednisolone.

Theophylline levels decreased, and dose increase of theophylline may be required. Drug levels of ARVs are not affected by theophylline.

WHO CAN SCREEN FOR, DIAGNOSE, AND TREAT ASTHMA AND COPD?

A peak flow meter can be used by a HCW, including a lay HCW, trained in its use and interpretation of the result. Making a differential diagnosis between asthma and COPD requires appropriate training and experience in the signs and symptoms of the two diseases. Inhaled medicine and monitoring of response to treatment should be by a trained HCW. Initiation of theophylline and prednisolone should be by an experienced healthcare provider who understands the drug interactions associated with theophylline and ARVs.

WHO NEEDS ROUTINE REFERRAL TO OR CONSULTATION WITH AN EXPERT PROVIDER?

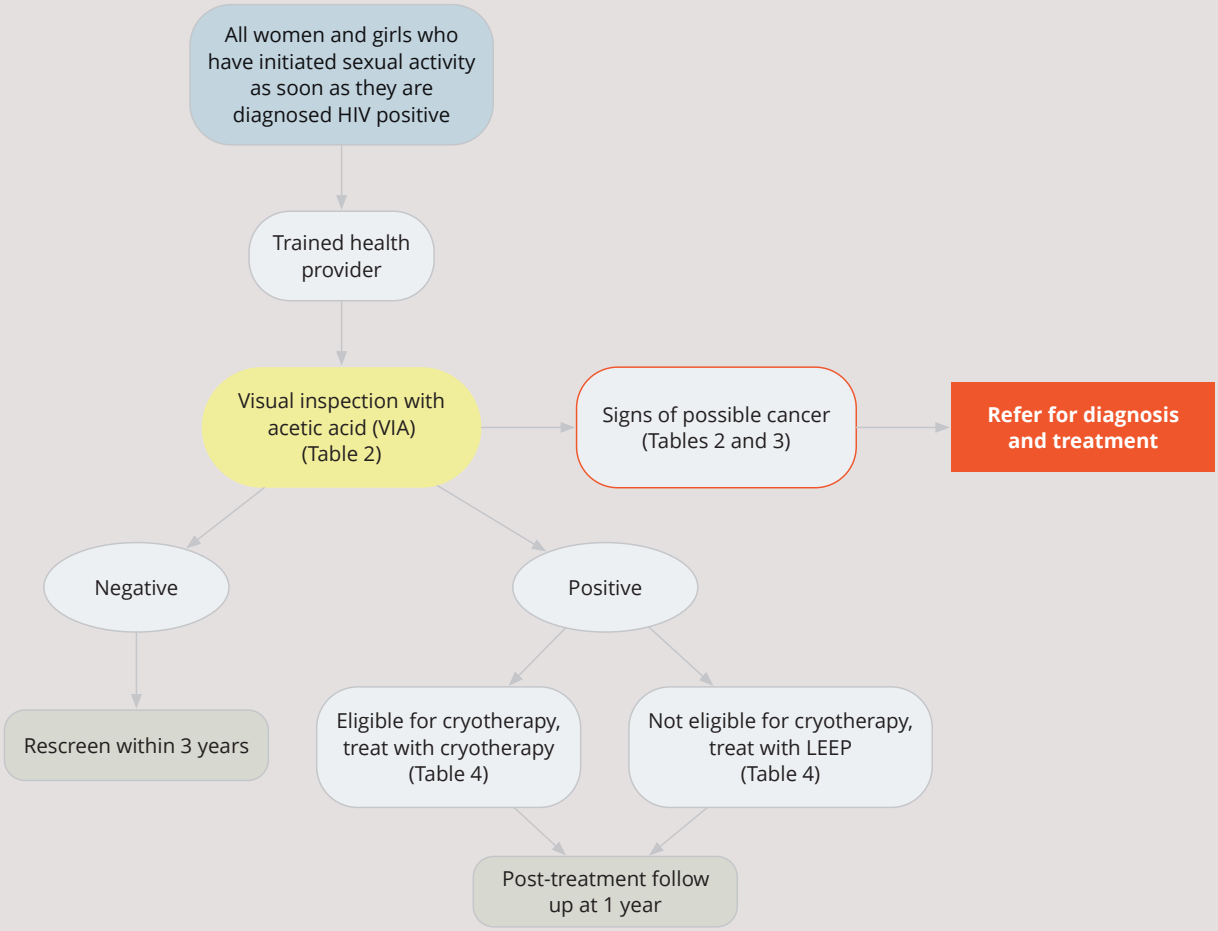
- Diagnosis of asthma or COPD is uncertain
- Asthma or COPD remains poorly controlled despite intervention
- Regular oral prednisolone is required to maintain control

WHO NEEDS IMMEDIATE REFERRAL

- Acute respiratory distress
- Status asthmaticus

PROTOCOL 5:
INTEGRATED MANAGEMENT OF CERVICAL CANCER AND HIV

ALGORITHM FOR CERVICAL CANCER CARE IN WOMEN AND GIRLS WITH HIV



Overview and Definitions

Cervical cancer is one of the leading causes of cancer death in women. Most deaths occur in LMICs. [98] The primary cause of cervical pre-cancer and cancer is persistent infection with one or more of the high-risk (or oncogenic) types of HPV. In most women and men who become infected with HPV, infection resolves spontaneously. A minority of HPV infections persist in women, which may lead to cervical pre-cancer. If not treated, cervical pre-cancer may progress to cancer 10 to 20 years later. Cervical intraepithelial neoplasia (CIN) is a premalignant lesion that may exist at any one of three stages: CIN1, CIN2, or CIN3. If left untreated, CIN2 or CIN3 (collectively referred to as CIN2+) can progress to cervical cancer. [98]

OTHER HPV-ASSOCIATED CANCERS

Other cancers caused by HPV include most anal cancers and a subset of tumors of the vulva, vagina, penis, oral cavity, and oropharynx. [99] People living with HIV have a higher incidence of these tumors relative to people who do not have HIV infection.[100] Anal cancer and anal intraepithelial neoplasia (AIN), the precursor of anal cancer, are more common in HIV-infected men who have sex with men (MSM), other men, and women compared with HIV-uninfected individuals as are anal and genital warts, vulvar intraepithelial neoplasia (VIN), and vaginal intraepithelial neoplasia (VAIN). [101, 102] There are limited data to support optimal screening and treatment approaches to anal cancer.[103] Screening for anal cancer with anal cytology should not be done without the availability of referral for treatment. [99] Treatment options, including cryotherapy and electrocautery, are associated with high rates of recurrence and repeated ablative treatment or a combination of treatment methods are often required for long-term clearance of AIN.[99]

CERVICAL CANCER AND HIV

Women and girls living with HIV are more likely to develop persistent HPV infection at an earlier age and to develop cancer sooner, up to 10 years earlier than HIV-negative women and girls and more frequently present with advanced disease. [98] It is estimated that approximately 1-2% of women have CIN2+ each year. This rate is reported to be higher in women of HIV-positive status, at 10%.[98] Cervical cancer is an AIDS-defining illness.

PRACTICE POINT

Women and girls living with HIV are at higher risk for cervical cancer. They should be screened as soon as they are diagnosed with HIV irrespective of age

SCREENING

Screening for cervical pre-cancer and cancer should be performed in women and girls who have initiated sexual activity as soon as the woman or girl has tested positive for HIV, regardless of age. In women who are of HIV-positive status or of unknown HIV status in areas with high endemic HIV infection, if the screening test is negative, the screening interval for repeat screening should be within 3 years. Women who have received treatment should receive post-treatment follow-up screening at 1 year. [98]

SCREENING STRATEGIES IRRESPECTIVE OF HIV STATUS

There are 3 different types of screening tests:

- Visual inspection with Acetic Acid (VIA); VIA is the WHO preferred strategy in resource-limited settings. [98]
- Conventional (Pap) test
- HPV testing for high-risk HPV types

The standard practice is to sequentially screen women using cytology (Pap test), and when cytology results are positive the diagnosis of CIN is based on subsequent colposcopy, biopsy of suspicious lesions, and then treatment only when CIN2+ has been histologically confirmed. In resource-limited settings, a 'screen and treat' (or 'see and treat') approach is recommended using a strategy of VIA and immediate, same visit (or as soon as possible) treatment with cryotherapy (or LEEP when not eligible).

TREATMENT STRATEGIES IRRESPECTIVE OF HIV STATUS

Available treatments include cryotherapy, large loop excision of the transformation zone (LEEP/LLETZ), and cold knife conization (CKC). In the absence of studies on the treatment of cervical cancer in women living with HIV, management is based on international and national guidelines for HIV-negative women. During the healing process after any procedure, women living with HIV might have increased (HIV) viral shedding.

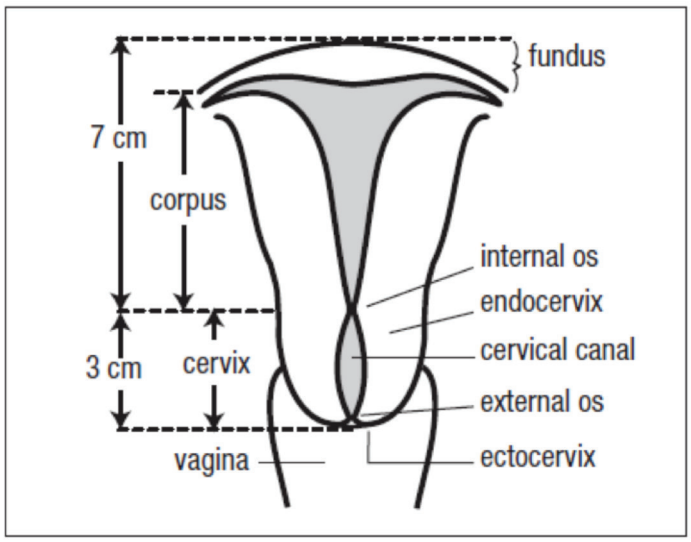
TABLE 1: SCREEN-AND-TREAT STRATEGIES IRRESPECTIVE OF HIV STATUS
1. In resource-limited settings, use a strategy of screening with VIA and treatment with cryotherapy (or LEEP when not eligible for cryotherapy)
2. Where resources permit, use a strategy of screening with an HPV test, VIA and treatment with cryotherapy (or LEEP when not eligible for cryotherapy)
3. In countries where an appropriate, high-quality screening strategy with cytology followed by colposcopy already exists, either an HPV test or cytology followed by colposcopy could be used
4. Cold knife conization (CKC) as treatment is not recommended in a screen-and-treat strategy

HPV VACCINATION

Two vaccines that prevent infections from high-risk HPV types 16 and 18 are licensed in most countries for use in both HIV-negative and -positive women and girls, have excellent safety records, and can be co-administered with other vaccines, such as those for diphtheria, tetanus and pertussis (DTP) and hepatitis B virus (HBV). One of the HPV vaccines, the quadrivalent vaccine, also prevents infections from HPV types 6 and 11, which cause 90% of anogenital warts or condyloma. The WHO recommends HPV vaccination for girls and boys in the age group of 9–13 years.[104] For those not vaccinated earlier, HPV vaccine is recommended for all PLHIV (men and women) up to age 26. [99] Two dose or three dose schedules are available. People living with HIV should also receive the three-dose schedule (at 0, 1-2, and 6 months schedule).[104] Schedule recommendations for PLHIV apply to both the bivalent and quadrivalent vaccines. It is not necessary to screen for HPV infection or HIV infection prior to HPV vaccination.

PROCEDURES

The cervix is the lower third of the uterus. The lower part of the cervix (ectocervix) lies within the vagina and is visible with a speculum; the upper two thirds of the cervix (endocervix) lies above the vagina and is not visible. Most cervical cancers originate in the area where the endocervix and ectocervix join.



VISUAL SCREENING METHOD – VISUAL INSPECTION WITH ACETIC ACID (VIA)

Visual inspection with acetic acid (VIA) is performed by a trained healthcare provider who applies a 3% to 5% acetic acid solution to the cervix and then observes the transformation zone of the cervix for 1 to 2 minutes for acetowhite epithelium, which is indicative of abnormal cellular changes. In most instances, the VIA-positive woman can be treated at the same visit with cryotherapy to ablate the transformation zone. Both VIA and cryotherapy can be conducted in the field, thus eliminating the need for a clinic visit altogether. This procedure has many advantages: VIA can be performed by a trained paramedical worker; it needs simple equipment; the results are immediately available; and treatment, if needed, can be provided at the same visit. To conduct VIA, the provider performs a speculum examination and applies 3–5% acetic acid to the cervix, and then looks to see if any white changes appear after waiting for 1–2 minutes. The VIA test is positive if there are raised and thickened white plaques or acetowhite areas that last more than 1 minute. VIA is negative if the cervical lining shows no changes. The provider should suspect cancer if a cauliflower-like (fungating) mass or ulcer is noted on the cervix (Table 2). The woman then needs to be referred directly to a higher-level facility.

TABLE 2: VIA	
1.	VIA should be performed by a trained provider
2.	Explain the procedure to the woman
3.	Perform a speculum examination and keep the speculum in place to perform the VIA test
4.	Adjust the light source in order to get the best view of the cervix
5.	Use a cotton swab to remove any discharge, blood or mucus from the cervix
6.	Confirm that you are able to see the entire transformation zone and identify the squamocolumnar junction (SCJ) and the area around it

TABLE 2: VIA
7. Apply acetic acid to the cervix
8. Wait 1-2 minutes to allow changes to develop
9. Inspect the SCJ carefully and be sure you can see all of it; look for any raised and thickened white plaques or acetowhite epithelium, giving special attention to the transformation zone
10. Use a fresh swab to remove any remaining acetic acid from the cervix and vagina
11. Close and remove the speculum, and place it in decontamination solution
12. Record your observations and the result of the test; draw a map of any abnormal findings on the patient record form
13. Discuss the results of the screening test with the woman: – If the test is negative (normal), tell her that she should have another test in 3-5 years, or as national guidelines recommend – If the test is positive (abnormal), tell her that she needs to be treated and discuss this with her – The VIA outcome is scored as invasive cancer when there is a clinically visible ulcero-proliferative growth on the cervix that turns densely white after application of acetic acid and bleeds on touch – If cancer is suspected, tell her what the recommended next steps are; she needs to be referred for further management (testing and treatment); make arrangements and provide her with all necessary forms and instructions before she leaves; and if you can make the appointment immediately, do so

TABLE 3: PRESENTING SYMPTOMS OF INVASIVE CERVICAL CANCER BY LEVEL OF SEVERITY (EARLY AND ADVANCED)	
Early	**Advanced**
• Vaginal discharge, sometimes foul-smelling • Irregular bleeding (of any pattern) in women of reproductive age • Post coital spotting or bleeding in women of any age, even young women • Postmenopausal or peri-menopausal spotting or bleeding • Consider sexually transmitted infection in the differential diagnosis	• As described in 'early' plus any of the following • Backache • Lower abdominal pain • Severe back pain • Weight loss • Decreased urine output (from obstruction of the ureters, or renal failure) • Leakage of urine or feces through the vagina (due to fistulae) • Swelling of the lower limbs • Breathlessness (due to anemia or, rarely, lung metastases or effusion)

TABLE 4: TREATMENT OF INVASIVE CERVICAL CANCER		
	Cryotherapy	**Loop electrosurgical excision procedure (LEEP)**
Eligibility	• Screen-positive women • Entire lesion and squamocolumnar junction are visible and the lesion does not cover more than three quarters of the ectocervix	• Screen-positive women • Lesion extends beyond the cryoprobe being used or into the endocervical canal
Not Eligible	Lesion is suspicious for invasive cancer (Table 2)	
Procedure	Cryotherapy eliminates precancerous areas on the cervix by freezing It involves applying a highly cooled metal disc (cryoprobe) to the cervix It is performed without anesthesia	LEEP is the removal of abnormal areas from the cervix using a loop made of thin wire powered by an electrosurgical unit. The loop tool cuts and coagulates at the same time, and this is followed by use of a ball electrode to complete the coagulation. LEEP aims to remove the lesion and the entire transformation zone. The procedure is performed under local anesthesia on an outpatient basis
Post procedure	Watery discharge for about 1 month Avoid sexual intercourse or use a condom until all discharge stops	Mild cramping for a few days and vaginal discharge for up to one month. Initially, this can be bloody discharge for 7-10 days Avoid sexual intercourse or use a condom until all discharge stops.
HIV positive women	Women with HIV many be at increased risk of HIV viral shedding during the healing process and **must** avoid intercourse or use condoms	
Who can perform the procedure	Health care providers (doctors, nurses and midwives) at all levels of the health system who are skilled in pelvic examination and trained in cryotherapy	LEEP is a surgical procedure and should only be performed by an appropriately trained health care provider LEEP is performed at secondary level facilities (i.e. district hospitals) or above.

WHO CAN SCREEN FOR CIN AND CERVICAL CANCER AND TREAT CIN?

A provider trained and experienced in the 'see-and-treat' strategy with access to VIA, cryotherapy, and LEEP.

WHO NEEDS ROUTINE REFERRAL TO OR CONSULTATION WITH AN EXPERT PROVIDER?

All HIV-positive women and adolescent girls, irrespective of age, should be referred to an expert provider if the facility does not offer comprehensive screening and treatment with VIA, cryotherapy, and LEEP.

WHO NEEDS IMMEDIATE REFERRAL

Women and adolescent girls with signs or symptoms of cervical cancer (Table 3) need immediate referral.

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