

HIV/AIDS 2013



Roy M. Gulick, MD, MPH
 Professor of Medicine
 Chief, Division of Infectious Diseases
 Weill Medical College of Cornell University
 New York City January 31, 2013

HIV/AIDS: Outline

- Epidemiology
- Virology
- Testing
- Transmission
- Pathogenesis
- Natural History
- AIDS-defining illnesses
- Antiretroviral therapy
- Prevention

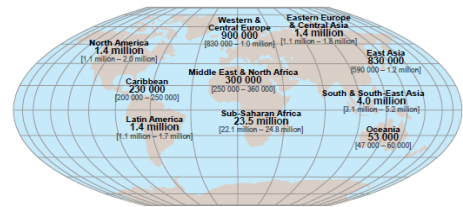
Morbidity and Mortality Weekly Report (MMWR)

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 | 2011



Total: 34.0 million [31.4 million – 35.9 million]

In 2011:

New HIV infections: 2.5 million [2.2, 2.8]

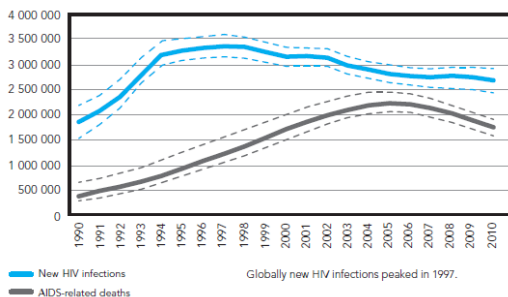
Deaths due to AIDS: 1.7 million [1.5, 1.9]

Adult (aged 15-49) prevalence 0.8%



UNAIDS World AIDS Day Report 2012

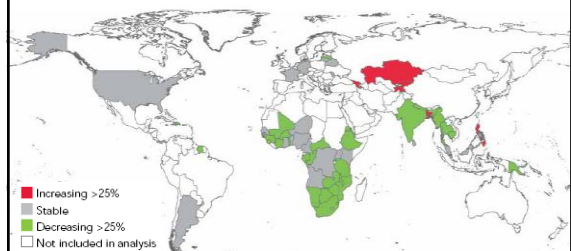
NEW HIV INFECTIONS AND AIDS-RELATED DEATHS



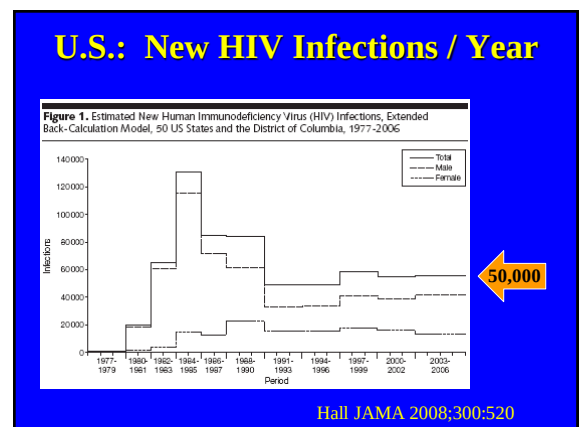
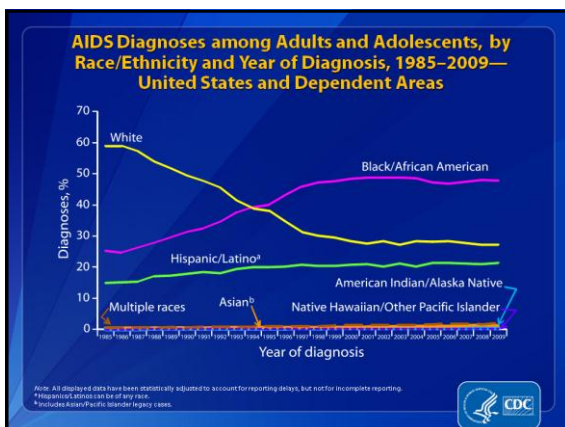
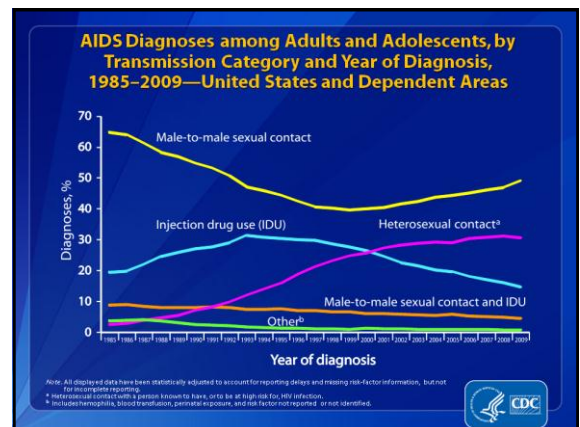
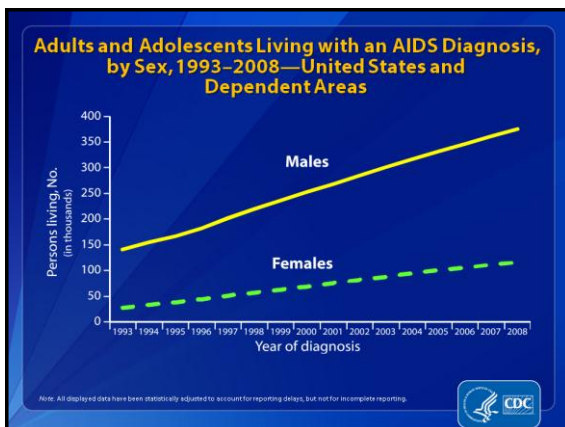
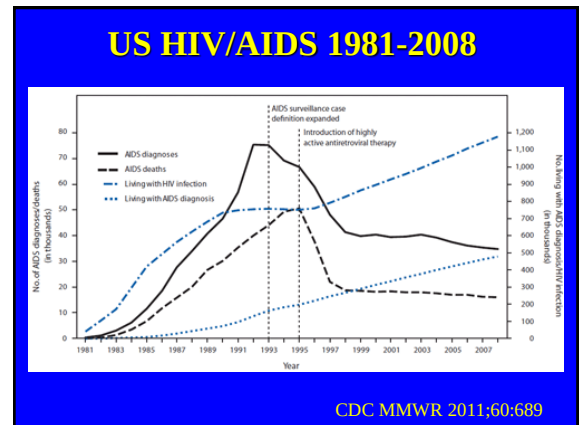
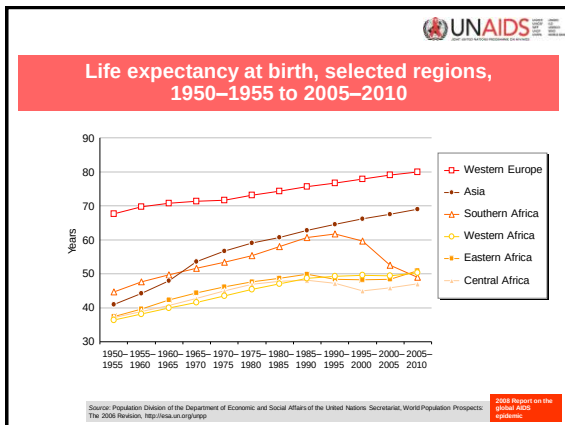
UNAIDS World AIDS Day Report 2011

Changes in the incidence rate of HIV infection, 2001 to 2009, selected countries

Source: UNAIDS



UNAIDS Report 2010



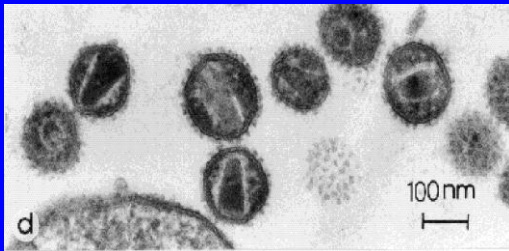
Early History of AIDS

- 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 History of HIV/AIDS

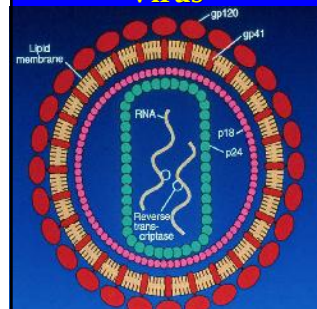
- 1994: AZT prophylaxis for perinatal transmission; 2-drug ART introduced into clinical practice
- 1996: 3-drug ART introduced into clinical practice
- 2000: Durban conference, move to bring ART to developing world gains momentum
- 2012: 6.6 million+ on ART in developing world

HIV-1 Virions



Gelderblom, Human Retroviruses and AIDS 1997

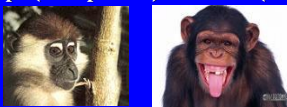
Human Immunodeficiency Virus



- 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+ T-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 (~1920)



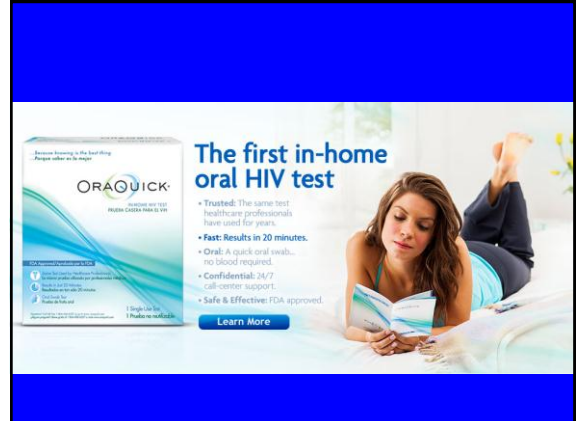
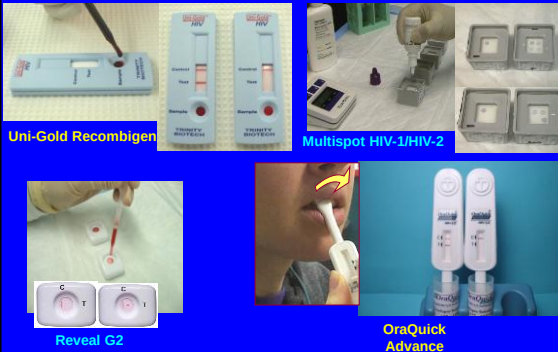
- ? Skin/mucous membrane exposure to infected animals (pets, food)

Hahn Science 2000;287:607
Sharp Philos Trans R Soc Lond B Biol Sci 2010;365:2487-94

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)

Diagnosis: Rapid Tests



Revised Recommendations Adults and Adolescents 9/06

- Routine, voluntary HIV screening for all persons 13-64 in health care settings, not based on risk
- Repeat HIV screening of persons with known risk at least annually
- Opt-out HIV screening with the opportunity to ask questions and the option to decline
- Include HIV consent with general consent for care; separate signed informed consent not recommended
- Prevention counseling in conjunctions with HIV screening in health care settings is not required

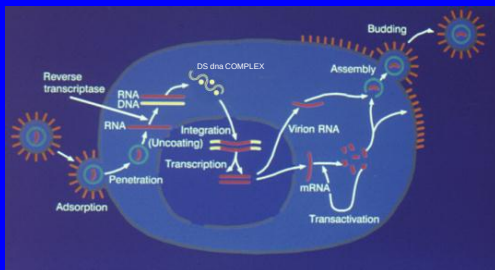


CDC

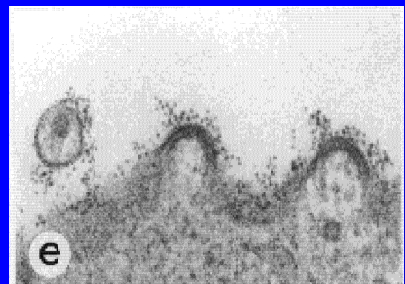
HIV Transmission Routes

- 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



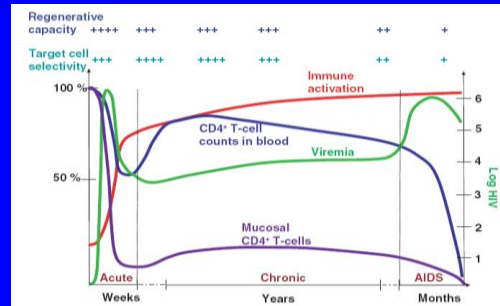
Budding HIV Virions



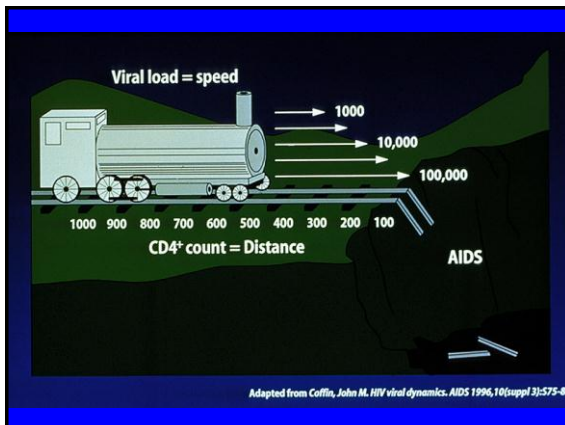
Viral Dynamics -- Summary

- 10 billion new virions created and cleared daily
- 2 billion CD4 cells destroyed daily (twice the rate of replacement by the hematopoietic system)

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):S75-81

CDC Adult AIDS Case Definition

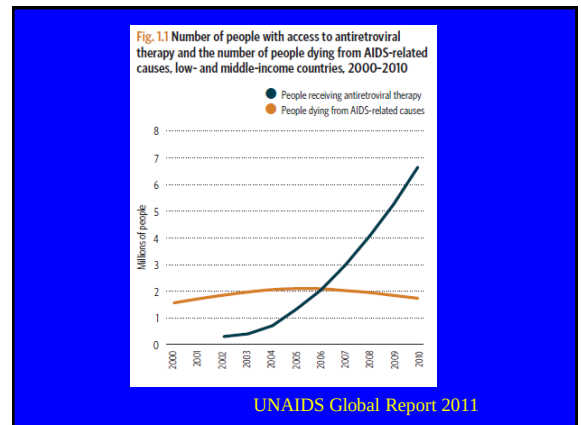
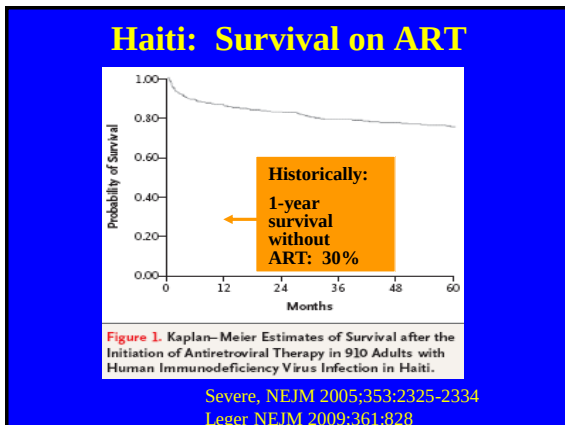
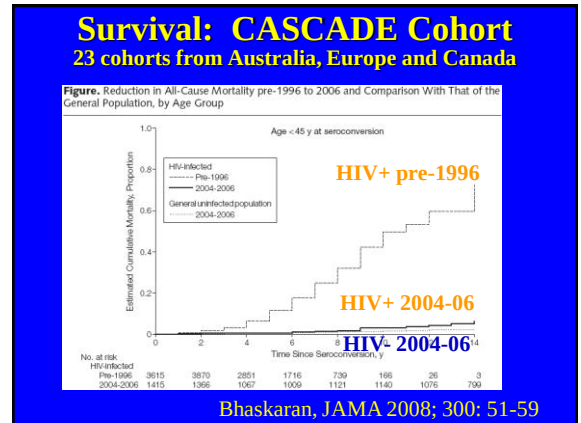
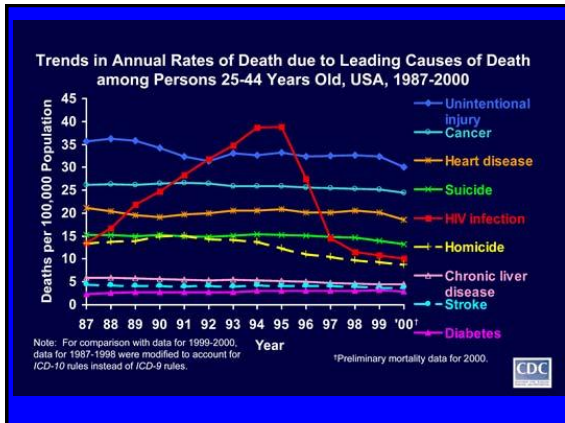
- 1982: "AIDS" -- list of diseases (definitive diagnosis) and disqualifying conditions
- 1985: HIV antibody testing added to definition
- 1987: presumptive diagnoses with a positive HIV antibody added
- 1993: CD4 <200 (without symptoms) and other diagnoses added

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
 - Mycobacterium tuberculosis (bacterium)
 - Cryptococcus (fungus)
 - Wasting disease



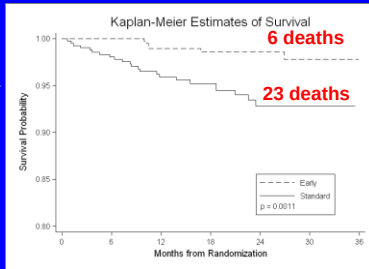
When to start ART?

When to Start?

	AIDS/symptoms	CD4 <200	CD4 200-350	CD4 >350
US DHHS 2012 www.aidsinfo.nih.gov	YES	YES	YES	YES
IAS-USA 2012 www.bhiva.org	YES	YES	YES	YES
UK 2012 www.europeanaidsclinicalsociety.org/	YES	YES	YES	certain patients
EACS 2012 www.who.int/hiv/pub/artv/art2010/	YES	YES	YES	certain patients
WHO 2010	YES	YES	YES	NO

CIPRA HT001 Study

- Randomized study (N=816 patients with CD4 200-350)
- Start immediately vs. wait until CD4 <200 or AIDS event
- DSMB stopped study early
- Mortality / TB ↓



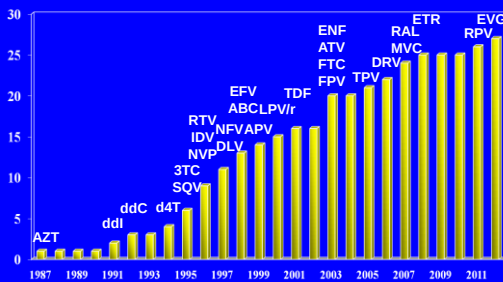
Fitzgerald NEJM 2010;363:257

ART

Easier, less toxic, and more potent therapy



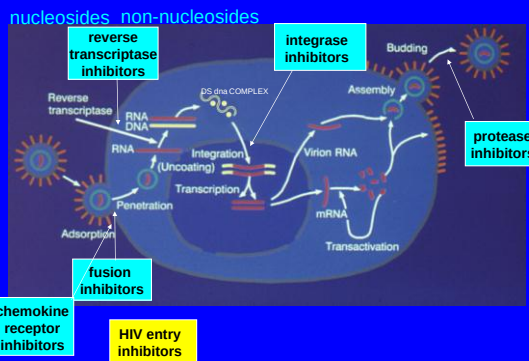
Antiretroviral Drug Approval: 1987 - 2013



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: 2013

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)
- rilpivirine (RPV)

protease inhibitors (PIs)

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

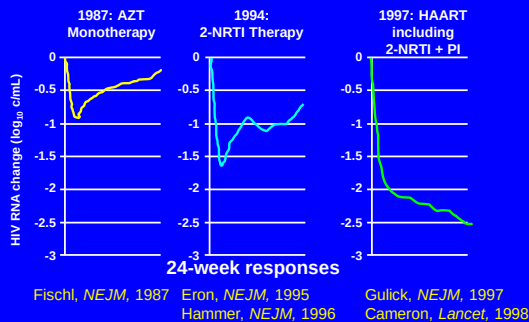
entry inhibitors (EIs)

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

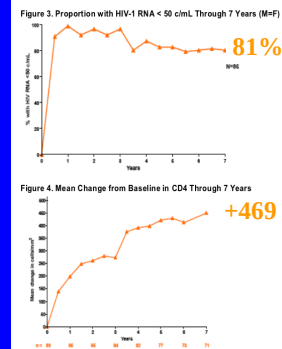
integrase inhibitors (IIs)

- raltegravir (RAL)
- elvitegravir (EVG)

Antiretroviral Activity: 1987-1997



Durability of ART: 7 years



Study 903E:
TDF+3TC+EFV

Cassetti
HIV Clin Trials
2007;8:164-72;
IAS 2008 abstract
#TuPE0057



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

Single Tablet Regimens

TDF/FTC/EFV (2006)



TDF/FTC/RPV (2011)



TDF/FTC/EVG/c (2012)

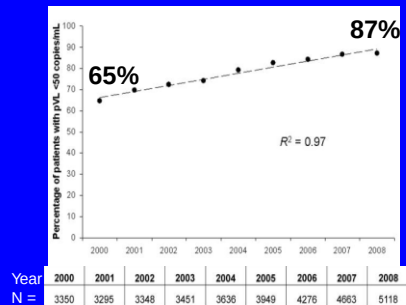


What to start? Preferred Regimens

- **NNRTI-based**
 - tenofovir/emtricitabine + efavirenz
- **PI-based**
 - tenofovir/emtricitabine + atazanavir/r
 - tenofovir/emtricitabine + darunavir/r
- **INSTI-based**
 - tenofovir/emtricitabine + raltegravir

U.S. DHHS Guidelines 3/27/12
www.aidsinfo.nih.gov

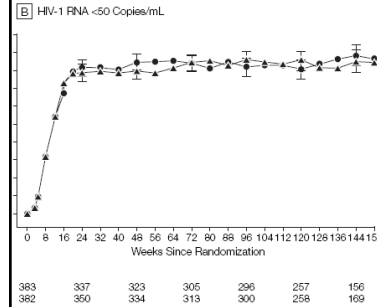
ART Responses in British Columbia 2000-2008



Gill CID 2010;50:98

ACTG 5095: 4-drugs?

Study population: HIV+, treatment-naïve (N=765)



ZDV/3TC/ABC + EFV
(4 drugs)
ZDV/3TC + EFV
(3 drugs)

Conclusion:
4-drug rx is
no better than
3-drug rx

Gulick JAMA 2006;296:769

Antiretroviral Drug Approval: 1987 - 2013

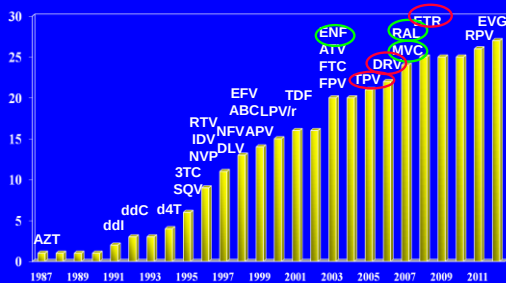
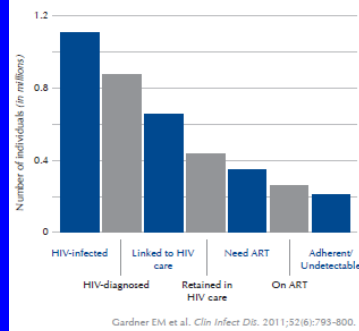


FIGURE 5: Number of HIV-Infected Persons Engaged in Selected Stages of the Continuum of HIV Care – United States



Gardner EM et al. Clin Infect Dis. 2011;52(6):793-800.



HIV Prevention Strategies

Abstain, Be faithful, Condoms,
Counseling & testing

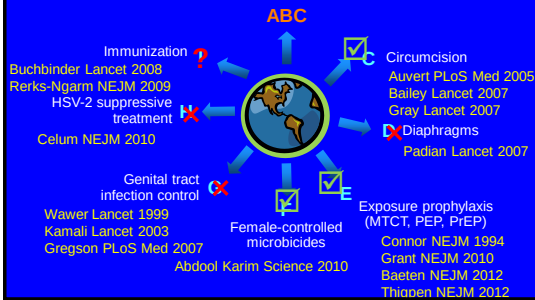
ABC

Adapted from Ramjee IAS Meeting 2006, #TUPL02

HIV Prevention Strategies

Adapted from Ramjee IAS Meeting 2006, #TUPL02

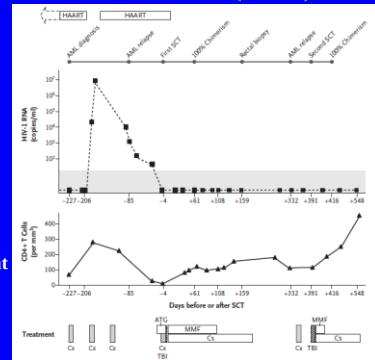
Abstain, Be faithful, Condoms,
Counseling & testing



HIV Cure (N=1)

HIV-1 RNA

CD4 cell count



Hutter NEJM 2009;360:692

Conclusions

- HIV/AIDS is a worldwide pandemic.
- In the U.S., ~20% of HIV+ people don't know they are infected.
- Routine HIV testing should be offered to ALL patients.
- Antiretroviral therapy (ART) ↓ HIV RNA, ↑ CD4 cell counts, prevents disease progression, and prolongs survival.
- Current ART consists of 3-drug therapy and is increasingly available worldwide.
- Current life expectancy for HIV+ people on therapy approaches that of the general population.
- Prevention of HIV infection continues to be key.

Acknowledgments

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



Cornell HIV Clinical Trials Unit

