HIV Update 2010

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Worldwide HIV Continues

• As many as 33 million individuals are living with HIV worldwide (2.1 million are kids)

• As many as 2.7 million individuals worldwide becoming infected during 2008 (5 million in 2005) (.4 million were under age 15)

• As many as 25 million individuals worldwide have died up to 2005 due to AIDS (2 million in 2008, .28 million were kids)

EVERY DAY 7,400 new cases (1/2 female, 1/6 kids) and 5,500 deaths (2008)
Adults and children estimated to be living with HIV, 2008

Total: 33.4 million (31.1 – 35.8)

December 2009
Coverage of IDI’s HIV/AIDS Training Programs as of August 2005

Training statistics (8/2005)
Total number of trainees:
- Medical doctors: 334
- Other health workers: 197
- Total: 531
Number of countries: 21

Source: Infectious Diseases Institute
Awareness of HIV Status among Persons with HIV, United States

Number HIV infected 1,039,000 – 1,185,000

Number unaware of their HIV infection 252,000 - 312,000 (24% - 27%)
Estimated HIV Incidence*—United States, 2006

56,300 new HIV infections in 2006

95% Confidence Interval: 48,200 to 64,500

*Based On Stratified Extrapolation Approach

Ref: JAMA, Vol 300, No. 5, August 6, 2008

Note: Data have been adjusted for reporting delay and cases without risk factor information were proportionately redistributed.
HIV Prevalence in Adults from Selected Countries in Sub-Saharan Africa and Subpopulations in the United States

Numbers of Reported AIDS Cases According to Metropolitan Statistical Area of Residence, Cumulative through 2007

AIDS Cases, Deaths, and Persons Living with AIDS, 1985-2004, United States

Note: Data have been adjusted for reporting delays.
Figure 1. Estimated Number of New HIV Infections, Extended Back-Calculation Model, 1977–2006

Estimated Percentage of New HIV Infections by Sex—United States, 2006

Women 27%

Men 73%

Note: Data have been adjusted for reporting delay.
Estimated Rate of New HIV Infections by Race/Ethnicity—United States, 2006

- American Indian/Alaska Native: 14.6
- Asian/Pacific Islander: 10.3
- Black/African American: 83.7
- Hispanic/Latino: 29.3
- White: 11.5

Rate per 100,000 population

Note: Data have been adjusted for reporting delay.
Figure 8. Estimated New HIV Infections, by Age, 2006

- 31% (30–39)
- 34% (13–29)
- 25% (40–49)
- 10% (≥50)

HIV Virus

- Transmission = Exchange, Sexual, Vertical
- Retroviruses in animals (primates, cattle, cats, mice, and chickens) cause lymphomas
  - in horses - anemia
  - in goats - encephalitis, arthritis
  - in sheep - Visna
- Retroviruses in humans
  (HTLV=human t-cell lymphotrophic virus)
  - HTLV-I Adult T-cell Leukemia (variants of Sezary cell leukemia and Mycosis Fungoides), ? myelopathy, ? Spastic paraparesis
  - HTLV-II Variant of hairy cell leukemia (T-cell)
  - HTLV-III HIV-1 and HIV 2 (African variant of HIV-1)
  - HTLV-IV Related to simian retrovirus, West Africa
T-cell-tropic strains of HIV-1, which are usually syncytium-inducing, require CXCR-4 as co-receptor. This receptor is found on T lymphocytes, but not monocytes. Monocytotropic strains, which are usually non-syncytium-inducing, require the CCR-5 receptor, which is found on both monocytes and T lymphocytes. This illustrates why these isolates can infect monocytes and primary lymphocytes, both of which express CCR-5, but not T-cell lines, which lack this co-receptor. By contrast, T-cell-tropic strains cannot infect monocytes because they lack the CXCR-4 co-receptor.
Three HIV-infected compartments continually replenish the virion supply\textsuperscript{1-3}

"In infected persons this replication is continuous, with very rapid kinetics."
—David D. Ho, MD

Three-compartment model of HIV infection dynamics\textsuperscript{1}

Biphasic viral load response supports targeted antiretroviral therapy\textsuperscript{4}

"[F]indings on viral dynamics provide not only a kinetic picture of HIV-1 pathogenesis, but also theoretical principles to guide the development of treatment strategies."
—David D. Ho, MD, and colleagues

Biphasic viral decay model reflects turnover rates of HIV-infected cells\textsuperscript{4}

Adapted from Perelson et al.\textsuperscript{1}
Based on multiple types of analysis, even when plasma viral load is as small as <1 copy/ml, approximately 350,000 actively producing cells (with approximately 4,000 copies/cell) remain in the body (Bucy-1998).

Prior talk of a cure has been replaced by a recognition of the need for long-term suppression of viral replication with ART and more conservative estimate regarding the potential for eradication.
Problems associated with development of an HIV vaccine

- The state of protective immunity in humans is unknown
- HIV mutates, and there are different strains
- The virus may be dormant within cells
- Transmission is possible from HIV-infected cells
- Lack of a perfect animal model for HIV impedes testing of vaccine’s effectiveness
Shortcomings of the Immune Response

• Extraordinary capacity of HIV to escape immune pressure through mutations and virus-regulated down-regulation of key molecules

• The depletion of CD4+ T cells through direct and indirect cytopathic effects and the subsequent loss of T helper activity

• Defects in the priming and function of HIV-specific effector T cells

• Skewed development and maintenance of HIV-specific memory T cells
Shortcomings of the Immune Response

• There is HIV rebound with interruption of HAART shows that the immune system is not able to control HIV resurgence. The key **long-lasting central memory T cells** fails or is depleted.

• Early in the infection there seems to be the creation of an immunological “hole” as HIV antigen mediated stimulation of **HIV-specific T cells** actually renders them highly susceptible to HIV infection.

• **Long-lasting central memory CD4+ T cells** are thought to be what is needed to control infection but these cells home to lymphoid organs and readily proliferate and differentiate into effector cells but paradoxically they become targets for HIV.

• Elite controllers and simians control HIV and SIV and both demonstrate increased survival capacity of CD4+ and CD8+ **Long-lasting central memory CD4+ T cells**.
The most common methods of transmission of HIV are:

- Unprotected sex with an infected partner
- Sharing needles with an infected person

Almost eliminated as risk factors for HIV transmission are:

- Transmission from an infected mother to her fetus
- Infection from blood products

Also, occupational exposure
Estimated Percentage of New HIV Infections by Transmission Category—United States, 2006

- Heterosexual contact*: 31%
- Male-to-male sexual contact: 53%
- Male-to-male sexual contact and injection drug use: 4%
- Injection drug use: 12%

*Heterosexual contact with a person known to have, or to be at risk for, HIV infection.
Note: Data have been adjusted for reporting delay. Cases without risk factor information were proportionately re-distributed.
Estimated Percentage of New HIV Infections by Sex and Transmission Category—United States, 2006
N = 54,230

**Male**
- Male-to-male sexual contact: 13%
- Male-to-male and injection drug use: 5%
- Injection drug use: 9%
- Heterosexual contact*: 72%

**Female**
- Injection drug use: 20%
- Heterosexual contact*: 80%

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

Note: Data have been adjusted for reporting delay and cases without risk factor information were proportionately redistributed. Data presented on blacks/African Americans, Hispanics/Latinos and whites only. The small number of new infections in Asians/Pacific Islanders and American Indians/Alaska Natives precludes further stratification.
### Estimated Per Act Risk for Acquisition of HIV, by Exposure Route

<table>
<thead>
<tr>
<th>Exposure Route</th>
<th>Risk per 10,000 exposures</th>
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<tbody>
<tr>
<td>Needle-sharing IVDU</td>
<td>67</td>
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<tr>
<td>Receptive Anal intercourse</td>
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<tr>
<td>Receptive penile-vaginal intercourse</td>
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<tr>
<td>Receptive oral intercourse</td>
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<tr>
<td>Insertive anal intercourse</td>
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<tr>
<td>Insertive penile-vaginal intercourse</td>
<td>10</td>
</tr>
<tr>
<td>Percutaneous needle stick</td>
<td>30</td>
</tr>
<tr>
<td>Blood transfusion (if donor +)</td>
<td>9000</td>
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</table>
Risk of Occupational Exposure to HIV

• Mucosal contact, contact with broken skin
  – Not quantified. Transmission by this route has been documented (pooled risk estimate: 0.1%)

• Bite wound
  – Not quantified. Possible route of transmission in 2 cases of non-occupational exposure.

• Infectious Material
  – Documented: Blood, blood products, bloody fluids, breast milk
  – Possible: Semen, vaginal fluid, cerebrospinal fluid, exudates, serosal fluids, amniotic fluid except if BLOODY
  – Unlikely: Saliva, urine, feces except if BLOODY
Recent Occupational Epidemiology

- **HIV**
  - 57 documented occupational infections in U.S. health care workers, 138 possible infections (June, 1999)

- **Hepatitis B**
  - 16,000/yr in 1983 compared to 400/year in 1995
  - 386/100,000 in 1983 to 9.1/100,000 in 1995

- **Hepatitis C**
  - 1-2% of health care workers infected (same as general population)
• NEVER RECAP NEEDLES, ONLY USE ONE HAND
• DISPOSE OF ALL SHARPS AND CONTAMNATED SUPPLIES IN DESIGNATED CONTAINERS
• BEWARE OF SHARPS, ALL THE TIME
PREVENTION

• NO BLOOD DONATIONS
• ALWAYS PRACTICE SAFER SEX (LATEX or POLYURETHANE CONDOMS)
• NEVER SHARE NEEDLES OR SYRINGES
• BLEACH TO CLEAN NEEDLES, SYRINGES and HIV EXPOSED SURFACES
Source Assessment: Laboratory Testing

- Do not delay PEP while awaiting source patient laboratory results. The decision to start PEP is based on the clinical risk assessment.
- Consider testing options:
  - rapid vs standard HIV antibody test kit
  - antibody testing vs direct virus assay
  - no option currently to test discarded needles
Expanded PEP Regimens

Expanded ≥3-drug PEP regimens:

- **Preferred:**
  - Lopinavir/ritonavir (Kaletra) + basic 2-drug regimen

- **Alternative:**
  - Atazanavir* ritonavir
  - Fosamprenavir ritonavir + basic 2-drug regimen
  - Indinavir** ritonavir
  - Saquinavir + ritonavir
  - Nelfinavir
  - Efavirenz***

*If atazanavir is coadministered with tenofovir, ritonavir must be included in the PEP regimen. **Avoid in late pregnancy. ***Teratogenic; avoid in pregnancy
Pre and post counseling must include EDUCATION
Ethical and Legal Issues

- Confidentiality vs anonymity
- Disclosure - who should patient tell
- Informing partners - the physician’s responsibility
- Discrimination
Physician’s disclosure of HIV/AIDS Status

• The physician is required to notify the state public health department of a patient’s status if positive for HIV/AIDS (see end of presentation for contact information)

• Then personnel of the health dept. is responsible for notifying the patient’s contacts
Physicians disclosure of HIV/AIDS information in KY

- The physician may choose to provide the health dept. with names of patients contacts if known, but it is not required of physician.
- Physician can only tell partner(s) or contacts if the patient has co-habitated with them longer than 1 yr.
- Physician can suggest that patient tell partner(s) or contacts and with patient’s permission tell partner(s).
- No other healthcare provider is permitted to disclose to partner(s) or contacts unless given permission by patient.
ATTITUDES AND BEHAVIORS FOR CARE PROVIDERS

• COMPASSION
• CONFIDENTIALITY
• CONTAIN ONES PREJUDICES
• CHERISH THE “GOLDEN RULE”
• CALL HIV HEALTH PROVIDER FOR QUESTIONS
• COMPLY WITH RULES FOR BLOOD AND WASTE PRODUCTS EXPOSURE
CDC: Make HIV tests part of routine medical care for all Americans 13-64

- 250,000 people may be infected and not know
- Treatment results in improved health
- Routine HIV testing may decrease transmission (changes in sexual behavior when tested +)
- Routine testing may reduce stigma
HIV Test

- Tests for antibody to HIV
- May take weeks to months to be positive following exposure
- After 2 positive ELISA tests, confirmatory Western Blot is done - takes 3 weeks
Schematic Representation of How a Western Blot Is Performed

1. Virus digested; digest separated into components by molecular weight
2. Proteins transferred to filter paper; reaction with test serum
3. Enzyme-conjugated antihuman antibody added
4. Substrate added and color noted
Four FDA-approved Rapid HIV Tests

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<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td></td>
<td>(95% C.I.)</td>
<td>(95% C.I.)</td>
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<tr>
<td><strong>Reveal G2</strong></td>
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<tr>
<td>- serum</td>
<td>99.8 (99.2 – 100)</td>
<td>99.1 (98.8 – 99.4)</td>
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<tr>
<td>- plasma</td>
<td>99.8 (99.0 – 100)</td>
<td>98.6 (98.4 – 98.8)</td>
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<tr>
<td><strong>Multispot</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- serum/plasma</td>
<td>100 (99.9 – 100)</td>
<td>99.9 (99.8 – 100)</td>
</tr>
<tr>
<td>- HIV-2</td>
<td>100 (99.7 – 100)</td>
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</table>
Collect oral fluid specimens by swabbing gums with test device.

Gloves optional; waste not biohazardous
Figure 2. Association of CD4+ T-cell numbers with viral burden and phenotype in individuals with rapid disease progression. ○ = non-syncytium-inducing phenotype; ● = syncytium-inducing phenotype.
Figure 1. Distribution of CD4+ Counts in HIV-Negative Heterosexual and Homosexual Men in San Francisco.

The CD4+ counts were determined by flow cytometry with standard methods. The subjects were seen an average of eight times at six-month intervals, and all observations are included.
Stages of HIV Infection
Stage 1

Initial Exposure:

may have a mild viral syndrome with or without an aseptic meningitis. Becomes seropositive after a variable latency period of months to years.
Typical Course of HIV-Infected Individual

- Primary infection
- ± Acute HIV syndrome
- Wide dissemination of virus
- Seeding of lymphoid organs
- Clinical latency
- Opportunistic diseases
- Constitutional symptoms
- Death

- CD4+ T lymphocyte count (cells/mm³)
- Plasma viremia (dilutional titer)

- Weeks
- Years

0 3 6 9 12 1 2 3 4 5 6 7 8 9 10 11+

1/2 1/4 1/8 1/16 1/32 1/64 1/128 1/256 1/512
The Immune Response

Stage 2

Asymptomatic Infection:
Seropositive
May be classified on basis of T4, T8 or WBC counts. May develop further or remain asymptomatic.
Typical Course of HIV-Infected Individual

Primary infection

± Acute HIV syndrome
Wide dissemination of virus
Seeding of lymphoid organs

Clinical latency

Opportunistic diseases

Constitutional symptoms

Death

CD4+ T lymphocyte count (cells/mm³)

Weeks

Years

Plasma viremia (dilutional titer)

1/512

1/256

1/128

1/64

1/32

1/16

1/8

1/4

1/2

0

0

3

6

9

12

1

2

3

4

5

6

7

8

9

10

11+

0
Follicular Dendritic Cell in Cervical Lymph Node of an Asymptomatic HIV-Infected Individual

Courtesy of Dr. Jan Orenstein.
Stage 3

Persistent Generalized Lymphadenopathy:

Palpable nodes in the absence of illnesses other than HIV
Typical Course of HIV-Infected Individual

- Primary infection
- ± Acute HIV syndrome
- Wide dissemination of virus
- Seeding of lymphoid organs
- Clinical latency
- Opportunistic diseases
- Constitutional symptoms
- Death
- Plasma viremia (dilutional titer)
Typical Course of HIV-Infected Individual

- **Primary Infection**: ± Acute HIV syndrome
  - Wide dissemination of virus
  - Seeding of lymphoid organs

- **Clinical Latency**

- **Opportunistic diseases**

- **Constitutional symptoms**

- **Death**

**CD4 T lymphocyte count (cells/mm³)**

- 0
- 100
- 200
- 300
- 400
- 500
- 600
- 700
- 800
- 900
- 1,000
- 1,100
- 1,200

**Weeks**

- 0
- 3
- 6
- 9
- 12

**Years**

- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11+

**Plasma viremia (dilutional titer)**

- 1/16
- 1/8
- 1/4
- 1/2
- 1
- 1/2
- 1/4
- 1/8
- 1/16
- 1/32
- 1/64
- 1/128
- 1/256
- 1/512

**PATHOPHYSIOLOGY AND IMMUNOPATHOGENESIS**
Dissolution of Follicular Dendritic Cells in the Germinal Center of a Cervical Lymph Node from a Patient with Advanced HIV Disease

Courtesy of Dr. Jan Orenstein.
Immune Memory

Usual Healthy CD4 Population

With the CD4+ count <200 cells but >100, may lose PCP memory cells

When the CD4+ count is <100 cells, MAC memory cells and others may be lost
The 1993 Expanded Definition Includes

- All HIV-infected persons who have <200 CD4+T lymphocyte counts per microliter, or a CD4+T lymphocyte percentage of total lymphocytes of <14
- Pulmonary tuberculosis
- Recurrent pneumonia
- Invasive cervical cancer
AIDS Indicator Conditions

- Candidiasis of esophagus, bronchi, trachea, or lung
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month’s duration)
AIDS Indicator Conditions (cont’d)

- Cytomegalovirus disease (other than liver, spleen, or nodes); retinitis (with loss of vision)
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcer(s) greater than 1 month’s duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month’s duration)
AIDS Indicator Conditions (cont’d)

- Kaposi’s sarcoma
- Lymphoma, Burkitt’s (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia
AIDS Indicator Conditions (cont’d)

- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of internal organ
- Wasting syndrome due to HIV
Figure 2. Erythematous cutaneous Kaposi’s sarcoma lesion of the ear.
Figure 5. Spherules of *Pneumocystis carinii* within an Alveolus (Methenamine Silver Stain, ×1000).
Lipodystrophy, Fat Accumulation and Syndrome X

- Increased hip-to-waist ratio
- Sunken cheeks and temporal wasting
- Reduced fat in buttocks, arms and legs
- Prominent veins in arms and legs
- Increased breast size
Lipoatrophy Associated with an HIV-Protease Inhibitor

A 53-year-old man had human immunodeficiency virus (HIV)-related lymphoma, which had been in remission since 1987, a CD4+ lymphocyte count of 510 cells per cubic millimeter, and an HIV RNA load of 5,000 copies per milliliter. The addition of the HIV-protease inhibitor indinavir (800 mg three times daily) to his antiretroviral regimen of zidovudine and lamivudine resulted in a decrease in the HIV RNA load to undetectable levels and an increase in the CD4+ count to 918 cells per cubic milliliter. Measurement of cholesterol (298 mg per deciliter [7.7 mmol per liter]; reference range, <200 mg per deciliter [5.0 mmol per liter]), triglycerides (289 mg per deciliter; reference range, <177 mg per deciliter [2.0 mmol per liter]), and C peptide (4.0 μg per liter; reference range, 0.9 to 1.8 μg per liter) while the patient was fasting revealed hypercholesterolemia, hypertriglycerideremia, and insulin resistance. Impaired glucose tolerance was diagnosed on the basis of a glucose tolerance test (blood glucose, 108 mg per deciliter [6.0 mmol per liter] during fasting and 176 mg per deciliter [9.8 mmol per liter] at two hours). Within three to seven months after the initiation of indinavir, fat wasting of the face (Panel A), arms, buttocks, and legs developed, and the leg and arm veins became prominent. There was concurrent central obesity (Panel B) and enlargement of the cervical submental fat pad, referred to as buffalo hump (Panel C). Loss of body fat was confirmed by dual-energy x-ray absorptiometry. Clinically, muscle mass and strength were normal, and there was no abdominal organomegaly, mass, or ascites. The fasting morning plasma cortisol concentration was 11 μg per deciliter (308 nmol per liter; reference range, 7 to 22 μg per deciliter [200 to 600 nmol per liter]). These changes have continued to progress during the 19 months of therapy. The patient expressed concern about continuing indinavir therapy because of the changes in his physical appearance and the potential risk of long-term cardiovascular disease.

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Buffalo Hump in a Patient with the Acquired Immunodeficiency Syndrome

A 52-year-old man infected with the human immunodeficiency virus (HIV) was treated with zidovudine and lamivudine when his CD4+ lymphocyte count dropped to 105 cells per cubic millimeter and the viral load was 225,000 copies of HIV RNA per milliliter. This treatment was continued for 15 months, but when the viral load tripled, the regimen was changed to highly active antiretroviral therapy consisting of two nucleoside analogues (stavudine and lamivudine) and an HIV-reverse transcriptase inhibitor (indinavir). Within six weeks after the initiation of therapy, the viral load fell to less than 500 copies per milliliter. One year later, the patient began to have difficulty restraining an asymptomatic buffalo hump of his skin. The results of an examination were unremarkable except for a painless, tender cervical dorsal fat pad that measured 16 cm by 14 cm (Panel A). Computed tomographic scans of the cervical region further defined the large and symmetric subcutaneous deposit of adipose tissue (Panels B and C). No abnormalities in endocrine function or lipid metabolism were detected, the CD4+ count was 360 cells per cubic millimeter, and the level of HIV RNA was less than 500 copies per milliliter. The buffalo hump continues to enlarge, and the patient is sufficiently concerned about his appearance to contemplate surgical removal of the hump. He is still receiving highly active antiretroviral therapy.

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Clinical Identification of the Metabolic Syndrome

Positive diagnosis based on presence of 3 or more of the following:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
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<tbody>
<tr>
<td>Abdominal obesity</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Waist circumference &gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
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<tr>
<td>HDL cholesterol</td>
<td></td>
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<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
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NCEP. JAMA. 2001;285(19):2486-2497. Copyright ©2001 American Medical Association. All rights reserved.
Other Problems we see in HIV

- Elevated lipids—cholesterol and HDL (CAD)
- Hypertension
- Diabetes—elevated insulin levels
- Anal and genital HPV: need for regular PAP smears and rectal exam
- Osteoporosis
- Neuropathy (similar to diabetic)
Other Problems we see in HIV

- Hepatitis B and C
- STDs especially syphilis
- Maintain vaccination record (Tdap, pneumococcal, hepatitis, and influenza) and PPD
- Aging and the eyes (cataracts) and teeth
- Occult issues: pulmonary hypertension
HIV Disease Monitoring

- **Viral load**
  Measure of HIV RNA in plasma
- **CD4+T - cell count**
  Measure of immune system status
Baseline HIV-1 RNA Values Predict Progression to AIDS

Proportion AIDS-free

RNA by bDNA Quartile
- ≤4,530/mL
- 4,531–13,020/mL
- 13,021–36,270/mL
- >36,270/mL

p < 0.001

JW Mellors et al., Pittsburgh MACS
CD4+ T-cell Counts Do Not Accurately Indicate Viral Load

HIV-1 RNA by bDNA (molecules/mL in thousands) vs. CD4+ T-cells/μL

Spearman Correlation = -0.27

JW Mellors et al., Pittsburgh MACS
Figure. Occurrence of AIDS-indicating conditions in the natural history of HIV infection, according to CD4+ cell count. (Modified and reprinted by permission of *The New England Journal of Medicine* 1992;324:1332–8.)
Viral load = speed

CD4+ count = Distance

AIDS

Adapted from Coffin, John M. HIV viral dynamics. AIDS 1996,10(suppl 3):575-603
Goal of Therapy

To reduce and maintain plasma HIV RNA levels (viral load) below the point of detection

<400 COPIES/ML

Ultrasensitive testing

<50 COPIES/ML
Intervention Strategies to Enhance Adherence

Patient Assessment

Psychosocial Support
Clinical Support
Educational Support
Treatment is a true cocktail requiring at least 3 effective drugs: The Arsenal:

- Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
- Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Protease Inhibitors (PIs)
- Nucleotide Reverse Transcriptase Inhibitors
- Fusion Inhibitors
- Co-receptor antagonists
- Integrase Inhibitors
Treatment - 2010

- Asymptomatic patients:
  Treat: < 350 cells/mm$^3$
  Recommend Treat: 350-500 cells/mm$^3$

- Patients with CD4$^+$ cell count >500 cells/mm$^3$:
  50% panel members Treatment
  50% panel members Optional

~READ DISCUSSION SECTION – NOT JUST BULLET POINTS ~
What have we learned?

• Drugs do not eradicate HIV.
• Drugs effect QOL.
• Drugs require vigilant adherence.
• Drugs are expensive.
• Drugs only work if you can access them.
Strategies for Improving the Efficacy and Durability of Protease Inhibitor Therapy

Incomplete Suppression Leads to Resistance

Increase Potency

Increase Plasma Levels

Increase Potency and Increase Trough Levels
Resources in Kentucky

- Four Ryan White clinics
  - Paducah, Heartland Cares
  - Louisville, WINGS
  - Henderson, Matthew 25
  - Lexington, Bluegrass Care Clinic

[www.mc.uky.edu/kyaetc](http://www.mc.uky.edu/kyaetc) has contact information for clinics
Kentucky resources cont.

• Kentucky AIDS Education and Training Center
• 859-323-9969 or email jdedwa6@email.uky.edu

www.mc.uky.edu/kyaetc
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Inhibit reverse transcriptase enzyme
- Plagued with drug resistance and intra-class resistance
- Multiple newer combination drug products
<table>
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<td>d4T-MP</td>
<td>3TC-MP</td>
<td></td>
</tr>
<tr>
<td>ddA-MP</td>
<td>ZDV-DP</td>
<td>ddC-DP</td>
<td>CBV-DP</td>
</tr>
<tr>
<td></td>
<td>d4T-DP</td>
<td>3TC-DP</td>
<td></td>
</tr>
<tr>
<td>ddA-DP</td>
<td>ZDV-TP</td>
<td>ddC-TP</td>
<td>CBV-TP</td>
</tr>
<tr>
<td></td>
<td>d4T-TP</td>
<td>3TC-TP</td>
<td></td>
</tr>
<tr>
<td>ddA-TP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Activation of Nucleoside Analogue**

- Thymidine: ZDV, ZDV-MP, ZDV-DP, ZDV-TP
- Cytidine: ddC, ddC-MP, ddC-DP, ddC-TP
- Guanosine: ABC, ABC-MP, CBV-MP, CBV-DP, CBV-TP

**Enzymes and Processes**

- **5' Nucleotidase**
- **Adenylate Synthetase & Adenylate Lyase**
- **Adenylate Kinase & PRPP Synthetase**
- **NTP Kinase**
- **Deoxycytidine Kinase**
- **CMP/COmp Kinase**
- **Adenosine Phosphotransferase**
- **Cytosolic Enzyme**
- **Kinase**
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abbreviation</th>
<th>Brand Name</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>AZT</td>
<td>(Retrovir®)</td>
<td>Marrow suppression</td>
</tr>
<tr>
<td>Didanosine</td>
<td>ddI</td>
<td>(Videx EC®)</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Stavudine</td>
<td>d4T</td>
<td>(Zerit®)</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>3TC</td>
<td>(Epivir®)</td>
<td>Headache, Nausea</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>FTC</td>
<td>(Emtriva®)</td>
<td>Headache, Nausea</td>
</tr>
<tr>
<td>Abacavir</td>
<td>ABC</td>
<td>(Ziagen®)</td>
<td>Hypersensitivity HLA-B5701, ?cardiac</td>
</tr>
</tbody>
</table>

Combivir® AZT/3TC
Trizivir® AZT/3TC/ABC
Truvada® FTC/TF
Epzicom® 3TC/ABC
Nucleotide Reverse Transcriptase Inhibitors

- Inhibit reverse transcriptase enzyme
- Requires less intracellular phosphorylation and activation
- Fanconi Syndrome

Tenofovir (Viread®)
300mg PO QD
Efficacy against Hep B
Nausea/vomiting
Non-nucleoside Reverse Transcriptase Inhibitors

- Structurally distinct from the NRTIs
- Resistance remains a problem as does cross-resistance
Non-nucleoside Reverse Transcriptase Inhibitors-1\textsuperscript{st} generation

Nevirapine (Viramune\textsuperscript{®}) 200 mg qd x 2 weeks
Rash, Diarrhea then 200 mg BID

Delavirdine (Rescriptor\textsuperscript{®}) 400 mg TID
Rash, Headache

Efavirenz (Sustiva\textsuperscript{®}) 600 mg Qhs
Rash, CNS Disengagement
Atripla®
Emtricitabine 200 mg + Tenofovir 300 mg + Efavirenz 600 mg

- First triple therapy single pill option
- Gold standard
- Unprecedented manufacturer cooperation
- Cost comparable
- Single co-pay
- 1 PO Q hs
2008-2\textsuperscript{nd} generation \textit{NNRTI} \\ Etavirine (Intelence\textsuperscript{®})

- Formerly TMC125
- Second generation NNRTI
- Higher resistance ceiling [K103N] [Y181C]
- 200 mg PO BID
- Salvage therapy
- Rash, diarrhea
- D/I: (several) Tip, fAMP, ATA
Protease Inhibitors

• Among the most potent of the antiviral medications
• Resistance develops quickly, especially in cases of non-adherence
• Wide intra-class resistance
• Boosting
## Protease Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir (Invirase®)</td>
<td>500 mg BID</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Ritonavir (Norvir®)</td>
<td>600 mg BID</td>
<td>D/I, GI distress, perioral tingling</td>
</tr>
<tr>
<td>Indinavir (Crixivan®)</td>
<td>800 mg q8h</td>
<td>Nephrolithiasis, increased bilirubin</td>
</tr>
<tr>
<td>Nelfinavir (Viracept®)</td>
<td>1250 mg BID</td>
<td>Diarrhea, nausea</td>
</tr>
</tbody>
</table>
## Protease Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/Ritonavir (Kaletra®)</td>
<td>2 Caps BID</td>
<td>Nausea, HyperTG, diarrhea</td>
</tr>
<tr>
<td>Fosamprenavir (Lexiva®)</td>
<td>700 mg BID (variable)</td>
<td>Nausea, diarrhea</td>
</tr>
<tr>
<td>Atazanavir (Reyataz®)</td>
<td>400 mg QD</td>
<td>Increased bilirubin</td>
</tr>
<tr>
<td>Tipranavir (Aptivus®)</td>
<td>500 mg BID (boosted)</td>
<td>Nausea, diarrhea</td>
</tr>
<tr>
<td>Darunavir (Prezista®)</td>
<td>600 mg BID (boosted)</td>
<td>Nausea, diarrhea</td>
</tr>
</tbody>
</table>
Integrase Inhibitors
Raltegravir (Isentress®)

- Newest anti-HIV class
- “Years” of research
- Tx experienced and naïve patients only
- 400 mg PO BID
- HA, NV, ↑CPK
- UGT1A1 Glucuronidation
- D/Is: Tip/Rit, Rif
- Cost: $27.00/day ($2.00/d less than MAR)
Fusion Inhibitors

• Enfurvitide (Fuzeon®)
  90mg SQ BID
  $$
  Injection site reactions
  Salvage therapy
Co-Receptor Antagonists

• AKA “chemokine receptor blockers”
• Block either CCR5 or CXCR4
• Concern regarding trophism [CXCR4 associated with increased virulence]
• Theoretical concerns: malignancy, infection, others?
Maraviroc
(Selzentry®; Celsentri®)

• First of the class – CCR5 antagonist
• Indicated for tx experienced patients only, but best in naïve patients!!!
• Requires trophic assay before use - $$$ [TroFile™]
• Dose: 150 mg PO BID – varies with concurrent drug use [interactions]
• Pneumonia? Malignancy? Cardiovascular complications? Trophic conversion?
Figure 4. Chemokine Receptors as Obligate Coreceptors for HIV Entry into Cells and Chemokine Inhibition of HIV Entry.

HIV glycoprotein 120 (gp120) binds to CD4, resulting in a conformational change that exposes the V3 loop in gp120 and permits subsequent interaction with a chemokine receptor. To gain entry into cells, macrophage-tropic (M-tropic) HIV-1 uses CCR5 predominantly, and the T-cell-tropic (T-tropic) HIV-1 uses CXCR4 predominantly. Macrophage inflammatory proteins (MIP) 1α and 1β and the RANTES (regulated upon activation normal T-cell expressed and secreted) chemokine, ligands for CCR5, block M-tropic HIV-1 from entering cells. Stromal-cell-derived factor 1 (SDF-1), a ligand for CXCR4, blocks T-tropic HIV-1 from entering cells.
Effect of HAART On Viral Replication

- Adherence to Therapy
- Introduce HAART
- Adherence to Therapy, Inconsistent
- Viral Load
- Adherence to Therapy, Erratic or Inconsistent
- Selects mutants

Durable Suppression
Treatment - 2010

- **Treat:**
  - Symptomatic patients
  - Pregnant patients
  - HIV associated nephropathy
  - Hep B co-infected (when Hep B tx is indicated)

- Resistance testing:
  - Genotype early/Phenotype late
TREATMENT PRARADIGM
SHIFTs

- CD4 < 350
- Viral Load > 5,000
- CD4 < 500
- Viral Load > 100,000

QOL  
Dosing  
Resistanc e  
$
Treatment Regimens

- Typical backbones:
  - 2 NRTIs + 1 NNRTI
  - 2 NRTIs + 1 PI
  - 2 NRTIS + INSTI
Treatment Regimens
Medication Selection

- **Downgrades**
  - Kaletra® (except in pregnancy)

- **Recommendations**
  - Atripla®
  - Truvada®+Ral
  - Truvada®+Ata/rit
  - Truvada®+Dar/rit
Treatment Regimens
‘What Not To Use’

• Ata plus Ind
• DDI plus D4T
• Two NNRTI combinations
• EFV in women of childbearing potential
• 3TC and FTC
• ETV and unboosted PIs
• ETV and boosted ATA or fAMP
• NVP in naïve females with CD4\(^+\) > 250 or males > 400
• Unboosted Dar, Saq, Tip
• AZT plus D4T
<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantage</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotyping</td>
<td>- Availability</td>
<td>- Indirect measure</td>
</tr>
<tr>
<td></td>
<td>- Days to results</td>
<td>- Expert interpretation required</td>
</tr>
<tr>
<td></td>
<td>- Less technical</td>
<td>- Minor species not tested</td>
</tr>
<tr>
<td>Phenotyping</td>
<td>- Direct measure of susceptibility</td>
<td>- Costly</td>
</tr>
<tr>
<td></td>
<td>- More familiar reporting results ($IC_{50}$, $IC_{90}$)</td>
<td>- Weeks to results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- More technical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Minor species not detected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Breakpoints undefined</td>
</tr>
</tbody>
</table>
CNS Penetration

• High: AZT, Abacavir, Delavirdine, Nevirapine, Boosted (Fosamprenavir or Indinavir or Lopinavir)

• Less: D4T, 3TC, FTC, Efavirenz, Unboosted (Fosamprenavir or Lopinavir or Indinavir)

• Least: Tenofovir, DDI, DDC, Nelfinavir, Boosted Saquinavir, Ritonavir, Boosted Tipranavir, Enfuvirtide, Maraviroc
What's New?

- FDA Approved (February 2010)
  
  *Ritonavir Melt Extrusion Tablet (MALTREX)*
  
  - 100 mg (cost comparable to caps)
  - No refrigeration requirement
  - GI?
  - Take with food
What’s New?

• Ritonavir is bad …
  tolerability
  DIs (inhibition > induction)
  dyslipidemia

*Bonus boosting:*

Elvitegravir (INSTI)
Vicriviroc (R5 blocker)
What’s New?

- Other enhancers:
  GS-9350 (tablet, CYP specific, lipid neutral)
  The QUAD study
  Truvada + Elvitegravir + GS-9350?
  SPI-452
What’s New?

• Rilpavirine (TMC 278)
  Phase III
  second generation NNRTI
  chemically related to etravirine
  long $t_{1/2}$
  rash and CNS effects
  Fixed dose with Truvada®
Where are we going?

- Inside HIV and its regulatory genes:
  - *tat* – transactivator
  - *gag* – viral capsid proteins
  - *pol* – reverse transcriptase
  - *env* – envelope
  - *nef* – retards replication

- Others: *rev, vif*
Where are we going?

- ‘Maturation Inhibitors’
  - bind gag protein and prevent its proteolytic cleavage (independent of PIs)
  - gag essential to viral capsid formation
  - ‘maturation’ occurs following viral exit
  - required for particle infectivity
Maturation Inhibitors
HIV Capsid
Bevirimat

Bevirimat Targets Gag at the CA-SP1 Cleavage Site

CD4 cell

untreated

budding HIV particle

Treated

CA-SP1 cleavage site between Gag codons 363-364

BEVIRIMAT
Medication Burden

“HIV treatment only marginally better than HIV disease itself.”

- **Zidovudine**: “I have no energy.”
- **Nelfinavir**: “I’m having 10-12 BM per day!”
- **Stavudine**: “I need methadone for the pain!”
- **PIs**: “Look what has happened to my face!”
- **Ritonavir**: “I can’t stop throwing up!”
- **Atazanavir**: “I’m yellow!”
- **Efavirenz**: “I’m too scared to go to sleep!”
- **Indinavir**: “I have a horrible pain in my side!”
Increased Risk for Age-Related Comorbidities Among Patients With HIV

- Cardiovascular disease (CVD), including myocardial infarction (MI)
- Non-AIDS-related malignancies
- Bone disease (especially osteoporosis)
- Neurocognitive disorders
- Nonalcoholic fatty liver disease

Complications That May Be More Frequent or More Severe in Patients With HIV

• Hepatitis B and C coinfection
• Progressive multifocal leukoencephalopathy
• Tuberculosis
• Antiretroviral therapy (ART)-associated lipoatrophy
• Bone and kidney toxicities of some ART agents
• HIV-associated immune reconstitution inflammatory syndrome
Metabolic Syndrome, HIV, and Older Age

• Metabolic syndrome is a clustering of metabolic risk factors for both CVD and type 2 diabetes\(^1\)
• National Cholesterol Education Program (NCEP) definition includes\(^2\)
  – Abdominal obesity
  – Atherogenic dyslipidemia
  – Raised blood pressure
  – Insulin resistance
  – Proinflammatory state
  – Prothrombotic state
• Patients with metabolic syndrome may also be at increased risk for other conditions including polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer\(^1\)
Prevalence of Metabolic Syndrome Increases With Advancing Age


Ford ES. JAMA. 2002;287(3):356-359. Copyright ©2001 American Medical Association. All rights reserved.
Older Age and Increased Metabolic Risk in HIV+ Population: Several Recent Studies

- Older age was significantly associated with increased risk of metabolic syndrome\(^1\)
- Age >40 was an independent risk factor for
  - Lipodystrophy (OR 1.7, 95% CI, 1.1-2.7)
  - Glucose intolerance/diabetes mellitus (OR 2.6, 95% CI, 1.1-6.3)\(^2\)
- Risk for MI or coronary artery disease (CAD) was greater in patients >40 years of age
  - OR 9.05 ± 7.87 vs 3.65 ± 7.43\(^2\)
- Age was independently associated with metabolic syndrome
  - OR 1.20, 95% CI, 1.17-1.40 per 5 years older\(^3\)
- Older age was independently associated with risk of new-onset diabetes mellitus\(^4\)

CI, confidence interval; OR, odds ratio

Complications

- Fanconi syndrome
- **Drug toxicity:** AZT, tenofovir, DDI, sustiva, nevirapine, nelfinavir
- Dental, eye care
- Vaccinations: hep A, hep B, pneumvax, Tdap, influenza
- PPD
- Hypertension
- Venereal disease, mainly syphilis
- Testosterone and birth control
- anxiety
- housing
Incidence of Non-AIDS-Defining Cancers Is Increasing in the Population With HIV

• Incidence of cancers increased in the ASD/HOPS cohort (1992-2003)
  – Anal cancer (RR=1.96, \(P<.001\))
  – Prostate cancer (RR=1.83, \(P=.009\))
  – Melanoma (RR=1.55, \(P=.047\))
  – Colon cancer (RR=1.40, \(P=.028\))
  – Hodgkin lymphoma (RR=1.36, \(P=.032\))

Management Considerations in Older Patients With HIV

- Regular screening and health maintenance
- Baseline evaluations of cardiovascular risk
- Routine monitoring of
  - Fasting lipid and glucose levels
  - Renal function
  - Markers of bone disease
- Dyslipidemia is frequently observed in both older people and in HIV-infected patients
  - May require use of lipid-lowering therapy
  - Response to such therapy may be inferior in HIV-infected persons
- For cancer screening, the same procedures performed in the general population should be applied
Interactions Between ART Agents and Antihypertensive Drugs

• There are important drug interactions between calcium channel blockers and PIs and NNRTIs
  – Especially amlodipine, nifedipine, and verapamil
• Carvedilol interacts with both PIs and NNRTIs
• Beta blockers should be used with caution in combination with atazanavir due to the possibility of additive prolongation of the QT interval
• More information can be found at www.hiv-druginteractions.org
• The full JNC 7 report on hypertension can be found at www.nhlbi.nih.gov/guidelines/hypertension

JNC 7, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NNRTIs, nonnucleoside reverse transcriptase inhibitors; PIs, protease inhibitors
Reporting a case in KY

• Form to be completed found on

http://chfs.ky.gov/dph/epi/reporting.htm

KY reports cases by name; this information is kept confidential in the state health department
Reporting a case in KY

- A case of HIV or AIDS must be reported in **5 days** to:

  For reports in Jefferson, Henry, Oldham, Bullitt, Spencer, Shelby and Trimble counties, call Nikki White, Surveillance Nurse Consultant with the Louisville Metro Health Department: (502) 574-6574.

  For reports in all other Kentucky counties contact: Medina Tipton, Surveillance Coordinator or Peace Julie Nakayima, MPH, Epidemiology Program Coordinator (866) 510-0008 or (502) 564-0536
Bluegrass Care Clinic

- Bluegrass Care Clinic
  University of Kentucky Chandler Medical Center
  800 Rose Street
  MN 672
  Lexington KY 40536-0298
  phone: 800-333-8874 or 859-323-5544
  fax: 859-257-2040
  Alice C. Thornton, Project Director

- Website: [www.mc.uky.edu/bluegrasscareclinic](http://www.mc.uky.edu/bluegrasscareclinic)
Kentucky Resources cont.

- Care Coordinator Program for social service issues
  www.mc.uky.edu/kyatec

- Community Based Organizations
  www.mc.uky.edu/kyatec