Overview of HIV

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

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Historical Perspective

HIV-1 identified officially 05 JUN 1981 (US) CDC

MMWR report of 5 unusual

*Pneumocystis jirovecii* pneumonia cases

Origin: Non-human primates W Africa, ~1900

HIV-1: S Cameroon; evolution of Simian Immunodeficiency Virus HIV-2:

S Senegal – W Cote d’Ivoire, SIV

Early expectations – vaccine in 2 years

(M. Heckler- DHHS, 1984)

Search for cure and implementation of prevention strategies continues...2013
Knowledge Check

How many new HIV infections occurred in 2012 worldwide?

Globally new HIV infections peaked in 1997

[Graph showing the number of people affected by HIV and AIDS-related deaths over time from 1990 to 2012.]
Adults & children living with HIV | 2013

Number of people (millions), by WHO region

- Eastern Mediterranean: 280 000 [200 000–420 000]
- Western Pacific: 1 300 000 [1 100 000–1 700 000]
- Europe: 2 100 000 [1 900 000–2 200 000]
- Americas: 3 200 000 [2 800 000–4 000 000]
- South-East Asia: 3 400 000 [2 900 000–4 000 000]
- Africa: 24 700 000 [23 500 000–26 100 000]

Total: 35 000 000 [33 200 000–37 200 000]
Over 6,300 New HIV Infections Day in 2012

~ 95% are in low / middle income countries
~ 700 are in children < 15 years of age
~ 5,500 are in adults ≥15 years:
  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, 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**
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

- **What is HIV?**
  - HIV
    - Human
  - Immunodeficiency
    - Virus

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

- HIV is a **retrovirus** and its genetic material, RNA, must be converted into DNA during replication.
- HIV must enter other cells in order to replicate.
- HIV primarily uses CD4+ T cells for reproduction.
  - CD4 receptors on T-helper 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 + T cell

• Stage disease and guide clinical management
• CD4+ T Helper cells = CD4 T cells = CD4 count
  • CD = Cluster of Differentiation
  • Measured by Flow Cytometry
  • Normal range 500 – 1400 cells/mm³
  • A 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
Natural History of HIV Infection

Modified from Fauci, 2000
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 T cell counts

ART – Antiretroviral therapy

VL used in determining when to initiate ART

Monitoring the response to ART
HIV RNA levels 1 year after untreated infection are relatively stable and predict subsequent disease progression. (Data are from the Multicenter AIDS Cohort Study (MACS), Mellors et al. Science 272: 1167-1170)
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 Study

Which of the following is the most likely diagnosis?

Acute HIV infection Infectious mononucleosis Streptococcal pharyngitis Influenza
Acute HIV Infection

Modified from Fauci, 2000
Symptoms of Acute HIV Infection

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

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

- **Pharyngitis**

- **Mouth:**
  - Sores
  - Thrush

- **Esophagus:**
  - Sores

- **Muscles:**
  - Myalgia

- **Liver and spleen:**
  - Enlargement

- **Lymph nodes:**
  - Lymphadenopathy

- **Skin:**
  - Rash

- **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>


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

Modified from Fauci, 2000
Advanced Stages of HIV / AIDS

CD4 < 200 mm³
Opportunistic infections
Immunocompromised = Increased risk

In US:
Pneumocystis pneumonia, Kaposi’s sarcoma

In Sub-Saharan Africa: diarrhea, tuberculosis

Prophylaxis for OIs becomes important

What one receives for prophylaxis 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/mm³ regardless of the presence or absence of symptoms

WHO stages
Clinical staging guideline
Still used in field where CD4 & VL results may be limited

AIDS defining conditions
Serious conditions in people with HIV that define stage

*P. jirovecii* 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/blood products)

HIV INFECTION
# Risk of Specific Exposures

Table 1. Estimated per-act probability of acquiring HIV from an infected source, by exposure route.

<table>
<thead>
<tr>
<th>Exposure route</th>
<th>Risk per 10 000 exposures to an infected source</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>9250</td>
<td>(8900–9610)</td>
</tr>
<tr>
<td>Needle-sharing injection drug use</td>
<td>63(^b)</td>
<td>(41–92)</td>
</tr>
<tr>
<td>Percutaneous needle stick</td>
<td>23</td>
<td>(0–46)</td>
</tr>
<tr>
<td>Sexual exposure(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receptive anal intercourse</td>
<td>138(^c)</td>
<td>(102–186)</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>11(^d)</td>
<td>(4–28)</td>
</tr>
<tr>
<td>Receptive penile–vaginal intercourse</td>
<td>8(^e)</td>
<td>(6–11)</td>
</tr>
<tr>
<td>Insertive penile–vaginal intercourse</td>
<td>4(^e)</td>
<td>(1–14)</td>
</tr>
<tr>
<td>Receptive oral sex</td>
<td>Low(^f)</td>
<td>(0–4)</td>
</tr>
<tr>
<td>Insertive oral sex</td>
<td>Low(^f)</td>
<td>(0–4)</td>
</tr>
<tr>
<td>Vertical transmission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother-to-child transmission</td>
<td>2260(^g)</td>
<td>(1700–2900)</td>
</tr>
</tbody>
</table>

\(^a\) Patel et al., 2014
HIV Diagnostics: Serology vs. RDT

Serology
Detection of serum IgG antibody against HIV-1 antigens
Positive tests confirmed with repeat tests or corroborating laboratory data (e.g. western blot) 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
     - Test Results POSITIVE: Report Test Results as POSITIVE
     - Stand alone VCT or other setting: Ask client to come back after 2-4 weeks for repeat test
     - Health Facility with well-equipped lab: Do Long ELISA and/or Western Blot
HIV Diagnosis

Rapid Immunoasay - RIA
Uni-Gold Recombigen and OraQuick Advance
HIV-1/2

Results in 10-12 minutes

Positive HIV-1

Reactive Control

Results in 20 minutes

Positive HIV-1/2

Reactive Control
Military HIV Screening Process

DoDI 6485.01 requires biannual screening for Soldiers
Positive screens are sent to WRAIR for confirmatory testing
Have to be confirmed within 30 days per AR600-110
Additional samples tested if positive Results sent to
reporting/notification POCs, PHC

New positives/mo: ~30
Incl. dependents, DA civilians Army has highest
incidence in DoD Still less than general population
HIV Diagnostics and Reference Laboratory

All incident infections verified by second independent specimen; discordant results resolved by 3rd independent specimen.

WB IND/NEG, Aptima Reactive cases Reflex to HIV-1 viral load, Health Care Provider contacted for test request.

HIV-1 Western Blot

Qualitative RNA PCR (Aptima)

Quantitative HIV-1 RT PCR

HIV-3 Presumptive Positive

Quantitative HIV-2 RT PCR

HIV-2 DNA Real Time PCR

HIV-2 Presumptive Positive

2 of 3 Tests Reactive

NEG HIV-1

HIV Ag/Ab Combo Screening

Non-Reactive

Report "HIV Negative"

Report "HIV Positive"

Report "Acute HIV-1 Infection"

Incident Infection Full or Partial Length Sequencing

Request Test Request from submitting entity/health care provider

HIV DIAGNOSTICS AND REFERENCE LABORATORY
9100 Brookesville Road, BLDG 508, Silver Spring, MD 20910

Serology Clinical Test Request Form

<table>
<thead>
<tr>
<th>TEST REQUESTED</th>
<th>SPECIMEN REQUIREMENT</th>
<th>DRAW TUBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Algorithm†</td>
<td>4 ml serum or plasma (cold pack/frozen)</td>
<td>SST/EDTA</td>
</tr>
<tr>
<td>Acute HIV Algorithm</td>
<td>4 ml serum or plasma (cold pack/frozen)</td>
<td>SST/EDTA</td>
</tr>
</tbody>
</table>

SHIP FROZEN IF SAMPLE WILL NOT BE RECEIVED AT HDRL WITHIN 72 HOURS.

PATIENT IDENTIFICATION

Patient Name must include: First Name*, Last Name*, DOB†

POC* (Required)

Physician Name*

Clinic / Center*

Center Address*

Telephone Number

Specimen Draw Date / Time†:

Sample Source (circle): Frozen / Refrig / Ambient

Sample Shipping (circle): Dry Ice / Cold Pack / Ambient

Patient Name* Alternate POC Name

Alternate POC Phone

(Commercial # only, please include area/country code)

*Required
Common Problems

Wrong test requested or out of order Viral load test ordered first due to clinical presentation

Needs to be a screen test or it won’t trigger algorithm or be reported to PCM,
PHC Genotypes ordered unnecessarily

Viral load needs to be > 1000 cp/mL

Test request forms, sample tubes not filled out completely

Confirmation kits not processed correctly Confirmed HIV+ individuals exempt
from biannual testing requirement
Health Care Personnel - Exposure to HIV

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 non-intact 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 needle-stick injury is about 3 per 1000 with no prophylaxis

Once 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)
Management of Health Care Personnel Exposed to HIV

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
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.

<table>
<thead>
<tr>
<th>Raltegravir (Isentress®; RAL)</th>
<th>Tenofovir DF (Viread®; TDF) + emtricitabine(Emtriva™; FTC); available as Truvada™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir (Prezista®; DRV) + ritonavir (Norvir®; RTV)</td>
<td>Tenofovir DF (Viread®; TDF) + lamivudine (Epivir®; 3TC)</td>
</tr>
<tr>
<td>Etravirine (Intelence®; ETR)</td>
<td>Zidovudine (Retrovir™; ZDV; AZT) + lamivudine (Epivir®; 3TC); available as Combivir®</td>
</tr>
<tr>
<td>Rilpivirine (Edurant™; RPV)</td>
<td>Zidovudine (Retrovir™; ZDV; AZT) + emtricitabine (Emtriva™; FTC)</td>
</tr>
<tr>
<td>Atazanavir (Reyataz®; ATV) + ritonavir (Norvir®; RTV)</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Kaletra®; LPV/RTV)</td>
<td></td>
</tr>
</tbody>
</table>

*CDC, 2005*
Current ARV Medications

• PI
  – Atazanavir (ATV)
  – Darunavir (DRV)
  – Fosamprenavir (FPV)
  – Indinavir (IDV)
  – Lopinavir (LPV)
  – Nelfinavir (NFV)
  – Ritonavir (RTV)
  – Saquinavir (SQV)
  – Tipranavir (TPV)

• II
  – Raltegravir (RAL)
  – Elvitegravir (EVG)
  – Dolutegravir (DTG)

• Fusion Inhibitor
  – Enfuvirtide (ENF,T20)

• CCR5 Agonist
  – Maraviroc (MVC)

NRTI
Abacavir (ABC) Didanosine (ddI) Emtricitabine (FTC)
Lamivudine (3TC)
Stavudine (d4T) Tenofovir (TDF) Zidovudine (AZT, ZDV)

NNRTI
Delavirdine (DLV)
Efavirenz (EFV)
Etravirine (ETR)
Nevirapine (NVP)
HIV Prevention: Turning the Tide
Leading the Battle Against HIV

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.
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
References

UNAIDS REPORT ON THE GLOBAL AIDS EPIDEMIC
WWW.UNAIDS.ORG/EN/KNOWLEDGECENTRE/HIVDATA/GLOBAL REPORT

DHHS GUIDELINES FOR USE OF ART IN ADULTS AND ADOLESCENTS
WWW.AIDSDATA.NIH.GOV/GUIDELINES

MILITARY HIV RESEARCH PROGRAM
WWW.HIVRESEARCH.ORG

INTERNATIONAL AIDS VACCINE INITIATIVE (WWW.IAVI.ORG/PAGES/HOME)

STEP PAPER: BUCHBINDER ET AL. LANCASTER, 2008 RV144 THAI TRIAL PAPER:
RE K KS-NG ARM ET AL. NEJM, 2009