Interdisciplinary Case Conference

HIV: Still Deadly After All These Years

Tuality Health Education Center
December 7, 2007
2:00PM-4:00PM
“In a 2006 survey, 26% of respondents thought HIV could be caught by kissing, 16% thought sharing a drinking glass was a risk and 10% thought that touching a toilet seat might pass on HIV”.


_Data from Center for Disease Control and Prevention_
Global HIV/AIDS Statistics

Data from: UNAIDS, 2007 AIDS Epidemic Update; December 2007
Global HIV/AIDS Statistics

Data from: UNAIDS, 2007 AIDS Epidemic Update; December 2007
Patients living with HIV/AIDS in November 2007

North America 1.3M (3.9%)
Caribbean 0.23M (0.7%)
Latin America 1.6M (4.8%)

Western & Central Europe 0.76M (2.3%)
North Africa & Middle East 0.38M (1.1%)
Sub-Saharan Africa 22.5M (67.8%)

Eastern Europe and Central Asia 1.6M (4.8%)
East Asia 0.8M (2.4%)
South and South East Asia 4M (12%)
Oceania 0.08M (0.2%)

Data from: UNAIDS, 2007 AIDS Epidemic Update; December 2007
Estimated rates (per 100,000 population) for adults living with HIV infection (not AIDS) or with AIDS, 2007

Divisions of HIV/AIDS Prevention National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
HIV diagnoses by ethnicity in 2005 in US (33 states only)

Patients Diagnosed with AIDS in USA

Dr. Casey Arendt
School of Pharmacy
What’s the difference between “HIV” and “AIDS”?

Dr. Casey Arendt
School of Pharmacy
HIV vs. AIDS

- Human immunodeficiency virus
  - HIV is an infectious agent

- Acquired immune deficiency syndrome
  - AIDS is the name for the condition that HIV infection produces when it has run its course
HIV infection causes AIDS

How does infection with HIV lead to immune deficiency?
HIV kills cells of the immune system

- HIV only infects cells that have CD4 receptors on their surface.
- CD4+ cells are key cells in initiation of an immune response to infection.
  - Helper T cells
  - Macrophages
- HIV infects and kills the very cells that allow us to mount an immune response.
Initial symptoms of HIV infection

If you were recently infected with HIV, would you be able to tell without a lab test?
HIV infection proceeds through three phases

- **Acute phase (new infection)**
  - Viral load is high, CD4+ levels drop
  - Patient is highly infectious
  - ~50% of patients are asymptomatic
  - Others experience flu-like symptoms 2-6 weeks postinfection

- **Chronic phase**
  - Infection contained by anti-HIV antibodies
  - Low viral load, CD4+ levels drop slowly
  - Lasts for many years even in untreated patients
  - Prolonged greatly by highly active antiretroviral therapy (HAART)
  - May or may not progress to AIDS in treated patients

- **AIDS**
  - CD4+ levels are low (immune deficiency), viral load high
  - Disease symptoms arise
Defining AIDS
(Acquired Immune Deficiency Syndrome)

What causes the observable symptoms of AIDS? What are they?
Immune deficiency leads to high burden of secondary infections

- Clinical definition of AIDS (Centers for Disease Control, 1993)
  - Evidence for HIV infection
  - AND one or both of the following:
    - CD4+ cell count ≤ 200/mm³ (normal, 600-1000/mm³)
    - Presence of AIDS-diagnostic secondary infection

- Too few T cells remain to recognize infectious agents and mount immune response

- Pathogens take advantage of poor immune function
  - Many of these rarely cause disease in immune-competent individuals
Examples of AIDS-related opportunistic infections

- *Pneumocystis carinii* pneumonia (PCP)
  - Already in the lungs of most of us
  - Most common secondary infection of AIDS
  - Symptoms: night sweats/fever, dry cough, shortness of breath
- Candidiasis/thrush
- Kaposi’s sarcoma
  - Poor outcomes associated with lung and GI tract lesions
- GI tract infections from contaminated food/water
  - Common symptom: chronic diarrhea
AIDS disease burdens

- Opportunistic infections and/or reactivation of latent infections
  - Viral
  - Fungal
  - Parasitic
  - Bacterial
- Cancer
  - Kaposi’s sarcoma, lymphomas
- Neurological symptoms
- Muscle and fat wasting
- Side-effects of antiretroviral therapy
  - Lipodystrophy (“buffalo hump”)
  - GI distress
  - Hepatotoxicity
Summary

- High HIV viral loads $\rightarrow$ depletion of CD4$^+$ helper T cells $\rightarrow$ poor immune function
- HIV infection itself is relatively asymptomatic (acute and chronic phases)
- AIDS is defined clinically by:
  - presence of HIV infection
  - low CD4$^+$ cell count
  - onset of secondary infections
- Secondary infections lead to many of the symptoms experienced by AIDS patients:
  - Fever, night sweats
  - Chronic diarrhea
  - Involuntary weight loss
  - Cough, shortness of breath
  - Others...
Routes of Transmission

• Sexual Contact
  – Vaginal Sex
  – Anal Sex
  – Oral Sex

• Sharing Needles / Syringes
  – Sharing “Works”
  – Other Risks Associated With Substance Use
    • Increased Sexual Desire
    • Decreased Inhibitions = Decreased Use of Safe Sex Practices
Routes of Transmission

• Mother – To – Child – Transmission (MTCT)
  – During Pregnancy
  – During Delivery
  – Via Breastfeeding

• Blood Transfusion or Exchange of Clotting Factors
  – Very Rare in countries that screen blood
  – There are still some countries that DO NOT screen blood
Patients newly diagnosed with HIV in 2005 in US

MSM = Men having Sex with Men
IDU = Injection Drug Users

Data from HIV Alliance, Volume 11, Number 2, Autumn 2005
“Universal Precautions”

• The blood and bodily fluids of EVERY person should be treated as though it is infected
  – Reduce potential exposure to HIV, Hep B, and Hep C
    • Blood, semen, vaginal fluid, CSF; vomit, urine, feces that may contain blood
  – Includes practices to decrease risk of needle stick – how you cap a needle after using it
  – Also to prevent transmission from the health care provider
“Positive Prevention”

• In the past, patients with HIV have been left out of prevention campaigns
  – Educating patients already infected is the most effective way to prevent new infections
“Positive Prevention”

• Purposes are to help People Living With HIV/AIDS (PLWH/A) to:

  – Protect their sexual health
    • Including the ability to have a healthy sex life
    • The ability of woman to have children that are not infected
    • Sero-discordant couples - testing

  – Avoid infection with other Sexually Transmitted Infections (STIs)
    • Co-infection with STIs can increase the risk of HIV transmission
    • STIs can be more severe in patients with HIV (such as herpes virus, HPV)
“Positive Prevention”

– Delay HIV disease progression
  • Potential for “re-infection” or “super-infection”
  • Risks of acquiring other infections (such as from using dirty water when injecting substances, Hep C from sharing needles)

– To Prevent Transmission
“Positive Prevention”

• Main Points for Health Care Providers:
  – Patients with HIV have the right to have a healthy sex life
  – HAVE THE CONVERSATION
    • Talk to your patients about sex
    • Talk to your patients about substance use
    • Talk to your patients about partner testing
  – Be Prepared to Answer Basic Questions about transmission and testing
Resources

• For Patients (and Clinicians)
  – County Public Health Department
  – www.cascadeaids.org (and www.ohsu.edu/partnership)
  – www.hivstopswithme.org

• For Clinicians
  – www.aidsetc.org (www.northwestaetc.org)
  – hivinsite.ucsf.edu/insite
  – www.hopkins-aids.edu
The HIV Life Cycle

aidsinfo.nih.gov/other/hivlifecycle.html
The HIV Life Cycle

Life cycle animation from Boehringer Ingelheim
www.youtube.com/watch?v=RO8MP3wMvqg
or
Potential targets:

- block virus attachment and entry
- inhibit three main HIV enzymes:
  - reverse transcriptase
  - integrase
  - protease
- block virus budding
Attachment:
October 2007, FDA approves a new drug (maraviroc) from Pfizer that blocks CCR5, a co-receptor molecule on the human host cell.

Entry:
Enfuvirtide, marketed as Fuzeon, is the only FDA approved drug that prevents HIV from fusing with a cell's membrane.
Inhibit three main HIV enzymes:

1. reverse transcriptase

Reverse transcriptase is necessary to generate DNA from the viral RNA.

- Nucleoside analog reverse transcriptase inhibitors (NRTIs or nukes)
- Nucleotide analog reverse transcriptase inhibitors (NtRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
Inhibit three main HIV enzymes:

1. reverse transcriptase

**Nucleoside Reverse Transcriptase Inhibitors (NRTIs or nukes)**

There are several NRTI's available.

* **Combivir** (zidovudine, Lamivudine)
* Epivir (Lamivudine)
* Zerit (D4T)
* Videx (Videx EC, ddI)
* AZT (Retrovir, zidovudine) *first drug in 1986*
* Ziagen (Abacavir)
* Trizivir (Abacavir + AZT + Epivir)
* Emtriva (emtricitabine)
* Epzicom (lamivudine + abacavir)
Inhibit three main HIV enzymes:

2. integrase

The integrase is required to integrate viral DNA into the host genome.

October 2007, the FDA approved the Merck drug Isentress (Raltegravir), an integrase enzyme inhibitor (first drug to inhibit integrase).
Inhibit three main HIV enzymes:

3. protease

The protease is necessary to process the viral proteins (reverse transcriptase and integrase)

First protease inhibitor was on market in 1995

- Agenerase
- Aptivus
- Crixivan
- Fortovase
- Invirase
- Kaletra
- Lexiva
- Norvir
- Prezista
- Reyataz
- Viracept
Block virus budding

Despite ongoing research, no approved medication available yet.
Currently, there are 30 antiretroviral drugs approved by the FDA to treat people infected with HIV.  
(Source: www.niaid.nih.gov/factsheets/treat-hiv.htm)

These drugs fall into four major classes:

• block virus attachment and entry
  • inhibit reverse transcriptase
    • inhibit integrase
    • inhibit protease
The complete elimination of HIV from an infected individual has never been achieved.

Viral DNA “hides” in host genome.
Mechanisms and Prevalence of HIV Resistance
What is Resistance?

• The term ‘resistance’ is used to describe HIV viral particles (virions) that are no longer susceptible to specific antiviral medications.

• Resistant HIV virions have undergone genetic mutations (i.e., changes to their RNA).
• Antiviral drugs target viral enzymes.

• When viral targets are mutated the interaction between the antiviral medications and the viral targets is decreased or less effective.

Therefore, viral mutation results in decreased drug effectiveness and increased viral replication.
Resistance Movie

http://www.youtube.com/watch?v=TvNOmwRh0I0
How HIV Resistance Arises

HIV produces many different versions of itself in a patient's body (although the huge majority are the normal form).

Drugs kill all of these virus particles except those that are resistant to the drugs.

The resistant virus particles continue to reproduce. Soon the drug is no longer effective for the patient.
Indicators of Resistance

Viral Load Test:

• This test involves taking a blood sample from a patient and then measuring the concentration of virions in the blood (i.e., viral load).

• The test is conducted every two to eight weeks during the initial treatment and then every three to four months during long-term treatment.

• Patients infected with resistant HIV virions will display increased viral load as resistant virions are able to replicate easily compared to non-resistant virions.
Factors Leading To Genetic Mutation and Resistance

1. HIV replicates at an incredibly fast rate!
   - Several billion new virions can be produced each day in the untreated patient.

2. HIV reverse transcriptase (RT) is especially error prone.
   - It is estimated that RT generates one to five errors during each replication of the HIV genome.
Resistance in HIV Protease Inhibitors

HIV Protease Inhibitors:
- Invirase™ (saquinavir)
- Norvir™ (ritonavir)
- Crixivan™ (indinavir)
D30N: Mutation of an aspartic acid amino acid to an asparagine amino acid results in resistance to a specific protease inhibitor, nelfinavir (Viracept®).

I54V: Mutation of an isoleucine amino acid to a valine amino acid contributes to resistance to protease inhibitors as a class.

by Dr. Ladislau Kovari, Wayne State University School of Medicine, Detroit
What is the impact of resistance?

1. Resistance diminishes the effectiveness of drug therapy.

2. Potentially, virions can be produced that are resistance to all current therapies.

Patients compliance to the treatment regimen is especially important with HIV/AIDS.
Prevalence of HIV Resistance

• 2001 Report:

“In the U.S., as many as 50 percent of patients receiving antiretroviral therapy are infected with virus that express resistance to at least one of the available antiretroviral drugs.”

• 2004 Report (132,500 patients with HIV):

“76% of patients had resistance to one or more antiretroviral drugs.”

![Drug resistance chart]

*Drug resistance detected*
What actions are taken to reduce the probability of resistance?
Why are there so many drugs on the market in each category?

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Multi-class Combination Products</th>
<th>Protease Inhibitors (PIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Name</strong></td>
<td><strong>Multi-class Combination Products</strong></td>
<td><strong>Protease Inhibitors (PIs)</strong></td>
</tr>
<tr>
<td>Atripla</td>
<td>efavirenz, emtricitabine and tenofovir disoproxil fumarate</td>
<td>Agenerase (amprenavir, APV)</td>
</tr>
<tr>
<td>Combivir</td>
<td>lamivudine and zidovudine</td>
<td>Aptivus (tipranavir, TPV)</td>
</tr>
<tr>
<td>Emtriva</td>
<td>emtricitabine, FTC</td>
<td>Crixivan (indinavir, IDV)</td>
</tr>
<tr>
<td>Epivir</td>
<td>lamivudine, 3TC</td>
<td>Invirase (saquinavir mesylate, SQV)</td>
</tr>
<tr>
<td>Epzicom</td>
<td>abacavir and lamivudine</td>
<td>Kaletra (lopinavir and ritonavir, LPV/RTV)</td>
</tr>
<tr>
<td>Hivid</td>
<td>zalcitabine, dideoxycytidine, ddC</td>
<td>Lexiva (Fosamprenavir Calcium, FOS-APV)</td>
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<tr>
<td>Retrovir</td>
<td>zidovudine, azidothymidine, AZT, ZDV</td>
<td>Norvir (ritonavir, RTV)</td>
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<tr>
<td>Trizivir</td>
<td>abacavir, zidovudine, and lamivudine</td>
<td>Prezista (darunavir)</td>
</tr>
<tr>
<td>Truvada</td>
<td>tenofovir disoproxil fumarate and emtricitabine</td>
<td>Rezataz (atazanavir sulfate, ATV)</td>
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<tr>
<td>Truvada</td>
<td>tenofovir disoproxil fumarate and emtricitabine</td>
<td>Viracept (nelfinavir mesylate, NFV)</td>
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<td>Viracept</td>
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<td><strong>Fusion Inhibitors</strong></td>
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<tr>
<td>Fuzeon</td>
<td>enfuviridine, T-20</td>
<td><strong>Entry Inhibitors - CCR5 co-receptor antagonist</strong></td>
</tr>
<tr>
<td>Zerit</td>
<td>stavudine, d4T</td>
<td>Selzentry (maraviroc)</td>
</tr>
<tr>
<td>Zidovine</td>
<td>abacavir sulfate, ABC</td>
<td><strong>HIV integrase strand transfer inhibitors</strong></td>
</tr>
<tr>
<td><strong>Brand Name</strong></td>
<td><strong>Multi-class Combination Products</strong></td>
<td><strong>HIV integrase strand transfer inhibitors</strong></td>
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<tr>
<td>Rescriptor</td>
<td>delavirdine, DLV</td>
<td><strong>Isentress</strong></td>
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<td>Sustiva</td>
<td>efavirenz, EFV</td>
<td>raltegravir</td>
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<tr>
<td>Viramune</td>
<td>nevirapine, NVP</td>
<td><strong>Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)</strong></td>
</tr>
</tbody>
</table>
HAART “Highly active antiretroviral treatment”

HAART = 3 or more agents simultaneously
1) Fusion inhibitors
2) RT inhibitors
3) Protease inhibitors
Multidrug therapy kills more

Fusion inhibitor

RT inhibitor

RT & Fusion inhibitor

Multiple target regimen
HAART

reduces viral plasma levels by >95% in two weeks
Multi-dosing

- “Drug-resistant HIV strains can develop if a person takes less than 95% of their pills...The fewer pills, the better they are able to achieve that 95% threshold”
  (Bridges, AP/Forbes, 7/12/07)

- **Atripla** = Truvada + Sustiva
  - One pill, Once a day

Tonight's dinner pills are: (top row) Truvada, 2 Viramune, 2 Ziagen, Tricor (lowers cholesterol), low dose Aspirin (thins blood), Proscar (reverses hair loss), (middle row) 2 Quinapril HCL (lowers blood pressure), 2 Tylenol, 2 Benadryl, 3 Ribavirin, (bottom row) 8 K-Pax capsules (custom multi-vitamins for HIV disease)
Cost of HAART- In U.S.

- 60% of HIV-positive people who are receiving antiretrovirals in the U.S. are taking Truvada (tenofovir and emtricitabine) and Sustiva (efavirenz)
  - 3 pills, 2x day = $1150.00/ month

- Atripla = Truvada + Sustiva
  - One pill, Once a day = $1150.00/ month
Cost of HAART - Internationally

- World Health Organization estimates that two million people in developing countries (or 25% of those in need in developing countries) receive HAART
- International costs vary by government contract

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<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td>Lamivudine 150 mg*</td>
<td>214</td>
<td>80</td>
<td>87</td>
<td>59</td>
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<td>174</td>
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<td>Stavudine 30 mg*</td>
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<td>Didanosine enteric coated capsule 250 mg</td>
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<td>Zidovudine 300 mg + lamivudine 150 mg*</td>
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<td>426</td>
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<td>(3,361)*</td>
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<td>(2,395)*</td>
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<td>Ritonavir 100 mg*</td>
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<td>(2,512)*</td>
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<td>Efavirenz 90 mg/ml</td>
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Nunn et al, PLOS