HIV/AIDS:
35 years later

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Disclosure

Nothing to disclose
Objectives

• Review the history and epidemiology of HIV
• Discuss factors for transmission
• Discuss signs and symptoms of acute and chronic HIV infection
• Discuss recommendations for diagnosis and when to start therapy
• Discuss HIV exposure prophylaxis and prevention
30 Years of HIV/AIDS in the US

• [https://www.youtube.com/watch?v=kc0_Rh6f6dw#t=12](https://www.youtube.com/watch?v=kc0_Rh6f6dw#t=12)
Epidemiology

• Since the start of the epidemic:
  • 78 million people have been infected
  • 39 million people have died

• Currently:
  • 35 million people living with HIV/AIDS
  • 1.5 million people died of AIDS-related illnesses worldwide in 2013

• Prevalence is estimated at 0.8% worldwide

• Sub-Saharan Africa remains most severely affected
  • 1 in 20 adults living with HIV
  • This accounts for nearly 71% of the PLHIV
Adult HIV prevalence (15–49 years), 2013
By WHO region

Prevalence (%) by WHO region
- Western Pacific: 0.1 [0.1–0.1]
- Eastern Mediterranean: 0.1 [0.1–0.1]
- South-East Asia: 0.3 [0.3–0.4]
- Europe: 0.4 [0.3–0.4]
- Americas: 0.5 [0.4–0.6]
- Africa: 4.5 [4.2–4.7]

Global prevalence: 0.8% [0.7–0.8]

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

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Rates of Diagnoses of HIV Infection among Adults and Adolescents, 2013—United States and 6 Dependent Areas

N = 47,958  Total Rate = 18.0

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.
Rates* of Persons Living with HIV Disease, by County of Residence,** Reported through 2013, Florida

Statewide Rate:
529.0 Per 100,000 Population
N=102,189

*Rates are based on 2013 population (denominator) data from Florida CHARTS.
**County rates exclude data from the Department of Correction.
Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2013—United States and 6 Dependent Areas

N = 47,958

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting.

a Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

b Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.
# Estimated Incidence of HIV Infection, Overall, and by Sex, 2007-2010 — United States

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. (95% CI)</td>
<td>No. (95% CI)</td>
<td>No. (95% CI)</td>
<td>No. (95% CI)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39,600 (34,900–44,300)</td>
<td>35,500 (31,300–39,700)</td>
<td>34,400 (30,300–38,400)</td>
<td>38,000 (33,400–42,600)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>13,600 (11,500–15,600)</td>
<td>12,000 (10,100–13,900)</td>
<td>10,600 (9,000–12,300)</td>
<td>9,500* (8,100–10,900)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>53,200 (47,000–59,400)</td>
<td>47,500 (42,000–53,000)</td>
<td>45,000 (39,900–50,100)</td>
<td>47,500 (42,000–53,000)</td>
</tr>
</tbody>
</table>

Note: Because column totals for estimated numbers were calculated independently of the values for the subpopulations, the values in each column may not sum to the column total.

*CI = Confidence Interval. Confidence intervals reflect random variability affecting model uncertainty but may not reflect model-assumption uncertainty; thus, they should be interpreted with caution.

* Indicates significantly different (p<0.05) from the 2008 estimate for the same group.
Trends in Annual Age-Adjusted* Rate of Death Due to HIV Infection, United States, 1987–2010

Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.

*Standard: age distribution of 2000 US population
Trends in Annual Age-Adjusted* Rate of Death among Persons with Diagnosed HIV Infection Ever Classified as Stage 3 (AIDS), United States, 1987–2010

*Standard age distribution of 2000 US population
Very Basic Virology - Retrovirus

- HIV-1 and HIV-2 derived from Simian Immunodeficiency Virus (SIV)
- Primate to human transmission, multiple different occurrences
1. Replicate via reverse transcription of viral RNA into DNA
   - Reverse transcriptase does not double check = high mutation/error rate
   - 10-100 more errors than human DNA Polymerase

2. Incorporated into the host genome
Virology

• Exceptional survival advantages
  • Integration into the host DNA
  • High mutation rate
  • Ability to remain latent
  • Targets cells of the immune system such as CD$_4^+$ and macrophage cells – decreases cellular immunity
  • Replicates intracellularly
HIV Transmission – Sexual

• Predominant method
  • Homosexual and heterosexual – attribution varies geographically

• Contraction risk varies
  • Multiple sexual partners
  • Prevalence of HIV in the geographic region
  • Sexual practices, unprotected sex
  • Concomitant sexually transmitted disease (e.g. herpes)
  • HIV viral load of the infected partner
  • HAART treatment
  • Genital irritation/trauma (e.g. excessive use of spermicides)
Decisions about sexual activity and condom use have a major effect on the risk for HIV transmission.

That's why it's so important to always practice safe sex.

This chart shows how the relative risk for a person living with HIV transmitting HIV to a person without the disease varies according to sexual activity and condom use. For example, insertive oral sex with a condom has a low risk for HIV transmission. But receptive anal sex without a condom is 2,000 times riskier. Not having sex is the best way to protect against the transmission of HIV. But if you are having sex, it's important to know that all sex is not the same when it comes to transmitting HIV. 

*ACT* AID$ | HIVMA | AID$
HIV Transmission

• Injectable drug use
  • Duration of drug use
  • Frequency of needle sharing
  • Prevalence of HIV in the community
  • Socioeconomic status/homelessness

• Blood/blood products and tissues
  • Routine serologic testing of blood donations began in 1985 in the US**
    • **Does not prevent all transmission – window still exists**
  • Organ transplantation (avascular tissues not associated)
HIV Transmission

• **Perinatal (vertical) transmission**
  • May occur at any stage (in utero -> breastfeeding)
  • Reduced with anti-retroviral therapy (before and during labor)
  • Reduced with Cesarean section birth
  • Chorioamnionitis, preterm birth and/or prolonged rupture of membranes

• **Occupational exposure**
  • *Percutaneous*, cutaneous and mucus membrane exposure to blood/fluids
  • Risk is very low – reduced further with post-exposure prophylaxis
  • Reduced with new safety activated infusion devices and education
Body Fluids and HIV Infection

• High Risk of Infection
  • Blood
  • Semen
  • Vaginal fluid
  • Breast milk
  • Amniotic fluid
  • Cerebrospinal fluid
  • Synovial fluid

• Low Risk of Infection**
  • Feces
  • Nasal fluid
  • Saliva
  • Sweat
  • Tears
  • Urine
  • Vomit

**Unless contaminated with blood**
Stages of HIV Infection

- Acute
- Clinical Latency
- AIDS
Typical course of human immunodeficiency virus (HIV) infection. The complex, multifactorial, multiphasic, and overlapping factors of the immunopathogenic mechanisms of HIV disease are shown. Throughout the course of HIV infection, virus replicates and immunodeficiency progresses steadily, despite the absence of observed disease during the so-called clinical latency period. Immune activation and cytokine secretion vary among HIV-infected persons, sometimes increasing dramatically as disease progresses. Immune activation and cytokine secretion play a major role in pathogenesis. Adapted from reference 2 by permission of Pantaleo et al. 1993; 328:327-35.
Acute HIV Infection

• Fever
• Lymphadenopathy
• Sweats
• Myalgia
• Arthralgia
• Headache
• Photophobia
• Rash
• Malaise

• Lethargy
• Sore throat
• Anorexia
• Nausea/vomiting/diarrhea
• Mucocutaneous ulcers
• Aseptic meningitis*
• Myelopathy*
• Radiculopathy*
• Peripheral neuropathy*

*less common manifestations
Clinical Latency

- Patients are often asymptomatic
- Virus replicates at a slow rate
- Gradual decline of CD$_4$+ cells
- **Average** duration is 10 years but highly patient specific
HIV Clinical Latency – all created equal?

- Rapid progressors – latency of ≤5 years, viremia
- Typical progressors – average latency (~10 years), viremia
- Long-term non-progressors – latency of decades, viremia
- Elite controllers – permanent latency, no detectable viremia
AIDS

- CD$_4^+$ ≤ 200 or CD$_4$% ≤ 14

- AIDS-defining conditions
  - HIV associated nephropathy
  - HIV associated dementia/encephalopathy
  - Wasting syndrome
  - Malignancies (Kaposi’s Sarcoma, NHL, Cervical cancer)
  - Host of infectious processes
## Opportunistic Infections

<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>Associated Infection Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 200</td>
<td><em>Pneumocystis</em> pneumonia, Bacterial pneumonia, Coccidiodomycosis</td>
</tr>
<tr>
<td>≤ 100</td>
<td>Toxoplasmosis, Histoplasmosis, Cryptosporidiosis</td>
</tr>
<tr>
<td>≤ 50</td>
<td>Mycobacteria avium complex, Cytomegalovirus</td>
</tr>
<tr>
<td>Anytime</td>
<td>Tuberculosis, Syphilis, Herpes simplex virus</td>
</tr>
</tbody>
</table>
Diagnosis of HIV

- **Clinical Presentation**
  - Opportunistic infections
  - Acute retroviral infection (clinical suspicion)
  - History and physical (risk factors/skin lesions)

- **Laboratory Tests – Screening**
  - Rapid ELISA – detects IgG and IgM
    - Require confirmation with western blot!
    - False positive/negatives
  - Antigen – detects p24 antigen (earlier detection)
Diagnosis of HIV
Diagnosis of HIV

• Confirmatory Assays
  • Western Blot – detects IgG (gold standard in US)
  • Immunofluorescence – detects IgG

• Nucleic Acid Testing
  • HIV RNA testing – can be used for screening and confirmatory testing
  • Used to tested pooled donated blood
  • Costly
  • Less sensitive in long-term non-progressors and elite controllers
HIV Testing – in your home?

- Uses saliva as a testing source
  - Rich in IgG antibodies but little to no infectious virus
  - Eliminates need for blood draw and reduces potential needle stick injuries

- Recently FDA approved for home-use (2012)
  - Positive results must be confirmed by laboratory testing
  - False-negatives can occur in early infection
  - HAART therapy decreases the sensitivity

Screening Recommendations

• CDC
  • Routine testing for all patients age 13 – 64 in healthcare settings
  • All pregnant women (at presentation and again at 28-32 weeks)
  • All patients with tuberculosis
  • All patients seeking treatment for an STD
  • Annual testing for all patients at high risk

• Screening should be voluntary
  • Oral or written information that testing will be performed
  • Opt-out versus opt-in
Highly-Active Antiretroviral Therapy

• HAART: combination therapy to treat HIV infection
  • At least three drugs active against the virus from two classes
  • Work on different steps in the replication cycle

• Goals of therapy
  • Reduce associated morbidity
  • Prolong survival
  • Suppress HIV viral load
  • Prevent transmission
HAART Therapy Classes

• Nucleoside/nucleotides
• Non-nucleosides
• Protease inhibitors
• Entry inhibitors
• Integrase inhibitors

Mandell, Douglas, and Bennett. 2010.
When to Start Therapy

1. When the patient is willing and able to commit to treatment
2. Pregnancy
3. AIDS defining illness
4. Acute opportunistic infection (caution: immune reconstitution)
5. Rapidly declining CD4
6. Viral load > 100,000
7. Hepatitis B or C co-infection
8. CD4 ≤ 350
When to Start Therapy – CD4 Count

- Earlier initiation reduces HIV associated morbidity and/or mortality
- Reduces the severity of the CD4 nadir
- Breakpoint continues to increase
  - CDC recommends starting in everyone with HIV regardless of CD4 count
  - WHO recommends starting in patients with CD4 <500
- Concerns with collateral damage and adherence (cost, toxicities)
What to start?

• Always use 3 active drugs from 2 or more classes

• NEVER stop once started. Drug Holidays do NOT work
Prevention

What works?
Abstinence (not practical)
Treatment of other STDs (HSV)
Circumcision
PEP
PrEP
TasP
Post-exposure Prophylaxis (PEP)

- Initially developed for occupational exposures
  - Separate guidelines for occupational versus non-occupational exposures

- Three main contraction routes
  - Percutaneous injury (0.3% risk)
  - Mucous membrane contact (0.09% risk)
  - Non-intact skin contact (chapped, abraded, dermatitis) (very low risk)

- Not all body fluids are considered infectious
Post-exposure Prophylaxis (PEP)

• High risk exposure:
  • Device visibly contaminated with blood
  • Percutaneous injury directly into vein/artery
  • Deep injury
  • High vial load

• Source patient screening (do not delay treatment)

• Antiretroviral should begin as soon as possible
  • Policy and Procedure in place for significant exposures
  • Needle stick kits ("STIK Kits")
Post-exposure Prophylaxis (PEP)

• Agents should be selected based on recommendations and tolerability
  • Special considerations (pregnancy, drug interactions)
  • Expert consultation if needed (e.g. resistance, delay in treatment)

<table>
<thead>
<tr>
<th>Preferred Regimen</th>
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<tbody>
<tr>
<td><strong>Truvada</strong></td>
</tr>
<tr>
<td>(Emtricitabine/Tenofovir)</td>
</tr>
<tr>
<td>1 Tablet PO Daily</td>
</tr>
<tr>
<td><strong>Isentress</strong></td>
</tr>
<tr>
<td>(Raltegravir)</td>
</tr>
<tr>
<td>400 mg PO twice daily</td>
</tr>
</tbody>
</table>

• Continue prophylaxis regimen for a full 4 weeks
Pre-exposure Prophylaxis (PrEP)

• 2010: homosexual/MSM findings (Truvada)
  • FDA Approved Indication

• 2011: heterosexual study findings (Truvada)
  • FDA Approved Indication

• 2013: injection drug users findings (Tenofovir)
  • CDC recommends Truvada

Should not be used in patients with unknown/positive HIV status.
Pre-exposure Prophylaxis (PrEP)

• Contingent upon:
  • Routine screening (quarterly)
  • Use of other mechanisms to prevent infection
  • Adherence (daily versus PRN dosing)

• Controversies/Questions
  • Increased risky practices (patients feel “safe”)
  • Widespread resistance
  • HIV eradication
  • Relationships

• Bottom-Line
  • It works – Study settings show 92% risk reduction
  • Real world? 85-90%
Treatment as Prevention (TasP)
Prevention of HIV-1 Infection with Early Antiretroviral Therapy

TasP

RCT

• 1763 serodiscordant couples
• Randomized to for the infected partner to receive early ART (CD4>500) or delayed (350-500)
• 1 transmission event in the early ART group
• Decreased transmission by 96%
• Recent “real-world” study in China by 67% (M. Cohen)
Cure: Will we ever get there?

BERLIN CASE – only cure on record
  • BMT not practical in everyone

Barriers
  • Viral Reservoirs: what cells (t_{1/2}) and where (i.e. CNS)
  • Viral Latency: Integration of the genome into the host DNA
Reservoirs

• First considered in 1997 – persistent viral replication despite HAART

• HIV can infect multiple cell types – reactivation potential variable
  • CD4+ cells
  • Macrophages
  • Dendritic cells
  • Astrocytes
  • Hematopoietic stem cells
  • Lymphoid Tissue (gut, spleen)
Figure 2. An overview of viral reservoirs and their relative contribution to plasma viremia.

Steady-state levels of plasma viral RNA reflect the cumulative production of virus from the various cellular reservoirs and the turnover of virus-producing cells in those reservoirs. When viral replication is inhibited by HAART, plasma viral RNA decays in four distinct phases, suggesting that the various viral reservoirs are turned over to very different extents as a result of HIV-1 infection. The first phase reflects virus produced predominantly from activated CD4+ T cells. In the second phase, macrophages may be the main source of virus, because the decay characteristics of plasma viremia in this phase approximates the lifespan of the tissue macrophage. Resting (G₁) T cells may also contribute to this more slowly turning over reservoir. The third phase reflects an extremely low and chronic production of virus from a stable reservoir. Presumably cells constituting this reservoir maintain a low and sustained output of virus, while simultaneously resisting cytopathic effects and killing by cytotoxic T lymphocytes. Resting CD4+ T cells or DCs may be the sources of virus in this covert reservoir. The fourth phase of decay is based on in vitro measurements of the frequency of latently infected CD4+ T cells, but FDCs harboring trapped virions might also be a long-lived source of infectious virus in this phase.


HIV-1 pathogenesis

Mario Stevenson
Insights to the Future

- Cure by reactivation of viral latency
  - Histone Deacetylase inhibitors – Panobinostat
- Infusion of broadly neutralizing HIV Antibodies
  - Caskey et al. Nature 2015
- Monoclonal neutralizing antibodies
  - Brouch et al. Nature 2013 (SHIV in rhesus monkeys)
- Gene Transfer Therapy
- Vaccine Development
Stopping HIV demands a multifactorial approach

- Education
  - Patient
  - Healthcare workers
- Screening
- Early HAART
- Universal precautions

- Sharps education
  - Never re-capping
  - Safety products available
- PEP/PrEP/TasP
  - Needle exchange programs
  - Vaccination?
Conclusions

• Effective HIV screening and patient education are critical to prevention

• Early HAART therapy is preferred, if the patient is ready

• Prophylaxis should be utilized

• Exposure policies/procedures should be in place to protect employees
Resources

• AIDSinfo.nih.gov
• Florida/Caribbean AIDS education and treatment center (FCAETC)
• CDC.gov
• www.aids.gov
• 24 hour hotline
• Infectious Diseases Physicians/Pharmacists
References

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Acknowledgements

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