HIV Basics: the History and Current State of the Epidemic

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USAID PEER/Liberia ID Lecture Series
24 September 2020
Goals

- Provide HIV in brief historical context
- Illustrate life cycle of HIV and demonstrate effects of various drug classes on disruption of life cycle
- Discuss basic treatment strategies
- Highlight useful sources of information
Origins
"The Hunter" Theory

Most cases of HIV are HIV-1 M (minimal clinical significance).

HIV-1 P from gorillas; maybe HIV-1 O too.

HIV-1 STANDS: HIV-1 M, HIV-1 N, HIV-1 O.

HIV-2 from Sooty Mangabey.

HIV-1 from Chimp.
Late 1800s - 1981

- HIV spreads ~1920-1950 along the Congo river: Brazzaville to Leopoldville (now Kinshasa)
- Haitian professionals training in Congo in mid-1960s return
- From there, virus jumps to US ~1969
- By 1960s, African doctors note rise in OIs and wasting in urban areas (eg Kinshasa/Brazzaville)
- Then...
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.

Patient 1: A previously healthy 33-year-old man developed P. carinii pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation CMV titer in October 1980 was 256; in May 1981 it was 32.* The patient’s condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual P. carinii and CMV pneumonia, but no evidence of neoplasia.
The 1980s: “And The Band Played On”

- Initially called “GRID”—Gay Related Immune Syndrome
- Mult causal etiologies espoused, including “poppers,” gay lifestyle; several scientists understood quickly that it was likely STV
- Also known as “4H Syndrome”—Homosexuals, Hemophiliacs, Haitians, and Heroin users
- AIDS coined July 1982
1980s con’t

- 1984: virus is identified (Gallo/Montagnier)
- 1985: China reports AIDS; last major populated region on earth to do so
- 1987: AZT approved
- By end of 1980s, \(~8\text{ million people}\) with HIV infection
- For more: *And The Band Played On*, Randy Shilts of San Francisco Chronicle (USA epidemic)
Where things stand now
2016 Estimated Prevalence ~37 M

~700,000 deaths/ year
Fortunately it’s not all bad news
Number of new HIV infections in 2016 and change since 2010

1.8 million people newly infected in 2016 globally

Decrease in number of new infections across the global population each year since 2010

- 60% in E. Europe and Central Asia
- 13% in Asia Pacific
- 4% in W. and C. Europe and N. America
- 9% in Western and Central Africa
- 29% in East and Southern Africa
- 5% in Latin America and Caribbean
- 9% in Middle East and North Africa
- 790,000 in East and Southern Africa
- 370,000 in Western and Central Africa
- 115,000 in Latin America and Caribbean
- 190,000 in E. Europe and Central Asia
- 270,000 in Asia Pacific

AVERT.org
Source: UNAIDS Data 2017
What does infection look like
Acute Retroviral Syndrome (~1-3 months)

CD4

Time

“AI DS”
(advanced HIV)
HIV VL

Viral Set Point

Time
Inverse correlation between viral load & CD4 decline

Untreated HIV is a train heading toward a cliff:
CD4 count = distance to the cliff (immune collapse);
Viral Load = speed of the train

Viral replication, kinetics & resistance
HIV Replication and Mutation
(highly simplified)

- Suppose $10^4$ virions/mL (ie VL = 10,000)
- RNA Pol error rate $\sim 1$ every $10^4$ nucleotides
- HIV genome is $10^4 \sim$ nucleotides long
- HIV replication produces $10^8$ virons/day
- *Given replication kinetics, all possible point mutations can be produced each day in untreated pts*
One additional agent (enfuvirtide) blocks entry from a different mechanism than CCR5 inhibition.
Treatment options as of 2020 by class

Reverse Transcriptase Inhibitors (NRTI, “Nukes”)
- 3TC (lamivudine)
- FTC (emtricitabine)
- TDF/TAF (tenofovir)
- ABC (abacavir)
- also: ddl, d4T, AZT (ZDV)

Reverse Transcriptase Inhibitors (NNRTI, or “Non-Nukes”)
- EFV (efavirenz)
- RPV (rilpiverine)*
- DOR (doravirine)
- ETR (etravirine)
- also: NVP (nevirapine)

Integrase Inhibitors
- DTG (dolutegravir)
- RAL (raltegravir)
- EVG (elvitegravir)
- BIC (bictegravir)
- CAB (cabotegravir)*

Entry Inhibitors
- MVC (maraviroc)

Fusion Inhibitors
- T20 (enfuvirtide)—SubQ

Protease Inhibitors
- ATV (atazanavir)
- DRV (darunavir)
- also: FPV (fosamprenavir), LPV/r (lopinavir), TPV (tipranavir), SQV (saquinavir), NFV (nelfinavir)

“Boosters”
- r (ritonavir)
- c (cobicistat)
HIV Replication and Mutation, reconsidered

RNA Pol error rate ~1 every $10^4$ nucleotides

HIV replication produces $10^8$ virons/day

One “pressure point” (ie, active medication) is not enough; virus will develop resistance mutations almost immediately

This is the reasoning behind HAART
HAART basics

- Basic strategy: pressure virus at *three* separate points
  - 2 nukes + integrase inhibitor (eg TDF/FTC + DTG), or
  - 2 nukes + protease inhibitor (eg TDF/FTC + DRV/r), or
  - 2 nukes + non-nuke (eg TDF/FTC + EFV—*but* this is 2nd line)

- OR:
  - Truvada plus Dolutegravir;
  - Truvada plus Atazanavir;
  - Truvada plus Efavirenz (or in one pill as Atripla)
HAART basics con’t

- Integrase Inhibitors favored over Protease Inhibitors because of once-daily dosing/combo pills
- Must consider many variables when prescribing
- For example: Hep B status, VL >100K, HLA status, CKDz, psych illness, cirrhosis, QTc, TB on rif, osteoporosis, other
Selected HIV web resources

You will need them.

Over and over.
### Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

**INSTI + 2 NRTIs:**

- DTG/ABC/3TC\(^*\) (AI)—if HLA-B\(^*\)5701 negative
- DTG + tenofovir\(^*\)/FTC\(^*\) (AI for both TAF/FTC and TDF/FTC)
- EVG/c/tenofovir\(^*\)/FTC (AI for both TAF/FTC and TDF/FTC)
- RAL\(^*\) + tenofovir\(^*\)/FTC\(^*\) (AI for TDF/FTC, All for TAF/FTC)

### Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

**Boosted PI + 2 NRTIs:** (In general, boosted DRV is preferred over boosted ATV)

- (DRV/c or DRV/r) + tenofovir\(^*\)/FTC\(^*\) (AI for DRV/r and All for DRV/c)
- (ATV/c or ATV/r) + tenofovir\(^*\)/FTC\(^*\) (Bl)
- (DRV/c or DRV/r) + ABC/3TC\(^*\)—if HLA-B\(^*\)5701—negative (BII)
- (ATV/c or ATV/r) + ABC/3TC\(^*\)—if HLA-B\(^*\)5701—negative and HIV RNA <100,000 copies/mL (Cl for ATV/r and CIII for ATV/c)

**NNRTI + 2 NRTIs:**

- EFV + tenofovir\(^*\)/FTC\(^*\) (Bl for EFV/TDF/FTC and BlI for EFV + TAF/FTC)
- RPV/tenofovir\(^*\)/FTC\(^*\) (Bl)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm\(^3\)

**INSTI + 2 NRTIs:**

- RAL\(^*\) + ABC/3TC\(^*\) (CII)—if HLA-B\(^*\)5701—negative and HIV RNA < 100,000 copies/mL

**Regimens to Consider when ABC, TAF, and TDF Cannot be Used:**

- DRV/r + RAL (BID) (CII)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm\(^3\)
- LPV/r + 3TC\(^*\) (BID)\(^*\) (CII)
HIV AND AIDS IN EAST AND SOUTHERN AFRICA REGIONAL OVERVIEW

East and Southern Africa (2019)
- 20.7m people living with HIV
- 6.7% adult HIV prevalence (ages 15-49)
- 730,000 new HIV infections
- 300,000 AIDS-related deaths
- 73% adults on antiretroviral treatment*
- 58% children on antiretroviral treatment*

*All adults/children living with HIV

Source: UNAIDS Data 2020

KEY POINTS
- East and Southern Africa is the region most affected by HIV in the world and is home to the largest number of people living with HIV.
- The HIV epidemic in this region is generalised but young women, men who have sex with men, transgender people, sex workers, prisoners and people who inject drugs are at an increased vulnerability to infection.
Clinical Studies of Integrase Inhibitors: A Comprehensive Review

Martin Markowitz, MD, discusses recent data from clinical studies involving the use of the integrase inhibitors raltegravir and elvitegravir. Click here to start.

Integrating New Antiretroviral Agents Into Therapeutic Strategies for Treatment-Experienced Patients

Interactive Virtual Presentation:
Watch, listen, and make treatment decisions as Eric S. Daar, MD, leads you through a series of real-life treatment scenarios.
HIV/AIDS News
From Medscape Medical News, TheHeart.org, Reuters and more

IL-7 Therapy Boosts Immune Response in Cancer Patients

Bush Urges Congress to Pass AIDS Funds

HIV-Related Mortality Near Normal in First 5 Years on HAART

FDA Safety Changes: Atripla, Halcion, Restoril

CVD is a "Major Killer" in HIV+ Patients, but Underrecognized by Doctors

HIV/AIDS CME

CME NY Course 2008: Recent Additions to ART Classes

CME NY Course 2008: Pharmacology of Antiretrovirals

CME NY Course 2008: HIV Resistance Issues

CME NY Course 2008: Progress in Antiretroviral Therapy

CME NY Course 2008: Host-Related Issues

HIV/AIDS Features

Immune Activation and AIDS Pathogenesis: What causes immune activation in HIV infection?

AIDS, July 9, 2008

CME NY Course 2008: Recent Additions to ART Classes

Medscape HIV/AIDS, July 9, 2008
Lots of stuff to do.

Go and learn.