Online Only Lectures – ID Bootcamp: HIV

Speaker: Roy Gulick, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

ID Bootcamp: HIV

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6/8/2022

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Disclosures of Financial Relationships with Relevant Commercial Interests

- No pharmaceutical or device company relationships.
- Co-Chair, U.S. DHHS Adult and Adolescent ART Treatment Guidelines Panel

ID Boards – Medical Content: 15% HIV

- Epidemiology (<2%)
- Pathogenesis (<2%)
- Lab testing (<2%)
- HIV Treatment Regimens (4.5%)
- Opportunistic Infections (5%)
- Malignancies (<2%)
- Other complications of HIV (2%)
- Related issues (<2%)

Morbidity and Mortality Weekly Report (MMWR): 1981

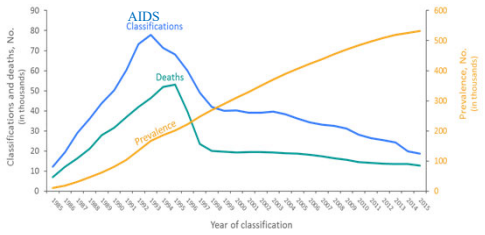
1981 June 5;30:250–2

Pneumocystis Pneumonia – Los Angeles

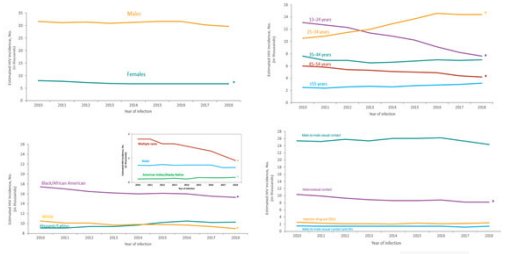
In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV)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

2022: >79 million people infected globally; ~1/2 have died

AIDS, Deaths, and Diagnosed HIV Infection Ever Classified 1985–2015 — US and 6 Dependent Areas



HIV Incidence ≥13 Years Old 2010–2018—U.S.



CDC

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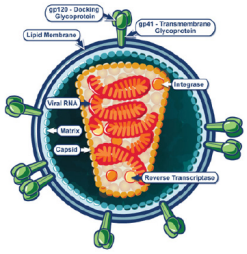
Human Immunodeficiency Virus (HIV)



- formerly HTLV-III; isolated 1983-4
- 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
- zoonosis from primates (~1900)
- target cell: CD4+ T-lymphocyte

Question 1

Which is the current sequence of initial and confirmatory HIV diagnostic testing?

A. ELISA, followed by Western Blot.
B. ELISA, followed by HIV RNA.
C. ELISA, followed by immunoassay.
D. HIV RNA, followed by Western Blot.
E. HIV RNA, followed by ELISA.
F. HIV RNA, followed by immunoassay.

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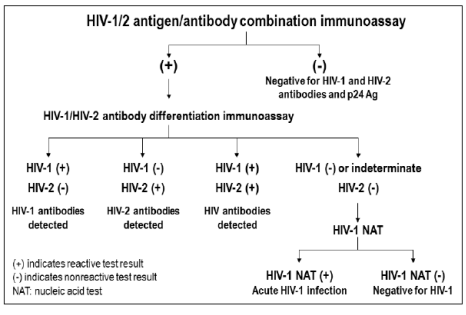
HIV Testing

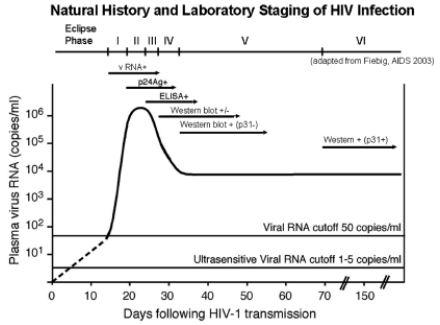
- HIV antibody testing (indirect)
  - Screening test: HIV-1, HIV-2 antibodies by ELISA
  - If repeatedly positive, proceed to confirmatory test
    - Immunoblot or 2nd HIV rapid test
  - 20-minute oral test and 1-minute blood test
- HIV viral testing (direct)
  - p24 antigen
  - viral culture
  - HIV RNA (viral load)
- Newer combination antibody + antigen test
  - window period 3 months → 2 weeks

Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens



CDC 6/14

Natural History and Laboratory Staging of HIV Infection



Cohen JID 2010;202:S270

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Question 2

Who should NOT be routinely offered HIV testing?

A. 32 year old pregnant woman in a stable relationship.
B. 23 year old sexually active monogamous gay man.
C. 75 year old former injection drug user.
D. 10 year old pre-pubescent girl.
E. All of them should be routinely offered HIV testing.

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U.S. Preventive Services Task Force (UPSTF)

Recommendations

- Screen adolescents and adults ages 15 to 65 for HIV infection.
- Screen all pregnant women.
- Younger adolescents and older adults who are at increased risk should also be screened.
- This is a grade A recommendation ("high certainty that the net benefit is substantial").

- Federal Rule: Private Insurance and Medicare must offer A or B services without a co-pay.

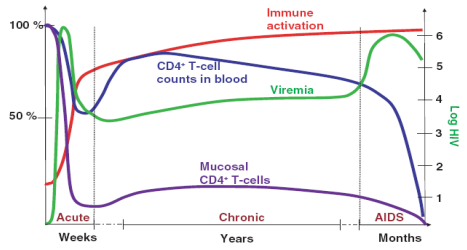
Ann Intern Med 2013;159:1-36

HIV Transmission Risks

Exposure from HIV+ source	Risk per exposure (%)	Risk per exposure (number)
Blood transfusion	93%	9/10
Needle-sharing injection drug use	0.6%	1/167
Percutaneous needle stick	0.2%	1/500
Receptive anal sex	1.4%	1/70
Insertive anal sex	0.1%	1/1000
Receptive penile-vaginal sex	0.08%	1/1250
Insertive penile-vaginal sex	0.04%	1/2500
Oral sex	low	very low
Mother-to-child	23%	1/4

Patel AIDS 2014;28:1509

Time Course of HIV Infection



Grossman Nature Medicine 2006; 12: 289-295

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

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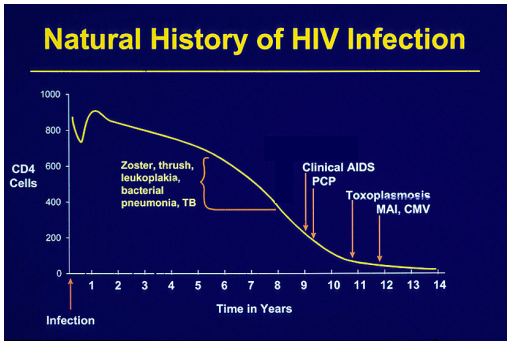
Opportunistic Infections (OI)

- Definition: Infection caused by an organism capable of causing disease only in a host whose resistance is lowered (by other diseases or by drugs)
- AIDS-related:
  - Bacterial: MAC, tuberculosis
  - Fungal: PCP, Cryptococcus, Histoplasma
  - Viral: CMV
  - Parasitic: Toxoplasma
  - Malignancies: Kaposi's sarcoma, NH-lymphoma

Natural History of HIV Infection



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 and prolong healthy survival

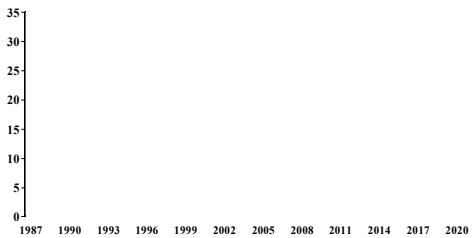
When to start ART?

Guidelines	AIDS/ sx	CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS '22 www.clinicalinfo.hiv.gov					
IAS-USA '20 JAMA 2020;324:1651-69					

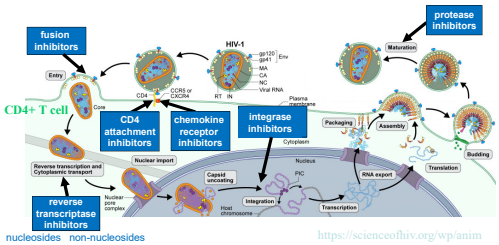
U.S. DHHS HIV Treatment Guidelines (1/22):

- ART is recommended for all persons with HIV to ↓ morbidity and mortality **(AI)** and to prevent transmission of HIV to others **(AI)**.
- Initiate ART immediately (or as soon as possible) after HIV diagnosis.

Antiretroviral Drug Approval: 1987 - 2022



Life Cycle of HIV



https://scienceofhiv.org/wp/animations/

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Approved ART: 2022*

nucleoside/tide RTIs (NRTIs)
- zidovudine (ZDV, AZT)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TAF, TDF)

NNRTIs
- nevirapine (NVP)
- efavirenz (EFV)
- etravirine (ETR)
- rilpivirine (RPV)
- doravirine (DOR)

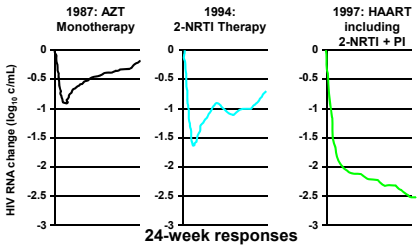
protease inhibitors (PIs)
- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- tipranavir (TPV)
- darunavir (DRV)

entry inhibitors (EIs)
- enfuvirtide (T-20, fusion inhibitor)
- maraviroc (MVC, CCR5 antagonist)
- ibalizumab (IBA, CD4 post-attachment inhibitor)
- fostemsavir (FTR, CD4 attachment inhibitor)

integrase inhibitors (IIs)
- raltegravir (RAL)
- elvitegravir (EVG)
- dolutegravir (DTG)
- bictegravir (BIC)
- cabotegravir (CAB)

*ddI, ddC, d4T, DLV, and APV (and FPV 1/24) discontinued from market

Antiretroviral Activity: 1987-1997



Fischl, *NEJM*, 1987 Eron, *NEJM*, 1995 Hammer, *NEJM*, 1996 Gulick, *NEJM*, 1997 Cameron, *Lancet*, 1998

Question 3

Which class of ART is recommended for initial HIV treatment for most patients?

A. All nucleoside analog (NRTI) regimen.
B. Non-nucleoside (NNRTI)-based regimen.
C. Protease inhibitor (PI)-based regimen.
D. Integrase inhibitor (INSTI)-based regimen.
E. Entry inhibitor (EI)-based regimen.

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What to start?

Recommended regimens:

1 or 2 nucleoside analogues + integrase inhibitor
bictegravir/tenofovir alafenamide (TAF)/emtricitabine (FTC)
dolutegravir/abacavir/lamivudine
dolutegravir + (FTC or lamivudine [3TC]) + (TAF or tenofovir disoproxil fumarate [TDF])
dolutegravir/3TC

Alternative regimens: non-nucleoside (NNRTI)-, protease inhibitor (PI)-, and elvitegravir (EVG)-based

U.S. DHHS HIV Treatment Guidelines 1/22

Approved Single-Tablet ART Regimens

TDF/FTC/EFV (2006)
TDF/FTC/RPV (2011)
TDF/FTC/EVG/c (2012)
ABC/3TC/DTG (2014)
TAF/FTC/EVG/c (2015)
TAF/FTC/RPV (2016)

DTG/RPV (2017)*
TAF/FTC/BIC (2018)
TAF/FTC/DRV/c (2018)
TDF/3TC/DOR (2018)
DTG/3TC (2019)

*FDA approved for maintenance therapy

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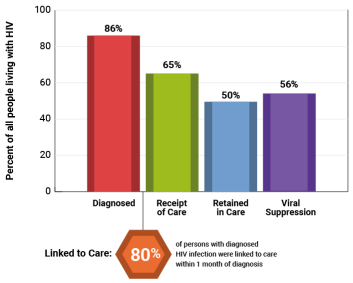
Cabotegravir (CAB)

- Integrase inhibitor similar to similar to dolutegr
- Potent in people with HIV (5, 10, 30, 60 mg ora
  Spreen HIV Clin Trials 2013;14:192
- Nanotechnology formulation; injectable
- Phase 3 studies of IM CAB/rilpivirine (RPV) for treatment switch demonstrated non-inferiority to standard oral treatment regimens
  - Orkin NEJM 2020;382:1124
  - Swindells NEJM 2020;382:1112
- U.S. FDA approved the combination of IM CAB + RPV monthly for switch treatment in January 2021
  - For patients undetectable on ART without a history of virologic failure, drug resistance, or chronic HBV infection

FDA APPROVED

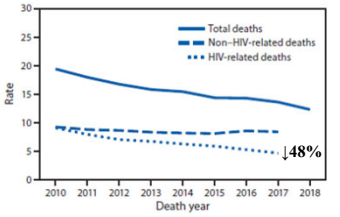
Prevalence-based HIV Care Continuum, U.S. and 6 Dependent Areas, 2018



www.hiv.gov

U.S. HIV Deaths: 2010-2018

FIGURE 1. Age-adjusted rates* of total deaths,† human immunodeficiency virus (HIV)–related deaths,§ and non–HIV-related deaths among persons aged ≥13 years with diagnosed HIV infection — United States, 2010–2018¶

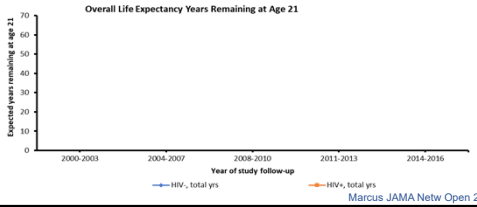


Bosh, MMWR 2020;69:1717-24

Kaiser: Life Expectancy of People with/without HIV

Cohort of adults with HIV in care 2000-2016 (N=39,000)
Matched 1:10 with uninfected (N=387,785)
Study population:
Avg 41 yo, Asian 5%/Black 25%/Latinx 24%/white 45%, MSM 70%, HS 20%, IDU 8%
Results: Narrowing of the survival gap – now 9 years shorter with HIV vs no HIV

- *No gap if ART initiated before CD4 < 500!*



Marcus JAMA Netw Open 2020;3:e207954

HIV Prevention Strategies

Adapted from Ramjee *IAS Meeting* 2006, #TUPL02

Abstain, Be faithful, Condoms, Counseling & testing

ABC

Immunization ?
Rerks-Ngarm NEJM 2009

HSV-2 suppressive treatment
Celum NEJM 2010

Genital tract infection control
Grosskurth Lancet 1995
Wawer Lancet 1999
Kamali Lancet 2003
Gregson PLoS Med 2007

Circumcision
Auvert PLoS Med 2005
Bailey Lancet 2007
Gray Lancet 2007

Diaphragms
Padian Lancet 2007

Exposure prophylaxis with ART
Connor NEJM 1994
Grant NEJM 2010
Cohen NEJM 2011
Baeten NEJM 2012
Thigpen NEJM 2012
Choopanya Lancet 2013, etc.

Female-controlled microbicides
Abdool Karim Science 2010
Marrazzo CROI 2013

Question 4

Which PrEP regimen is FDA-approved for at-risk men and women?

A. Daily tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC).
B. Daily tenofovir alafenamide (TAF)/FTC.
C. On-demand TDF/FTC.
D. On-demand TAF/FTC.
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E. All of the above.

HIV Prevention Strategy: PrEP

- Pre-exposure prophylaxis
- Strategy of administering HIV medications to uninfected, at-risk individuals
- Optimal drug candidates:
  - potent, safe, tolerable, and convenient
  - = co-formulated tenofovir/FTC
- Potential concerns:
  - used widely for treatment; drug resistance; toxicities (kidney, bone); cost (>$10,000/year)
- 2012: FDA approves TDF/FTC for PrEP
- 2019: FDA approves TAF/FTC for PrEP
- 2021: FDA approves injectable CAB for PrEP

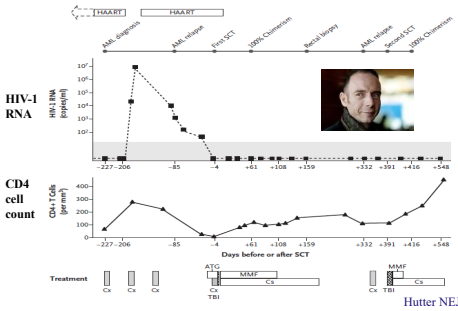
Recent PrEP Studies

Study (reference)	Study population	Design	Results: Reduction in HIV Infection
PROUD McCormack Lancet 2015;387:54-60	544 HIV- MSM in UK	TDF/FTC (daily) immediate vs. delayed	TDF/FTC immediate: **86% reduction**
IPERGAY Molina NEJM 2015;373:2237	400 HIV- MSM in France and Canada	TDF/FTC (on demand) vs. placebo	TDF/FTC: **86% reduction**
HPTN 083 Landovitz NEJM 2022;385:595	4570 HIV- MSM and transgender women globally	TDF/FTC (daily) vs. CAB injections (every other month)	CAB non-inferior and **superior** to TDF/FTC

Federal Plan to End AIDS by 2030

February 2019
https://www.hiv.gov/

HIV Cure (N=*1*) 3!



Hutter NEJM 2009;360:692

Cure #2
Gupta
Nature
2019;568:
244-248.

Cure #3
Bryson
CROI 2022
Abstract
#65

Conclusions

- HIV/AIDS is a worldwide pandemic.
- Routine HIV testing should be offered to ALL patients.
- Antiretroviral therapy (ART) ↓ HIV RNA, ↑ CD4 cell counts, prevents disease progression, and prolongs healthy 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 continues to be key.
- Cure research is in progress.

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Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
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- NY Presbyterian
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- Division of AIDS, NIAID, NIH
- The patient volunteers!

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