HIV CME

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Disclosures

• No conflicts of interest
Objectives

• Briefly review basic science
• Discuss epidemiology of HIV
• Discuss modes of transmission
• Review testing and consent protocols
• Briefly review available treatments
• Discuss Indications for Post-Exposure Prophylaxis
• Discuss Indications for Pre-Exposure Prophylaxis
• Review new data on life expectancy
The basics

• Human Immunodeficiency Virus (HIV) is a retrovirus
• The HIV virus attaches to CD4 cells, integrates into genome using reverse transcriptase and uses cells own machinery to make more virus.
• HIV infection leads to severe depletion of CD4 T cells in the gut-associated lymphoid tissue with subsequent reduced levels of circulating CD4 lymphocytes in the peripheral blood.
The Virion

Key to Terms

- **HIV capsid**: HIV’s bullet-shaped core that contains HIV RNA
- **HIV envelope**: Outer surface of HIV
- **HIV enzymes**: Proteins that carry out steps in the HIV life cycle
- **HIV glycoproteins**: Protein “spikes” embedded in the HIV envelope
- **HIV RNA**: HIV’s genetic material
An efficient pathogen

- Exceptional survival advantages
  - Integration into the host DNA
  - High mutation rate
  - Ability to remain latent
  - Targets cells of the immune system such as CD4+ and macrophage cells – decreases cellular immunity
  - Replicates intracellularly
HIV/AIDS

• After initial stabilization following infection, CD4 cell count declines at an average yearly rate of approximately 50 cells/mm³
• Progression to AIDS takes more than 10 years on average
• AIDS indicates a CD4 less than 200 or the presence of an AIDS defining illness
AIDS defining illnesses

- HIV associated nephropathy
- HIV associated dementia/encephalopathy
- Wasting syndrome
- Malignancies (Kaposi’s Sarcoma, NHL, primary CNS lymphoma, Cervical cancer)
- Host of infectious processes including:
  - Invasive candidiasis
  - PJP pneumonia
  - Recurrent bacterial pneumonia
  - Recurrent salmonellosis
  - TB at any site
  - Disseminated or extra-pulmonary MAC
  - Invasive HSV disease or CMV infection
  - Cryptococcosis, coccidioidomycosis or disseminated histoplasmosis
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
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]
Epidemiology

- At the end of 2012, an estimated 1.2 million persons aged 13 and older were living with HIV infection in the United States, including 156,300 (12.8%) persons whose infections had not been diagnosed.
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 Aged 18–64 Years Living with a Diagnosis of HIV Infection, Year-End 2008—United States

Data source: National HIV Surveillance System. Rates are not adjusted for reporting delays. Inset maps not to scale.

Data classified using quintiles
Overall total rate = 417.5
Race/Ethnicity of Persons Diagnosed with AIDS in 2010 in the 50 States and District of Columbia, by Region of Residence

- **American Indian/Alaska Native:** Northeast (<1%), Midwest (<1%), South (<1%), West (2%)
- **Asian:** Northeast (1%), Midwest (1%), South (1%), West (4%)
- **Native Hawaiian/Other Pacific Islander:** Northeast (<1%), Midwest (<1%), South (<1%), West (1%)
- **Multiple Races:** Northeast (2%), Midwest (2%), South (2%), West (1%)
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

0.1 to 100.0
100.1 to 200.0
200.1 to 300.0
> 300.0

*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

- Male-to-male sexual contact: 65%
- Injection drug use (IDU) – Males: 4%
- IDU – Females: 2%
- Male-to-male sexual contact and IDU: 3%
- Heterosexual contact\(^a\) – Males: 8%
- Heterosexual contact\(^a\) – Females: 17%
- Other\(^b\): <1%

\(^a\) 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.

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.
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
Transmission

• “Blood and sex”
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)
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

- Very Low Risk of Infection
  - Feces
  - Nasal fluid
  - Saliva
  - Sweat
  - Tears
  - Urine
  - Vomit

**Unless contaminated with blood**
Table 1. Estimated per-act risk for acquiring human immunodeficiency virus (HIV) from an infected source, by exposure act

<table>
<thead>
<tr>
<th>Exposure type</th>
<th>Rate for HIV acquisition per 10,000 exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenteral</strong></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>9,250</td>
</tr>
<tr>
<td>Needle sharing during injection drug use</td>
<td>63</td>
</tr>
<tr>
<td>Percutaneous (needlestick)</td>
<td>23</td>
</tr>
<tr>
<td><strong>Sexual</strong></td>
<td></td>
</tr>
<tr>
<td>Receptive anal intercourse</td>
<td>138</td>
</tr>
<tr>
<td>Receptive penile-vaginal intercourse</td>
<td>8</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>11</td>
</tr>
<tr>
<td>Insertive penile-vaginal intercourse</td>
<td>4</td>
</tr>
<tr>
<td>Receptive oral intercourse</td>
<td>Low</td>
</tr>
<tr>
<td>Insertive oral intercourse</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Other(^a)</strong></td>
<td></td>
</tr>
<tr>
<td>Biting</td>
<td>Negligible</td>
</tr>
<tr>
<td>Spitting</td>
<td>Negligible</td>
</tr>
<tr>
<td>Throwing body fluids (including semen or saliva)</td>
<td>Negligible</td>
</tr>
<tr>
<td>Sharing sex toys</td>
<td>Negligible</td>
</tr>
</tbody>
</table>


\(^a\) Factors that may increase the risk of HIV transmission include sexually transmitted diseases, acute and late-stage HIV infection, and high viral load. Factors that may decrease the risk include condom use, male circumcision, antiretroviral treatment, and preexposure prophylaxis. None of these factors are accounted for in the estimates presented in the table.

\(^b\) HIV transmission through these exposure routes is technically possible but unlikely and not well documented.
Testing

- Opt-in
- Opt-out
CDC 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 should be given
Opt-in

- Testing is universally offered, patients must elect to be tested.
- Example- all inmates are offered testing on entry into prison system.
- They must be offered pre-test counselling and post-test counselling.
Opt-out

• Everyone is tested unless they refuse
• This is done most effectively during pregnancy. Unless they object, everyone is tested.
• They must be offered pre-test counselling and post-test counselling.
Consent

- Written or verbal notification of testing must be obtained.
- In some states, written consent must be obtained.
- Mandatory reporting in all 50 states.
REPORTING AND CONSENT
LEGAL IMPLICATIONS
HIV Infection Reporting in Florida

HIV Case Reporting in Florida is based on a positive antibody or antigen test for HIV:

• HIV (not AIDS) cases became reportable in Florida on 07/1997, but only via confirmatory Western Blot (antibody) HIV tests. Reporting was NOT retroactive. Previously positive tests required re-testing with a confirmatory test before they could become reportable.

• Viral load (antigen) HIV tests became reportable in Florida on 11/20/2006.

• As of 2009, all states now have confidential name based HIV infection reporting.
Reporting Sources of HIV and AIDS Cases

- Private MDs
- Medical Records
- Death Certificates
- Laboratories
- Medical Examiners
- Counseling & Testing Sites
- Correctional Facilities
- Hospitals (ICD-9), Billing
- HIV Patient Care Clinics
- Registries (e.g., AZT, TB, Cancer)
- Reporting Sources of HIV and AIDS Cases

Surveillance for HIV/AIDS relies on reporting from the above sources. Additionally, local public health professionals are responsible for case finding and/or epidemiologic follow-up, resulting in a very high completeness of reporting.
Florida Law

- Health care providers performing HIV tests must have procedures in place for securing patient consent, testing samples and informing patients of test results.
- Florida's Omnibus AIDS Act requires, with few exceptions, health care providers ordering HIV tests to
  - (A) obtain the "informed consent" of the test subject,
  - (B) confirm positive preliminary test results through corroborating tests before informing the test subject of the result
- AND
  - (C) take "all reasonable efforts" to notify the test subject about the test results.
Informed Consent

• Disclose that the provider is required by law to report the test subject’s name to the local county health department if the HIV test results are positive;

• Alert the patient that as an alternative, the patient may secure the HIV test at a site that tests anonymously, the locations of which the provider must make available;

• Relate the extent of the confidentiality rights that adhere to the test results in the provider's patient records.
Documentation

• As with other medical procedures requiring informed consent, informed consent for HIV testing does not necessarily mean written consent.

• Except for donations of blood and other tissues and to obtain health or life insurance, Florida does not require providers to have the test subject sign a document authorizing the test.

• The health care provider need only enter a note in the medical record that the test was explained and consent was obtained.
Informed Consent Exceptions

• Following federal legislation and recommendations from CDC, Florida law in 1996 first imposed “mandatory offering” of HIV tests for all pregnancies upon presentation.

• In 2005, the statute was further amended to establish the present system of “opt out” testing, in which pregnant women are advised that the health care provider attending them will conduct an HIV test but that they have the right to refuse.

• The pregnant woman’s objection is required in writing, which must be placed in her medical record. §384.31, F.S.
Informed Consent Exceptions

- **Emergencies:** A provider may test without consent in "bona fide medical emergencies," but only if the provider documents in the medical record that the test results are medically necessary to provide appropriate emergency care or treatment to the test subject and the test subject is unable to consent. §381.004(2)(h)3,FS
Informed Consent Exceptions

- **Therapeutic Privilege**: The Act allows a "therapeutic privilege" that bypasses informed consent requirements when the provider's medical record documents that obtaining informed consent would be detrimental to the health of a patient suffering from an acute illness and that the test results are necessary for medical diagnostic purposes to provide appropriate care or treatment to the patient.
Available testing

- Screening Tests
  - Rapid ELISA – detects Antibody (IgG and IgM)
    - Require confirmation with western blot!
    - False positive/negatives
  - Antigen – detects p24 antigen (earlier detection)
  - 4th generation ELISA is combination Antibody and Antigen

- 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
Detection
Window Period

• Despite improved testing, it still exists
• Donated blood is tested using Qualitative RNA PCR in pooled groups
  • Approximately 10-15 day “window” from acquisition of infection to detectable PCR
• 4th generation ELISA- Antibody/Antigen testing (standard of care) have approximately 20 day “window”
• ELISA (IgG and IgM antibody testing) have 20-30 day “window”
• Western Blot takes 35-50 days to development of indeterminate result and 45-60 days until positive
Treatment

• Based on the START and TEMPRANO findings, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating ART for all HIV-infected patients, without contraindication, regardless of CD4 count.

• Treatment should include minimum 3 active drugs from 2 different drug classes (acting on different targets within the replication cycle)
HIV Drugs

- Nucleoside/nucleotides (NRTIs)
- Non-nucleosides (NNRTIs)
- Protease inhibitors (PIs)
- Entry inhibitors
- Integrase inhibitors
1. **Binding (also called Attachment):** HIV binds (attaches itself) to receptors on the surface of a CD4 cell.

   - CCR5 Antagonist

2. **Fusion:** The HIV envelope and the CD4 cell membrane fuse (join together), which allows HIV to enter the CD4 cell.

   - Fusion inhibitors

3. **Reverse Transcription:** Inside the CD4 cell, HIV releases and uses reverse transcriptase (an HIV enzyme) to convert its genetic material—HIV RNA—into HIV DNA. The conversion of HIV RNA to HIV DNA allows HIV to enter the CD4 cell nucleus and combine with the cell's genetic material—cell DNA.

   - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
   - Nucleoside reverse transcriptase inhibitors (NRTIs)

4. **Integration:** Inside the CD4 cell nucleus, HIV releases integrase (an HIV enzyme). HIV uses integrase to insert (integrate) its viral DNA into the DNA of the CD4 cell.

   - Integrate inhibitors

5. **Replication:** Once integrated into the CD4 cell DNA, HIV begins to use the machinery of the CD4 cell to make long chains of HIV proteins. The protein chains are the building blocks for more HIV.

6. **Assembly:** New HIV proteins and HIV RNA move to the surface of the cell and assemble into immature (noninfectious) HIV.

7. **Budding:** Newly formed immature (noninfectious) HIV pushes itself out of the host CD4 cell. The new HIV releases protease (an HIV enzyme). Protease acts to break up the long protein chains that form the immature virus. The smaller HIV proteins combine to form mature (infectious) HIV.

   - Protease inhibitors (PIs)
Treatment

- For a treatment-naive patient this generally consists of two nucleoside reverse transcriptase inhibitors in combination with a third active antiretroviral drug from one of three drug classes: an integrase strand transfer inhibitor, a nonnucleoside reverse transcriptase inhibitor, or a protease inhibitor with a booster (cobicistat or ritonavir).
Prevention

- Barrier protection
- Treatment as Prevention
- PrEP
- PEP
Barrier Protection

• In order for condom use to be effective in decreasing HIV prevalence, they need to be used consistently and with ongoing exposures, particularly in areas of high prevalence.

• Condoms are 90 to 95 percent effective when used consistently.
Decisions about sexual activity and condom use have a major effect on the risk for HIV transmission.
Treatment as Prevention

• The basic idea is that patients who are on effective therapy are less infectious than untreated individuals and therefore less likely to transmit HIV to others.
• Does it hold water?
In a study of 415 HIV-serodiscordant couples in Uganda, the baseline serum viral load was higher among transmitting partners than non-transmitting partners (90,000 versus 38,000 copies/mL, respectively).

For each log increase in viral load, there was a 2.5-fold increase in the risk of transmission.

In contrast, there were no HIV transmission events from HIV-infected partners whose baseline viral load was <500 copies/mL, suggesting a threshold viral level for transmission.
Further Data Confirms the Premise

  - They enrolled 1763 couples, a total of 39 HIV-1 transmissions were observed (incidence rate, 1.2 per 100 person-years); of these, 28 were virologically linked to the infected partner (incidence rate, 0.9 per 100 person-years).
  - Of the 28 linked transmissions, only 1 occurred in the early therapy group (hazard ratio, 0.04; 95% CI, 0.01 to 0.27; P<0.001).
  - They enrolled 1166 HIV serodifferent couples (HIV-positive partner taking suppressive ART) who reported condomless sex
  - Despite MSM couples reporting approximately 22,000 condomless sex acts and heterosexuals approximately 36,000, no phylogenetically linked transmissions occurred (11 new infections were diagnosed but unrelated to virologically suppressed partner.)
**PrEP**

- For HIV-uninfected patients who are at high risk for acquiring HIV, and are committed to medication adherence, pre-exposure prophylaxis (PrEP) using Truvada (emtricitabine-tenofovir) can reduce the risk of HIV transmission by more than 90 percent.
Indications for PrEP

- HIV-uninfected men and women who have a sexual partner who is HIV-infected and has a detectable viral load
- Men who have sex with men (MSM) and transgender women who have recently (e.g., within the last six months) reported high-risk sexual behaviors
- Heterosexually active men who infrequently use condoms and have sex with female partners who are from regions with generalized HIV epidemics or are at high risk of HIV infection (e.g., sex workers, women who use injection drugs).
- Heterosexual women who infrequently use condoms and have sex with partners who are at high risk of HIV infection (e.g., injection drug users, bisexual male partners, partners from areas where there is a high HIV prevalence).
- IV drug users who recently (i.e., the last six months) report sharing needles/equipment, even if they have initiated substance use treatment
Controversy

- Encourages high risk behavior
- “black market” Truvada
- Adherence
- Risk of resistant virus
  - Recently documented case of drug resistant HIV acquired while on PrEP
Efficacy of PrEP

• Studies have shown that PrEP reduces the risk of getting HIV from sex by more than 90% when used consistently.
• Among people who inject drugs, PrEP reduces the risk of getting HIV by more than 70% when used consistently.
PEP- occupational

• In the era before the introduction of potent antiretroviral therapy (ART) found the following:
  • HIV transmission occurred in 20 of 6135 cases (0.33 percent) following percutaneous exposure
  • One case of HIV was transmitted out of 1143 exposures (0.09 percent) on the mucosa of HCP
  • There were no cases after 2712 intact skin exposures
High risk exposures

• Deep injury (odds ratio [OR] 15)
• A device visibly contaminated with the patient's blood (OR 6.2)
• Needle placement in a vein or artery (OR 4.3)
• Terminal illness in the source patient (OR 5.6)
Protocols

• Source testing, baseline screening of HCW and counselling are necessary
• Start PEP within 72 hours after the initial exposure; PEP is likely to be less effective when administered after that period of time
• Should be available to HCWs 24 hours a day
• Treatment duration is 4 weeks
Preferred regimens

- Tenofovir-emtricitabine (300/200 mg once daily) plus dolutegravir (50 mg once daily)
- Tenofovir-emtricitabine (300/200 mg once daily) plus raltegravir (400 mg twice daily)
Guidelines from the Centers for Disease Control and Prevention (CDC) recommend PEP for a somewhat broader group of patients. If the source patient is known to be HIV infected, PEP is recommended when all the following conditions are met:

- Exposure within 72 hours of presentation AND
- Exposure to a fluid that could contain HIV such as blood, semen, vaginal secretions, rectal secretions, breast milk, or other body fluids (such as saliva and urine) if visibly contaminated with blood AND
- Exposure to a body site that can be a point of entry for HIV such as the vagina, rectum, eye, mouth, or other mucous membrane, non-intact skin, or percutaneous exposures (e.g., injection drug use)

If the HIV status of the source is unknown, the CDC guidelines recommend the need for PEP be determined on a case-by-case basis when the above conditions are met.
Drugs

- Same regimens as used for Occupational PEP
Non-sex exposures outside of workplace

- Needle or syringe sharing – 0.67 percent per needle-sharing contact
- Mucous membrane exposure to blood (eg, splash to eye) – 0.1 percent per exposure
- Other exposure (eg, human bite) – 0.004 percent
Conclusions

- Effective HIV therapies have made HIV a chronic disease.
- Widely applicable cure does not exist.
- Early HAART should be used unless a contraindication exists.
- A focus on prevention of transmission and keeping HIV-infected patients in care through education and outreach are a priority in public health.
- 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
Questions
References

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