

HIV/AIDS 2008



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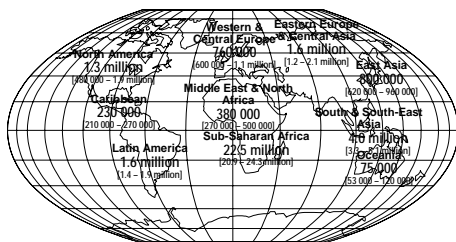
Morbidity and Mortality Weekly Report (MMWR)

1981 June 5,30:250-2

Pneumocystis Pneumonia – Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Adults and children estimated to be living with HIV, 2007



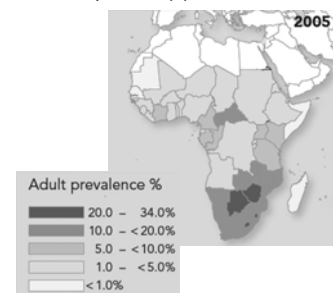
Total: 33.2 (30.6 – 36.1) million



Global HIV epidemic, 1990-2008

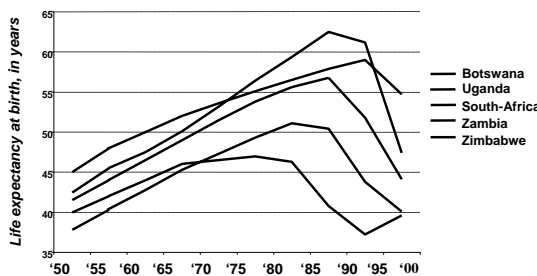
- 33+ million living with HIV
- ~2.5 million new infections/year
- ~2 million deaths/year
- 23 million in sub-Saharan Africa

HIV prevalence (%) in adults in Africa, 2005



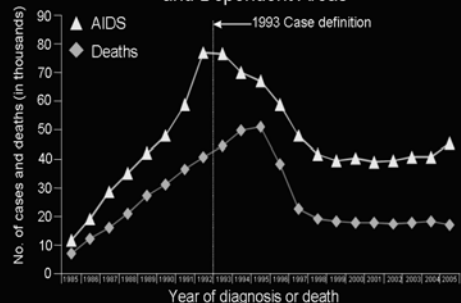
UNAIDS 2006-7

Changes in life expectancy in selected African countries with high HIV prevalence – 1950 to 2000



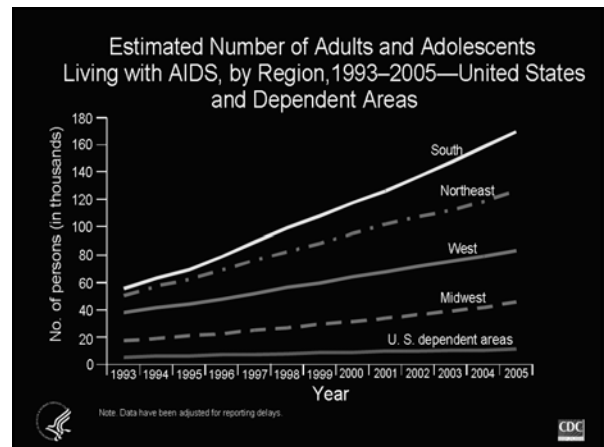
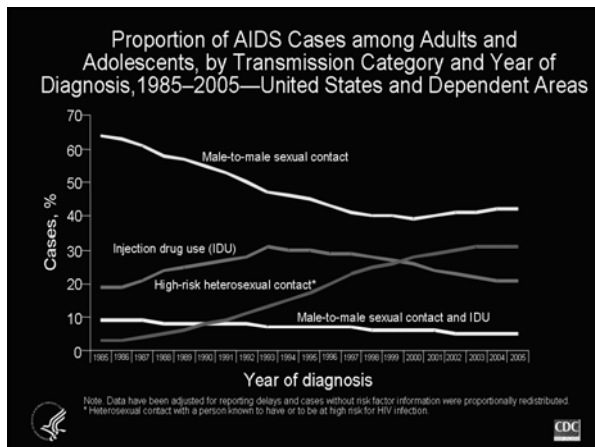
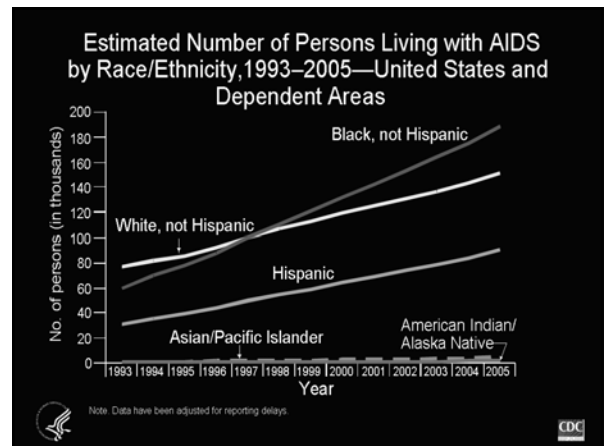
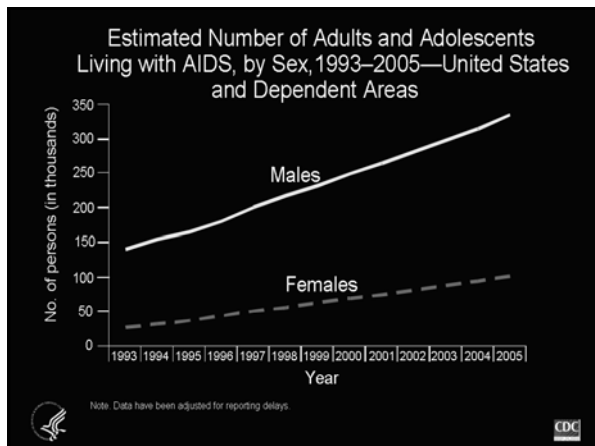
Source: United Nations Population Division, 1998

Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985-2005—United States and Dependent Areas



Note: Data have been adjusted for reporting delays.





Over 6800 new HIV infections a day in 2007

- >96% are in low-middle income countries
- ~1200 are in children <15 years of age
- ~5800 are in adults 15 years and older:
 - ~50% are among women
 - ~40% are among young people (ages 15-24)

World Health Organization | UNAIDS

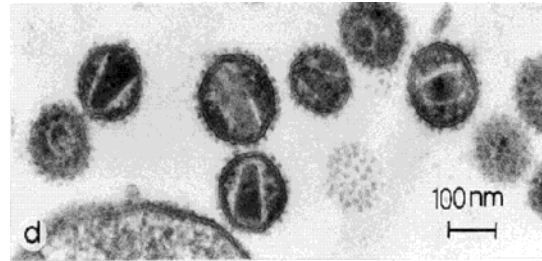
Early History of AIDS

- **1981:** reports of gay men with PCP, KS, CD4 depletion
 - then injection drug users, hemophiliacs, transfusion recipients
 - blood-borne; sexually transmitted
- **1983-84:** isolation of HIV-1
- **1985:** HIV-1 antibody testing available
- **1986:** isolation of HIV-2
- **1987:** first antiretroviral drug approved (AZT)
 - 25,000 Americans dead

(Later) Early History of HIV/AIDS

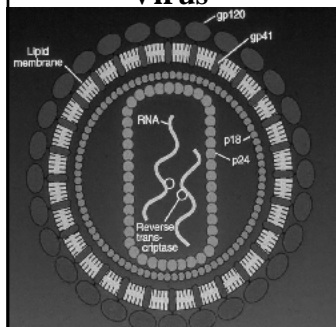
- 1988: PCP prophylaxis with Bactrim
- 1994: AZT prophylaxis for perinatal transmission; 2-drug ART introduced into clinical practice
- 1996: 3-drug ART introduced into clinical practice
- 2000: Durban conference, move to bring ART to developing world gains momentum

HIV-1 Virions




Gelderblom, Human Retroviruses and AIDS 1997

Human Immunodeficiency Virus



- formerly HTLV-III; isolated 1983
- human retrovirus – outer glycoprotein coat, inner protein coat and genetic material: RNA (2 strands)
- types: HIV-1 and HIV-2
- subtypes (clades): B most common in North America and Europe
- target cell: CD4+ lymphocyte

Origin of HIV

- Evidence for zoonosis
 - similarity of genomes, phylogenetic relationships, prevalence in normal host, geographic coincidence, plausible route of transmission
 - SIVsm (sooty mangabey) --- HIV-2
 - SIVcpz (chimpanzee) --- HIV-1 (~1930)
- 
- ? Skin/mucous membrane exposure to infected animals (pets, food)

Hahn et al. Science 2000;287:607

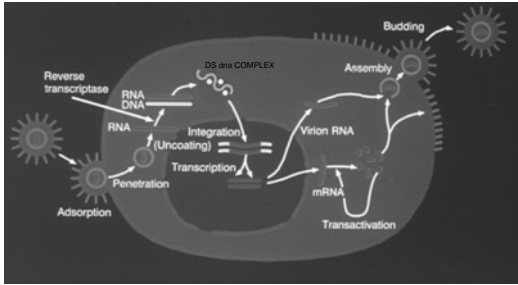
HIV Testing

- HIV antibody testing (indirect)
 - Window period ~3 months
 - Screening test: HIV antibody by ELISA
 - If repeatedly positive, proceed to confirmatory test
 - Confirmatory test: HIV antibody by Western Blot
 - 20-minute oral test now available
- HIV viral testing (direct)
 - p24 antigen
 - viral culture
 - HIV RNA (viral load)

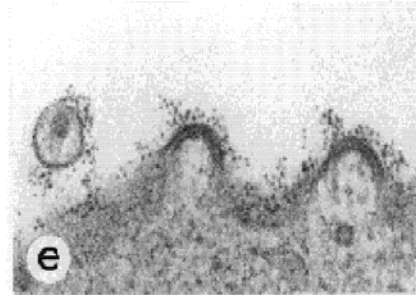
HIV Transmission Routes

- Sexual transmission
 - Low efficiency (~1% per contact)
- Injection drug use
 - High efficiency (~ 10% per contact)
- Blood , blood products, tissue
 - Very high efficiency (~ 90% per transfusion)
- Perinatal transmission (~25% per birth)
- Needlestick injury (~1/300 exposures)

Life Cycle of HIV



Budding HIV Virions



Viral Dynamics -- Summary

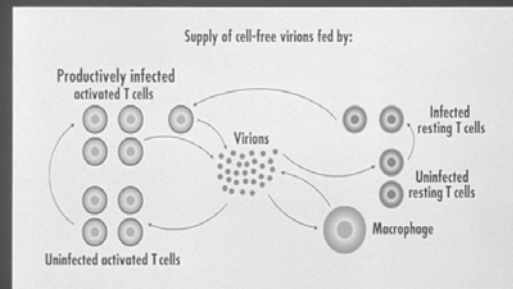
- 10 billion new virions created and cleared daily
- 2 billion CD4 cells destroyed daily (twice the rate of replacement by the hematopoietic system)
- Mechanism of CD4 cell destruction is poorly understood

Ho, Nature 1995;373:123

Wei, Nature 1995;373:117

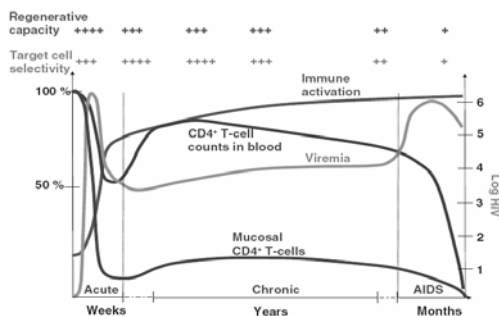
Perelson, Science 1996;271:1582

THREE-COMPARTMENT MODEL OF HIV INFECTION DYNAMICS

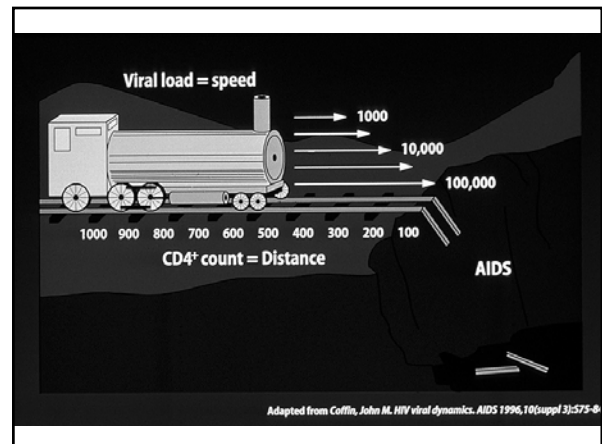


Adapted from Perelson et al., Science, 1996.

Time Course of HIV Infection



Grossman Nature Medicine 2006; 12: 289-295



Adapted from Coffin, John M. HIV viral dynamics. AIDS 1996,10(suppl 3):S73-8

CDC Adult AIDS Case Definition

- 1982: "AIDS" -- list of diseases (definitive diagnosis) and disqualifying conditions
- 1985: HIV antibody testing added to definition
- 1987: presumptive diagnoses with a positive HIV antibody added
- 1993: CD4 <200 (without symptoms) and other diagnoses added

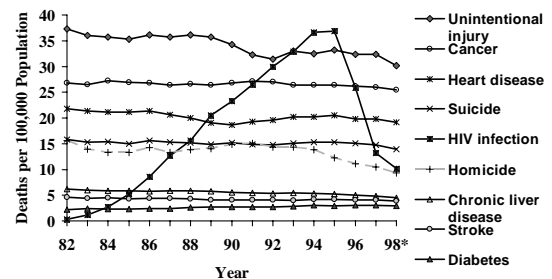
Opportunistic Infection (OI): Definition

- Infection caused by an organism capable of causing disease only in a host whose resistance is lowered (by other diseases or by drugs)

Examples of Common OIs/Malignancies

- Developed world
 - Pneumocystis carinii (fungus)
 - Cytomegalovirus (virus)
 - Toxoplasma gondii (parasite)
 - Mycobacterium avium complex (bacterium)
 - Kaposi's sarcoma (malignancy)
- Developing world
 - Cryptococcus (fungus)
 - Mycobacterium tuberculosis (bacterium)
 - Wasting disease

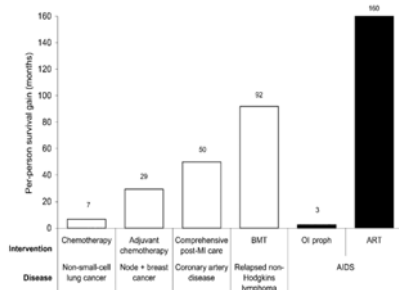
Annual Rates of Death from Leading Causes of Death Among Persons 25-44 Years Old, USA, 1982-1998



National Center for Health Statistics
National Vital Statistics System

*Preliminary 1998 data

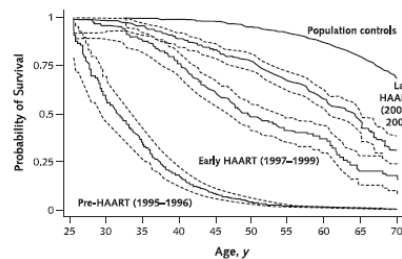
ART in U.S.: 3 million life-years saved!



Walensky, J Infect Dis 2006;194:11-19

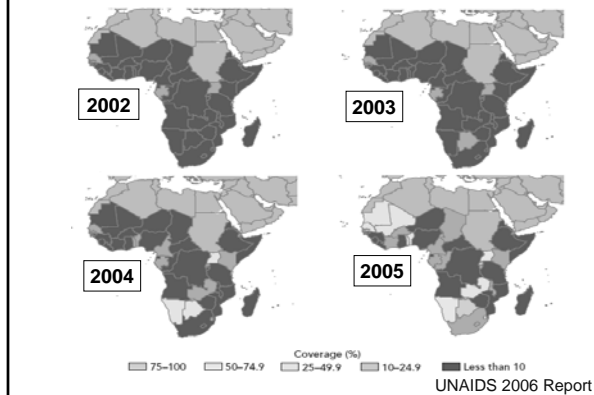
HIV Survival: Denmark

Figure. Survival from age 25 years.



Lohse, et al. Ann Intern Med 2007;146:87

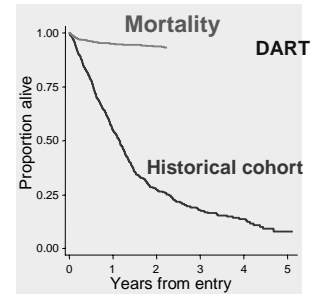
Africans on ART (% of those in need)



ART scale up: Uganda

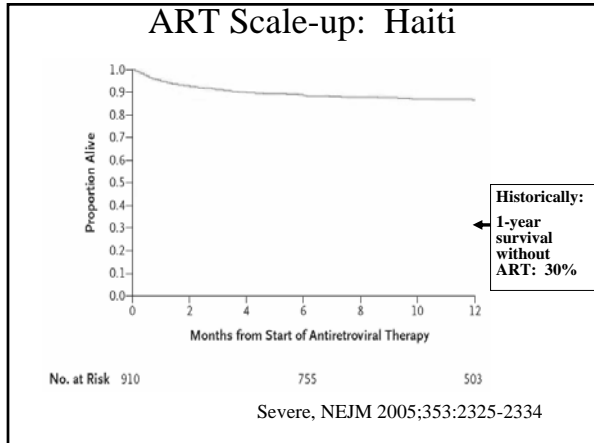
DART (n=1015) mortality (vs historical cohort 1995–2000)

- 17-fold reduction in mortality with ART
- 94% 2-year survival



Munderi P, IAC 2006, #THLB0208

ART Scale-up: Haiti



Progress in ART Scale Up

Achievements

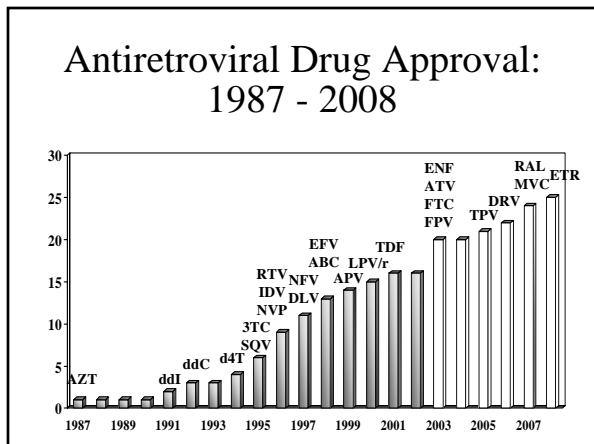
- 1.6 M people on ART
- 24% of 6.8 M in need; male=female
- 21 countries treating >50% in need; capacity growing
- Favorable outcomes in large cohorts
- \$8.3 B mobilized
- G-8 commitment: Universal access by 2010

Challenges

- 10–20% ART mortality in 1st year
- 73% present with CD4+ <100
- <5% of HIV+ children on ART
- <10% of HIV+ pregnant women receive PMTCT
- Less access and ART for IDUs
- Human resource, skill deficits
- Labs, toxicities, costs
- Sustainability – \$25 B needed

UNAIIDS 2006 Report

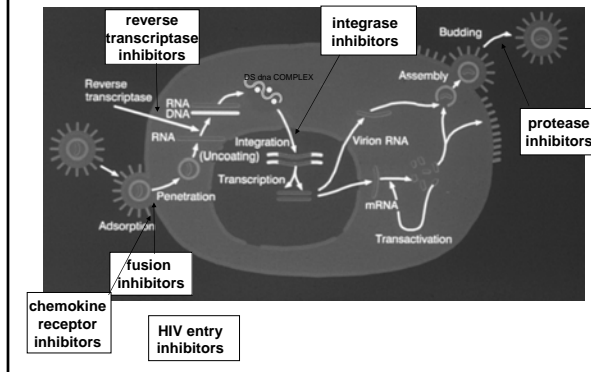
Antiretroviral Drug Approval: 1987 - 2008



Goal of Antiretroviral Therapy

- to suppress HIV RNA (viral load level) as low as possible, for as long as possible
- to preserve or enhance immune function
- to delay clinical progression of HIV disease

Life Cycle of HIV



Antiretroviral Drugs: 2008

nucleoside/tide RTIs (NRTIs)

- zidovudine (ZDV, AZT)
- didanosine (ddI)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TDF)

NNRTIs

- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETR)

protease inhibitors (PIs)

- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- fosamprenavir (FPV)
- tipranavir (TPV)
- darunavir (DRV)

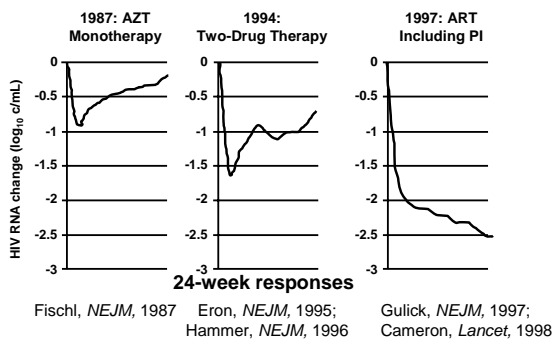
entry inhibitors (EIs)

- enfuvirtide (T-20, fusion inh)
- maraviroc (MVC, CCR5 inh)

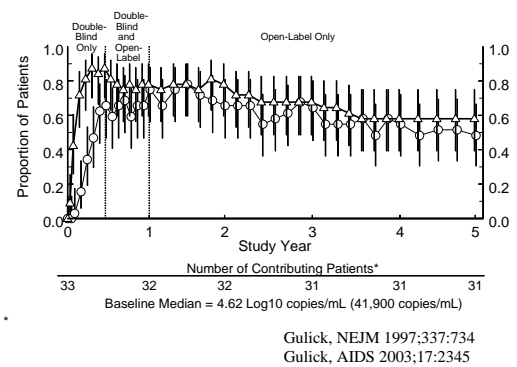
integrase inhibitors (IIs)

- raltegravir (RAL)

Antiretroviral Activity: 1987-1997



Proportions (95% CI) with HIV RNA <500 and <50 cps/ml: IDV/ZDV/3TC Treatment Group - Intent-to-Treat Analysis

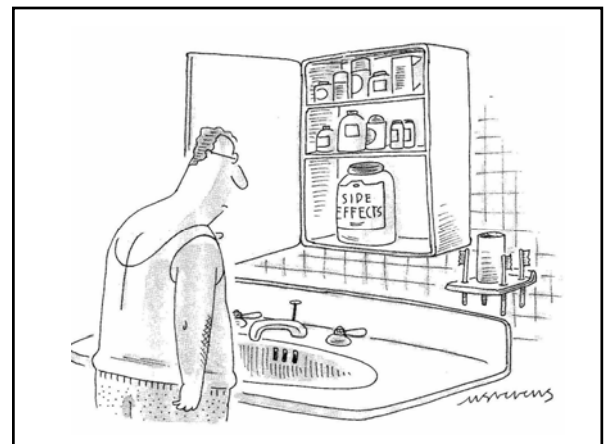


What to start? DHHS Treatment Guidelines

Recommended regimens:

- 2 nucs + NNRTI
 - preferred and alternative choices
- 2 nucs + PI (+/- RTV)
 - preferred and alternative choices

DHHS Guidelines, 12/1/07



3-drug Combination ART: 1996

	8AM	4PM	12 MID
AZT			
+			
3TC			
+			
IDV			

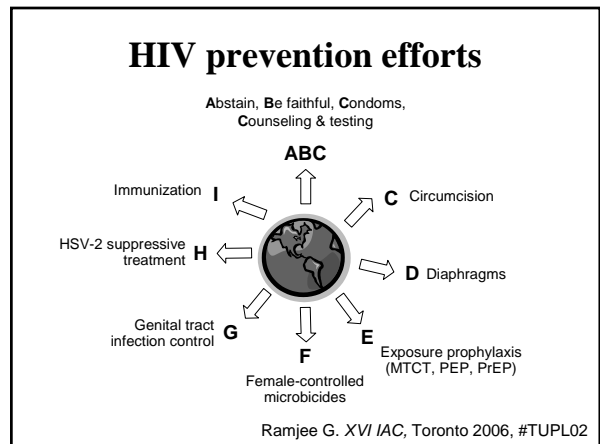
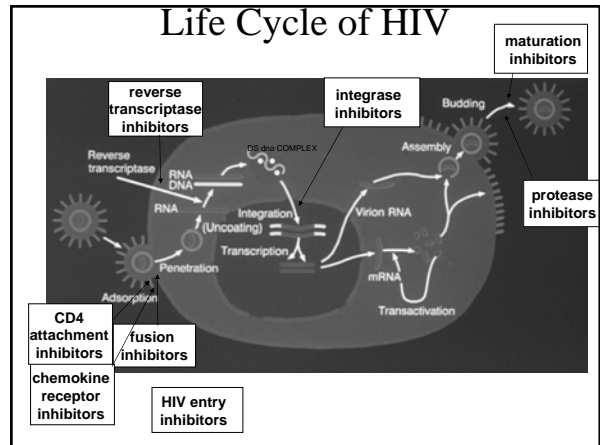
fasting (1 hour before/2 hours after meals)
1 liter of hydration/day

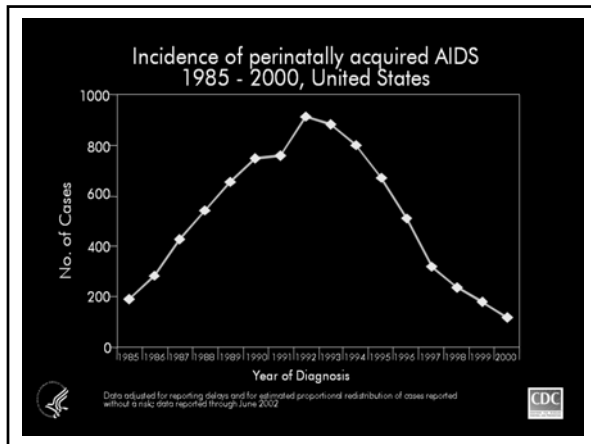
3-Drug Combination ART: 2008

TDF/FTC/EFV

Evidence for Immune Reconstitution with ART

- Decreased mortality
- Decreased morbidity
 - fewer opportunistic infections (OI)
 - discontinuation of OI prophylaxes possible
 - resolution of chronic OI without maintenance therapy
- Resolution of “untreatable” diseases
 - e.g. cryptosporidiosis, microsporidiosis, PML, malignancies
- Expansion of CD4 populations
- Improved lymph node architecture and immune function (e.g., DTH responses).





- ## Conclusions
- HIV/AIDS is a worldwide pandemic.
 - Worldwide, the most common mode of transmission is sexual contact.
 - HIV RNA levels and CD4 cell counts predict disease progression.
 - Antiretroviral therapy (ART) decreases HIV RNA and increases CD4 cell count, and thus prevents disease progression.
 - Current ART consists of 3-drug therapy and is increasingly available worldwide.
 - Prevention of HIV infection continues to be a key strategy.

- ## Acknowledgments
- Cornell HIV Clinical Trials Unit (CCTU)
 - Weill Medical College of Cornell University
 - AIDS Clinical Trials Group (ACTG)
 - Division of AIDS, NIAID, NIH
 - The patient volunteers!
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