Overview of HIV

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Outline

- Background and Epidemiology
- HIV Virology, Transmission, and Pathogenesis
- Acute HIV infection
- HIV Diagnostics
- Management of Health Care Personnel Exposed to HIV
  - Post-exposure prophylaxis
- HIV Prevention—turning the tide
Historical Perspective

- HIV-1 identified officially 05 JUN 1981 (US)
  - CDC MMWR report of 5 unusual Pneumocystis pneumonia cases
- Origin: non-human primates W Africa
  - HIV-1: S Cameroon; evolution of Simian Immunodeficiency Virus (SIV)
  - HIV-2: S Senegal – W Cote d’Ivoire, SIV
- Early expectations – vaccine in 2 years (M. Heckler- NIH Director)
- Search for cure and implementation of prevention strategies continues … 2013
HIV – Adult Prevalence Rate 2012

Adult HIV Prevalence Rate, 2012

Global HIV/AIDS Prevalence Rate = 0.8%

NOTES: Data are estimates. Prevalence rates include adults ages 15-49. The estimate for Sudan represents data for South Sudan. An estimate was not provided for Sudan.
How many new HIV infections occurred in 2012 worldwide?

a) 80,700  
b) 750,000  
c) 2,300,000  
d) 5,100,000
Adults and children estimated to be living with HIV | 2012

New infections: 2,300,000
Estimated Deaths: 1,600,000

Source: UNAIDS, 2013
Over 6,300 new HIV Infections a day in 2012

- About 95% are in low/ middle income countries
- ~ 700 are in children under 15 years of age
- ~ 5,500 are in adults aged 15 years and older, of whom:
  - 47% are among women
  - 41% are among young people (15-24)
- Epi center of epidemic:
  - Sub-Saharan Africa (70%)
Impact of AIDS on life expectancy in five African countries, 1970-2010

HIV – A Worldwide Threat

- Force readiness and protection
  - U.S. and Allied Forces

- Stability and security of many nation-states
  - Epidemic in the least developed, most unreliable regions of the world

- National Security Strategy:
  - Defuse regional conflicts
  - Prevent enemies from using WMD
  - Support global economic growth
  - Reduce the toll of HIV/AIDS and other infectious diseases

- All affect impact of global epidemic & DoD
HIV is an Enduring Problem in the Army

HIV-infected Soldiers
In Army (2013): 622

* Through 30 June 2013
HIV Virology, Pathogenesis and Transmission
HIV vs. AIDS

- HIV
  - Human
  - Immunodeficiency
  - Virus

- AIDS
  - Acquired
  - Immunodeficiency
  - Syndrome
HIV: Human Immunodeficiency Virus

- HIV must enter other cells in order to replicate

- HIV is a retrovirus and its genetic material, RNA, must be converted into DNA during replication

- HIV uses CD4 cells for reproduction
  - CD4 receptors on T-helper cells (T lymphocytes)
How HIV Works

1. Attachment to host CD4 cell

2. Reverse transcriptase makes DNA from the virus’s RNA

3. Integration into host cell’s nucleus

4. Reproduction of viral components

5. Assembly of new HIV viruses

6. Release
CD4

- Stage disease and guide clinical management

- CD4+ Helper T cells = CD4 T cells = CD4 count
  - CD = Cluster Determinant
  - Measured by Flow Cytometry
  - Normal range 500 – 1400 cells/mm³
  - Broad range because product of
    - white blood cell count
    - the percentage of lymphocytes,
    - percentage of lymphocytes that bears the CD4 receptor

- As HIV infects more CD4+ cells, CD4 count decreases
  - Effectively weaken the immune system

- CD4 percent
  - How many of your total lymphocytes (white blood cells) are CD4+
  - More stable than CD4 count
Viral Load

- Human immunodeficiency virus type 1 (HIV-1) RNA quantification = viral load measurement (VL)
- Used in management of persons infected with HIV-1
- VL is predictor of the time to progression to AIDS and death -- independent of CD4 cell counts
- ART – Antiretroviral therapy
  - VL used in determining when to initiate ART
  - Monitoring the response to ART
Natural History of HIV Infection

Modified from Fauci, 2000
Figure 2. HIV RNA levels 1 year after untreated infection are relatively stable and predict subsequent disease progression. Data are from the Multicenter AIDS Cohort Study.
Treatment

- Antiretroviral therapy = ART
- Antiretroviral Medications = ARVs
- HAART = Highly active antiretroviral therapy
- Combination therapy
  - Use medicines from TWO different drug classes
  - Block replication at different stages of life cycle
  - Effective in reducing viral load
HIV life cycle and mechanisms of anti-virals
Antiretroviral Medications (ARVs)

- Nucleoside- and Nucleotide-analog Reverse Transcriptase Inhibitors (NRTIs)
- Non-nucleoside analog Reverse Transcriptase Inhibitors (NNRTIs)
- Protease Inhibitors (PIs)
- Integrase inhibitors
- Entry Inhibitors (including fusion inhibitors)
- Pharmacokinetic Enhancers
Case

- 25 yo sexually active man presents with a 3-week hx of fever, fatigue, head ache, mild sore throat.
- On physical exam, the patient is alert & oriented.
- T 38.2 C. A maculopapular rash is present over trunk & face. A few ulcers are seen on soft palate.
- Cervical lymph nodes are slightly enlarged, and her neck is stiff.
- WBC 3.6, Hct 34%, platelets 90,000. Monospot & serum RPR are negative.
Case continued

Which of the following is the most likely diagnosis?

- Acute HIV infection
- Infectious mononucleosis ("Mono")
- Strep throat
- Flu
Acute HIV Infection

- Primary Infection
- Acute HIV syndrome
- Wide dissemination of virus
- Seeding of lymphoid organs
- Clinical Latency
- Constitutional Symptoms
- Opportunistic Diseases
- Death

CD4+ T Lymphocyte Count (cells/mm³)

HIV RNA Copies per ml Plasma

Modified from Fauci, 2000
Symptoms of Acute HIV Infection

Main symptoms of Acute HIV infection:

- **Systemic:**
  - Fever
  - Weight loss

- **Central:**
  - Malaise
  - Headache
  - Neuropathy

- **Pharyngitis:**

- **Mouth:**
  - Sores
  - Thrush

- **Esophagus:**
  - Sores

- **Skin:**
  - Rash

- **Lymph nodes:**
  - Lymphadenopathy

- **Muscles:**
  - Myalgia

- **Liver and spleen:**
  - Enlargement

- **Gastric:**
  - Nausea
  - Vomiting
**Frequency Symptoms in Acute HIV-1 Infection**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>&gt;80-90%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>&gt;70-90</td>
</tr>
<tr>
<td>Rash</td>
<td>&gt;40-80</td>
</tr>
<tr>
<td>Headache</td>
<td>32-70</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>40-70*</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>50-70*</td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td>50-70</td>
</tr>
</tbody>
</table>

*highest in younger patients, Vanhems. JAIDS 2002;31:318-321.
Advanced Stages & Opportunistic Infections

Modified from Fauci, 2000
Advanced Stages of HIV / AIDS

- CD4 < 200 mm$^3$

- Opportunistic infections
  - Immunocompromised = Increased risk
  - In US: Pneumocystis pneumonia, Kaposi’s sarcoma
  - In Sub-Saharan Africa: malaria, diarrhea, pneumonia
  - Prophylaxis for OIs becomes important
    - What you are prophylaxed for depends on:
      - Patient’s medical history
      - Patient’s environment
      - CD4 count
    - Review guidelines as needed – consult expert

- Know that under 200, patients at risk
AIDS

- CD4 cell count below 200/mm$^3$ regardless of the presence or absence of symptoms
- WHO stages
  - Clinical staging guideline
  - Still used in field where CD4 and VL results may be limited
- AIDS defining conditions
  - Serious conditions in people with HIV that define stage
    - P. carinii pneumonia
    - Esophageal candidiasis
    - Kaposi's sarcoma
    - Tuberculosis
Transmission Routes

- Unprotected sexual intercourse with an infected partner
- Vertical transmission (from mother to child)
  - in utero
  - during delivery
  - breastmilk
- Injection drug use (rare: infected blood products)

HIV INFECTION
Risk of Specific Exposures

Per Contact Transmission Rate

- Transfusion: 95%
- Untreated Perinatal Transmission: 15-30%
- Occupational Transmission:
  - Needle Stick: 0.3%
  - Mucous Membrane: 0.01-0.1%
HIV Diagnostics: Serology vs. RDT

- **Serology**
  - Detection of IgG antibody against HIV-1 antigens in serum
  - Positive tests confirmed with repeat tests or corroborating laboratory data (eg, Western blot assays)
  - False negative - rare but can be seen in acute infection

- **RDT = Rapid Diagnostic Test**
  - Low cost and available in minutes
  - Preferred now in US for point of care (and in field)
  - Blood, plasma, serum, saliva
HIV testing: serial algorithm

1. Collect Sample
2. Perform test using one rapid sensitive test as approved by MOH
   - Test Results NEGATIVE: Report Test Results as NEGATIVE
   - Test Results POSITIVE: Test specimen using second, different specific rapid test as approved by MOH
     - Test Results NEGATIVE: Report Test Results as POSITIVE
     - Test Results POSITIVE: Report Test Results as POSITIVE
3. Stand alone VCT or other setting: Ask client to come back after 2-4 weeks for repeat test
4. Health Facility with well-equipped lab: Do Long ELISA and/or Western Blot
Rapid Immunoassay - RIA

Uni-Gold Recombigen and OraQuick Advance HIV-1/2

Results in 10-12 minutes

Positive
HIV-1

Reactive
Control

Positive
HIV-1

Results in 20 minutes

Reactive
Control

Reactive
Control

Positive
HIV-1/2
What is Exposure?
- Contact with potentially infectious blood, tissue, or body fluids in a manner that allows for possible transmission of HIV
- A percutaneous injury (e.g., a needlestick or cut with a sharp object)
- Contact of mucous membrane or nonintact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis)

Body Fluids of Concern
- Concern: blood, semen, vaginal secretions, other body fluids contaminated with visible blood
- Not considered infectious unless they contain blood: feces, nasal secretions, saliva, gastric secretions, sputum, urine, and vomitus

Intact skin is an effective barrier against HIV infection
Management of Health Care Personnel Exposed to HIV

- Risk of transmission varies depending on type of exposure
  - High if source has high HIV viral load, large volume, deep exposure
  - Risk after exposure to body fluids is low
    - After a needlestick injury is about 3 per 1000 with no prophylaxis

- Once determined exposed → What next?
  - Determine HIV status of source patient
  - If Positive or Unknown,
    - RDT – test patient (if result within 2 hours)
    - Post Exposure Prophylaxis (PEP)
PEP = Post exposure prophylaxis

- Start as soon as possible – hours vs. days
- If unsure of regimen, start basic regimen vs. delay
- Administer for 4 weeks
  - Side effects common
  - GI – nausea, vomiting, diarrhea
  - Headache, fatigue
- Expert consultation recommended - Complex
Management of Health Care Personnel

PEP continued
- Re-evaluate exposed HCP within 72 hours of exposure
- Additional information about exposure or source patient
- If the source is found to be HIV negative, PEP should be discontinued

How often to test for HIV in exposed patient?
- Baseline, 6 weeks, 3 months and 6 months
- Most seroconverters – within 3 months

http://www.aids-ed.org/
### Which drugs to use?*

**Truvada™ 1 PO Once Daily**  
[Tenofovir DF (Viread®; TDF) 300mg + emtricitabine (Emtriva™; FTC) 200mg]**

**PLUS**

**Raltegravir (Isentress®; RAL) 400mg PO Twice Daily**

One drug or drug pair from the left column with one pair of nucleoside/nucleotide reverse transcriptase inhibitors from the right column.

| Raltegravir (Isentress®; RAL) | Tenofovir DF (Viread®; TDF) + emtricitabine (Emtriva™; FTC); available as Truvada™ |
| Darunavir (Prezista®; DRV) + ritonavir (Norvir®; RTV) | Tenofovir DF (Viread®; TDF) + lamivudine (Epivir®; 3TC) |
| Etravirine (Intelence®; ETR) | Zidovudine (Retrovir™; ZDV; AZT) + lamivudine (Epivir®; 3TC); available as Combivir® |
| Rilpivirine (Edurant™; RPV) | Zidovudine (Retrovir™; ZDV; AZT) + emtricitabine (Emtriva™; FTC) |
| Atazanavir (Reyataz®; ATV) + ritonavir (Norvir®; RTV) | |

*CDC, 2005*
## Current ARV Medications

<table>
<thead>
<tr>
<th>NRTI</th>
<th>PI</th>
<th>Integrase Inhibitor (II)</th>
<th>Fusion Inhibitor</th>
<th>CCR5 Antagonist</th>
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<tbody>
<tr>
<td>Abacavir (ABC)</td>
<td>Atazanavir (ATV)</td>
<td>Raltegravir (RAL)</td>
<td>Enfuvirtide (ENF, T-20)</td>
<td>Maraviroc (MVC)</td>
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<tr>
<td>Didanosine (ddl)</td>
<td>Darunavir (DRV)</td>
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<tr>
<td>Emtricitabine (FTC)</td>
<td>Fosamprenavir (FPV)</td>
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<tr>
<td>Lamivudine (3TC)</td>
<td>Indinavir (IDV)</td>
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<tr>
<td>Stavudine (d4T)</td>
<td>Lopinavir (LPV)</td>
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<tr>
<td>Tenofovir (TDF)</td>
<td>Nelfinavir (NFV)</td>
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<tr>
<td>Zidovudine (AZT, ZDV)</td>
<td>Ritonavir (RTV)</td>
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</table>

### NNRTI
- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)
HIV Prevention: Turning the Tide
The U.S. Military HIV Research Program conducts research to develop an effective preventive HIV vaccine and integrates prevention, treatment, diagnostics and monitoring as part of an international effort to protect U.S. and allied troops and reduce the impact of HIV infection worldwide.

www.hivresearch.org
When will an HIV Vaccine be available?

a. A vaccine is available now
b. Next year
c. 5 years
d. 10 years
e. Don’t know
RV144

- Modest results, but first sign of protection in humans
  - N=16,000 Thai volunteers at community risk
  - Canarypox vector x 4 + gp120 x 2
  - Modified intention to treat efficacy 31.2%
    (95% CI, 1.1 to 52.1; P = 0.04)
  - No effect on viral load

Modified Intention-to-Treat Analysis
QUESTIONS?

Thank you...
References

- UNAIDS Report on the Global AIDS Epidemic

- DHHS Guidelines for Use of ART in Adults and Adolescents

- Military HIV Research Program
  [www.hivresearch.org/home.php](http://www.hivresearch.org/home.php)

- International AIDS Vaccine Initiative
  [www.iavi.org/Pages/home.aspx](http://www.iavi.org/Pages/home.aspx)


- RV144 Thai Trial Paper: Rerks-Ngarm et al, NEJM, 2009