HIV/AIDS 2013
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HIV/AIDS: Outline
- Epidemiology
- Virology
- Testing
- Transmission
- Pathogenesis
- Natural History
- AIDS-defining illnesses
- Antiretroviral therapy
- Prevention

Morbidity and Mortality
Weekly Report (MMWR)

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.

In 2011:
New HIV infections: 2.5 million [2.2, 2.8]
Deaths due to AIDS: 1.7 million [1.5, 1.9]
Adult (aged 15-49) prevalence 0.8%

NEW HIV INFECTIONS AND AIDS-RELATED DEATHS

Source: UNAIDS

UNAIDS World AIDS Day Report 2011

Changes in the incidence rate of HIV infection, 2001 to 2009, selected countries

Source: UNAIDS

UNAIDS Report 2010
Early History of AIDS

• 1981: reports of gay men with PCP, KS, CD4 depletion
  • then injection drug users, hemophiliacs, transfusion recipients
  • blood-borne; sexually transmitted
• 1983-84: isolation of HIV-1
• 1985: HIV-1 antibody testing available
• 1986: isolation of HIV-2
• 1987: first antiretroviral drug approved (AZT)
  • 25,000 Americans dead

Later History of HIV/AIDS

• 1994: AZT prophylaxis for perinatal transmission; 2-drug ART introduced into clinical practice
• 1996: 3-drug ART introduced into clinical practice
• 2000: Durban conference, move to bring ART to developing world gains momentum
• 2012: 6.6 million+ on ART in developing world

HIV-1 Virions

Gelderblom, Human Retroviruses and AIDS 1997

HIV Testing

• HIV antibody testing (indirect)
  • Window period ~3 months
  • Screening test: HIV antibody by ELISA
  • If repeatedly positive, proceed to confirmatory test
  • Confirmatory test: HIV antibody by Western Blot
  • 20-minute oral test now available
• HIV viral testing (direct)
  • p24 antigen
  • viral culture
  • HIV RNA (viral load)

Origin of HIV

• Evidence for zoonosis
  • similarity of genomes, phylogenetic relationships, prevalence in normal host, geographic coincidence, plausible route of transmission
• SIVsm (sooty mangabey) --- HIV-2
• SIVcpz (chimpanzee) --- HIV-1 (~1920)
• ? Skin/mucous membrane exposure to infected animals (pets, food)

Human Immunodeficiency Virus

• formerly HTLV-III; isolated 1983
• human retrovirus – outer glycoprotein coat, inner protein coat and genetic material: RNA (2 strands)
• types: HIV-1 and HIV-2
• subtypes (clades): B most common in North America and Europe
• target cell: CD4+ T-lymphocyte

Hahn Science 2000;287:607
HIV Transmission Routes

- Sexual transmission
  - Low efficiency (~1% per contact)
- Injection drug use
  - High efficiency (~10% per contact)
- Blood, blood products, tissue
  - Very high efficiency (~90% per transfusion)
- Perinatal transmission (~25% per birth)
- Needlestick injury (~1/300 exposures)

Revised Recommendations
Adults and Adolescents 9/06

- Routine, voluntary HIV screening for all persons 13-84 in health care settings, not based on risk
- Repeat HIV screening of persons with known risk at least annually
- Opt-out HIV screening with the opportunity to ask questions and the option to decline
- Include HIV consent with general consent for care; separate signed informed consent not recommended
- Prevention counseling in conjunctions with HIV screening in health care settings is not required

Life Cycle of HIV

Budding HIV Virions
Viral Dynamics -- Summary

• 10 billion new virions created and cleared daily
• 2 billion CD4 cells destroyed daily (twice the rate of replacement by the hematopoietic system)

Time Course of HIV Infection

CDC Adult AIDS Case Definition

• 1982: “AIDS” -- list of diseases (definitive diagnosis) and disqualifying conditions
• 1985: HIV antibody testing added to definition
• 1987: presumptive diagnoses with a positive HIV antibody added
• 1993: CD4 <200 (without symptoms) and other diagnoses added

Opportunistic Infection (OI): Definition

• Infection caused by an organism capable of causing disease only in a host whose resistance is lowered (by other diseases or by drugs)

Examples of Common OIs/Malignancies

• Developed world
  • Pneumocystis carinii (fungus)
  • Cytomegalovirus (virus)
  • Toxoplasma gondii (parasite)
  • Mycobacterium avium complex (bacterium)
  • Kaposi’s sarcoma (malignancy)

• Developing world
  • Mycobacterium tuberculosis (bacterium)
  • Cryptococcus (fungus)
  • Wasting disease
Survival: CASCADE Cohort
23 cohorts from Australia, Europe and Canada

Bhaskaran, JAMA 2008; 300: 51-59

HIV+ pre-1996
HIV+ 2004-06
HIV- 2004-06

Survival: CAS Cad Cohort
Figure. Reduction in All-Cause Mortality pre-1996 to 2006 and Comparison With That of the General Population, by Age Group

Bhaskaran, JAMA 2008; 300: 51-59

Haiti: Survival on ART

Figure 1. Kaplan-Meier Estimates of Survival after the Initiation of Antiretroviral Therapy in 350 Adults with known Immunodeficiency Virus infection in Haiti.

Severe. NEJM 2005;353:2325-2334
Leger NEJM 2009;361:828

UNAIDS Global Report 2011

When to start ART?

<table>
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<tr>
<th>When to Start</th>
<th>AIDS symptoms</th>
<th>CD4 &lt;200</th>
<th>CD4 200-350</th>
<th>CD4 &gt;350</th>
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<td>WHO 2010</td>
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</tr>
</tbody>
</table>

www.aidsinfo.nih.gov
**CIPRA HT001 Study**

- Randomized study (N=816 patients with CD4 200-350)
- Start immediately vs. wait until CD4 <200 or AIDS event
- DSMB stopped study early
- Mortality / TB ↓

Fitzgerald NEJM 2010;363:257

**ART**

Easier, less toxic, and more potent therapy

**Antiretroviral Drug Approval: 1987 - 2013**

- to suppress HIV RNA (viral load level) as low as possible, for as long as possible
- to preserve or enhance immune function
- to delay clinical progression of HIV disease

**Life Cycle of HIV**

**Antiretroviral Drugs: 2013**

- nucleoside/tide RTIs (NRTIs)
  - zidovudine (ZDV, AZT)
  - didanosine (ddI)
  - stavudine (d4T)
  - lamivudine (3TC)
  - abacavir (ABC)
  - emtricitabine (FTC)
  - tenofovir (TDF)

- NNRTIs
  - nevirapine (NVP)
  - delavirdine (DLV)
  - efavirenz (EFV)
  - etravirine (ETR)
  - rilpivirine (RPV)

- protease inhibitors (PIs)
  - saquinavir (SQV)
  - ritonavir (RTV)
  - indinavir (IDV)
  - nelfinavir (NFV)
  - lopinavir/ritonavir (LPV/r)
  - atazanavir (ATV)
  - fosamprenavir (FPV)
  - tipranavir (TPV)
  - darunavir (DRV)

- entry inhibitors (EIs)
  - enfuvirtide (T-20, fusion inh)
  - maraviroc (MVC, CCR5 inh)

- integrase inhibitors (IIs)
  - raltegravir (RAL)
  - elvitegravir (EVG)
Antiretroviral Activity: 1987-1997

1987: AZT Monotherapy

1994: 2-NRTI Therapy

1997: HAART including 2-NRTI + PI

24-week responses

Fischl, NEJM, 1987
Eron, NEJM, 1995
Gulick, NEJM 1997
Hammer, NEJM, 1996
Cameron, Lancet, 1998

HIV RNA change (log_{10} c/mL)

1994: 2 - NRTI Therapy
1997: HAART including 2-NRTI + PI
1987: AZT Monotherapy

24-week responses

0 - 0.5
-1
-1.5
-2
-2.5
-3

0 - 0.5
-1
-1.5
-2
-2.5
-3

0 - 0.5
-1
-1.5
-2
-2.5
-3

Fischl, NEJM, 1987
Eron, NEJM, 1995
Gulick, NEJM 1997
Hammer, NEJM, 1996
Cameron, Lancet, 1998

3-Drug Combination ART: 1996

8AM

AZT + 3TC + IDV

4PM

fasting (1 hour before/2 hours after meals)

1 liter of hydration/day

12 MID

What to start?

Preferred Regimens

• NNRTI-based
  • tenofovir/emtricitabine + efavirenz

• PI-based
  • tenofovir/emtricitabine + atazanavir/r
  • tenofovir/emtricitabine + darunavir/r

• INSTI-based
  • tenofovir/emtricitabine + raltegravir

U.S. DHHS Guidelines 3/27/12
www.aidsinfo.nih.gov

Single Tablet Regimens

TDF/FTC/EFV (2006)

TDF/FTC/RPV (2011)

TDF/FTC/EVG/c (2012)

Durability of ART: 7 years

Study 903E: TDF+3TC+EFV

Cassetti
HIV Clin Trials
2007;8:164-72;
IAS 2008 abstract
#TaPE0057
ART Responses in British Columbia 2000-2008

ACTG 5095: 4-drugs?
Study population: HIV+, treatment-naive (N=765)

ZDV/3TC/ABC + EFV (4 drugs)
ZDV/3TC + EFV (3 drugs)

Conclusion: 4-drug rx is no better than 3-drug rx

Gulick JAMA 2006;296:769

Antiretroviral Drug Approval:
1987 - 2013

Antiretroviral Drug Approval:
1987 - 2013

HIV Prevention Strategies
Abstain, Be faithful, Condoms, Counseling & testing

ABC

Adapted from Ramjee IAS Meeting 2008, #TUPL182

FIGURE 5: Number of HIV-infected Persons Engaged in Selected Stages of the Continuum of HIV Care - United States

Cohen et al. CMAJ 2011;185(7):780-785
**Conclusions**

- HIV/AIDS is a worldwide pandemic.
- In the U.S., ~20% of HIV+ people don’t know they are infected.
- Routine HIV testing should be offered to ALL patients.
- Antiretroviral therapy (ART) ↓ HIV RNA, ↑ CD4 cell counts, prevents disease progression, and prolongs survival.
- Current ART consists of 3-drug therapy and is increasingly available worldwide.
- Current life expectancy for HIV+ people on therapy approaches that of the general population.
- Prevention of HIV infection continues to be key.

**Acknowledgments**

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