HIV Diagnosis and Treatment-A 25 Year Journey

Speaker: Peter A. Kreckel, R.Ph. is a graduate of the University of Pittsburgh, Bachelor of Science in Pharmacy, Magna Cum Laude, Class of 1981. He served as the President of the Pharmacy School Class of 1981 for 3 years, and President of the Pharmacy School Student Council for 2 years. During this time he received the Upjohn Achievement Award for leadership and academic achievement.

Speaker Disclosure: Peter Kreckel, RPh has no actual or potential conflicts of interest in relation to this program.

OBJECTIVES

• Review the history, prevalence, and current epidemiology of HIV infection and AIDS in the United States.

• State the current Florida Law on AIDS and its impact on testing, confidentiality of test results, and treatment.

• Provide an update on antiretroviral therapy (ARV) for HIV to include their mechanisms of action, efficacy, dosing, safety, and tolerability profiles.

• Describe the role pharmacists can play in educating and treating patients with HIV.

Accreditation:
- Pharmacists
- Pharmacy Technicians
- Nurses

Target Audience:
- Pharmacists
- Pharmacy Technicians
- Nurses

CE Credits:
1.0 Continuing Education Credit or 0.1 CEU for pharmacists/technicians

Program Overview: Take the journey to learning more about diagnosis and treatment of HIV since the beginning. This knowledge based activity is Florida approved and will provide you with updates on antiretroviral therapy and the pharmacist’s role in caring for these patients.

Expiration Date: 01/29/2013

Pharmacists
Pharmacy Technicians
Nurses

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<table>
<thead>
<tr>
<th>Year</th>
<th>Events</th>
</tr>
</thead>
</table>
| 1981 | - Increase in infections of PCP (pneumocystis carinii pneumonia) in California and New York  
- June: reports of 5 men in Los Angeles with PCP - the beginning of AIDS awareness in USA  
- December: other populations than gay men affected — injecting drug users |
| 1982 | - Theorized cause might be a sexually transmitted agent  
- September: “AIDS” acquired immune deficiency syndrome defined by the Center for Disease Control (CDC)  
- December: 20 month old child dies after multiple transfusion. Awareness of blood born pathogen transmitted in blood supply |
| 1983 | - Risk to hemophiliacs - Blood concentrates expose them to the blood of up to 5000 blood donors  
- Haitians included in groups at risk:  
  - 4-H club: homosexuals, hemophiliacs, heroin addicts & Haitians  
  - Some substitute “hookers” for Haitians  
- May: doctors at the Pasteur Institute in France isolate the virus they believe to cause AIDS. Named LAV “lymphadenopathy associated virus”  
- Fear grips the USA:  
  - San Francisco Police wear masks and gloves  
  - New York landlords evict AIDS patients  
  - An aggressive form of Kaposi Sarcoma reported in Zambia. |
| 1984 | - April 23 - Dr Robert Gallo at the National Cancer Institute isolates the virus that causes AIDS. Named HTLV-3 “human t-cell lymphotropic virus-3”.  
  - He predicts a vaccine will be ready for testing in 2 years. (25 plus years later - still no success)  
  - Soon will be available a commercially available test to detect the virus in the blood |
1985
- HTLV-3 is found to be the same virus as the LAV
- Ryan White, a 13-year-old hemophiliac, is barred from school
- CDC removes Haitians from risk group
- Rock Hudson dies of AIDS
- AIDS virus is found to be transmitted in breast milk

1986
- HIV name is agreed upon (Human Immunodeficiency Virus)
- AZT (azidothymidine) developed as an anticancer drug in 1964 is tested.
  - 2 groups tested in a placebo-controlled study
    - 1 patient in AZT group dies
    - 19 patients in placebo group die
    - Test stopped, because of ethical reasons

TODAY 25+ years
- Prophylaxis of opportunistic infection
- Early detection
- 28 antiretrovirals in 6 classes
- Understanding of the transmission
- Chronic disease state management

Legal/Legislative Issues: HIV Testing
Florida Statutes
Title XXIX
Chapter 381.004
Florida Statutes (2007)

- Title XXIX
  PUBLIC HEALTH
- Chapter 381
  PUBLIC HEALTH: GENERAL PROVISIONS
- 381.004 HIV testing.
  - (1) LEGISLATIVE INTENT.--The Legislature finds that the use of tests designed to reveal a condition indicative of human immunodeficiency virus infection can be a valuable tool in protecting the public health. The Legislature finds that despite existing laws, regulations, and professional standards which require or promote the informed, voluntary, and confidential use of tests designed to reveal human immunodeficiency virus infection, many members of the public are deterred from seeking such testing because they misunderstand the nature of the test or fear that test results will be disclosed without their consent. The Legislature finds that the public health will be served by facilitating informed, voluntary, and confidential use of tests designed to detect human immunodeficiency virus infection.

Pregnant Patients: Florida Law

- Florida law (§ 384.31, F.S.) requires a health care provider who attends a pregnant woman for conditions relating to her pregnancy to offer testing for HIV and counsel her on the availability of treatment if she tests positive.
- Document in writing if the pregnant woman objects to HIV testing, and keep in her chart. Still encourage testing.
- If pregnant women tests HIV negative: offer follow up testing 6 months later. Exposure window is 6 months from time of infection until detectable antibodies.
- If HIV positive, support is available thru Healthy Start Care Coordination System. Contact the Family Health Line at 1-800-451-BABY

HIV: The Virus

- Can only replicate inside virus, by commandeering the cells machinery.
- Retrovirus: Are RNA viruses and in order to replicate then must make a DNA copy of their RNA. The DNA genes allow virus to replicate.
- 2 billion viruses produced and cleared per day. Great chance for mutations.
- Lentiviruses: or “slow” virus—very long interval from initial infection until expression of symptoms.
- Primary target: CD4+ cells
What is a CD4+ Cell??

- **Role:** in the immune response, signals other cells in the immune system to perform special functions.
- **Healthy patients CD4+ levels:** 800-1200 cells per cubic millimeter.
- **AIDS by definition** is when CD4 counts drop below 200, risk of Pneumocystis carinii infection. Under 100 at risk for toxoplasmosis. Under 50 risk for Mycobacterium avium and Cytomegalovirus.

What happens to the body when infected?

- The rate of viral replication in productively infected CD4 cells is extremely high (one billion viral particles are produced every day).
- The immune system attempts to control the infection by producing vast numbers of cells, such as T helper cells. The battle between the viral infection and the cells of the immune system continues throughout the course of the infection.
- Eventually the virus’ ability to damage the immune system exceeds the body’s capacity to fight HIV.

**DRUGS LISTED IN ORDER BY SITE OF ACTION**

- **FUSION inhibitors**
- **ENTRY inhibitors**
- **REVERSE TRANSCRIPTASE inhibitors** (nucleoside/ non-nucleoside)
- **INTEGRASE inhibitors**
- **PROTEASE inhibitors**
Viral Fusion Inhibitor

**Mechanism:**
Blocks the fusion of the HIV virus into the host cell

**Adverse reactions:**
Injection site reactions, recurrent pneumonia, diarrhea, nausea, fatigue

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CCR5 Co-Receptor Antagonist

**Mechanism:**
Binds to a receptor called CCR5 on CD4 cell.

**Adverse reactions:**
Hepatotoxicity, cough, pyrexia, upper respiratory infections, abdominal pain, dizziness

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Nucleoside & Nucleotide Reverse Transcriptase Inhibitors

- The first class of Antiretrovirals
- First drug of class: Zidoduvidine (AZT) Retrovir® 1987
- Mechanism of Action: Competes with endogenous deoxynucleotides for the reverse transcriptase. NRTI prematurely stop DNA elongation. Stops virus from changing it's genes from RNA to DNA.
- Reverse transcriptase is involved in the production of a RNA-DNA double helix. A DNA copy of HIV RNA is synthesized using the viral RNA as a template.

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Class Effects of NRTI

- Take with food to decrease nausea (except didanosine)
- Renally eliminated- doses need adjusted for all except abacavir (alcohol dehydrogenase) and zidovudine (glucuronidation)
- Minimal Cytochrome P450 interaction
ARV Components in Initial Therapy: Dual-NRTI Pairs

**ADVANTAGES**
- Established backbone of combination therapy
- Minimal drug interactions

**DISADVANTAGES**
- Lactic acidosis and hepatic steatosis reported with most NRTIs (rare)

### NRTI

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Abbr</th>
<th>Dosage</th>
<th>COST per Month (AWP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emtriva</td>
<td>Emtricitabine</td>
<td>FTC</td>
<td>200mg daily</td>
<td>30 = $455.50</td>
</tr>
<tr>
<td>Epivir</td>
<td>Lamivudine</td>
<td>3TC</td>
<td>150mg BID or 300/day</td>
<td>30 = $450.48</td>
</tr>
<tr>
<td>Retrovir</td>
<td>Zidovudine**</td>
<td>AZT</td>
<td>300mg BID</td>
<td>30 = $526.36</td>
</tr>
<tr>
<td>Videx</td>
<td>Didanosine</td>
<td>ddl</td>
<td>250mg or 400mg daily</td>
<td>30 = $436.10</td>
</tr>
<tr>
<td>Viread</td>
<td>Tenofovir DF</td>
<td>TDF</td>
<td>300mg/day</td>
<td>30 = $744.85</td>
</tr>
<tr>
<td>Zerit</td>
<td>Stavudine**</td>
<td>d4T</td>
<td>20, 30 or 40mg BID</td>
<td>60 = $456.89</td>
</tr>
<tr>
<td>Ziagen</td>
<td>Abacavir</td>
<td>ABC</td>
<td>300mg BID or 600mg/day</td>
<td>60 = $605.31</td>
</tr>
<tr>
<td>Videx EC</td>
<td>didanosine</td>
<td></td>
<td>250-400mg daily</td>
<td>30 = $436.10</td>
</tr>
</tbody>
</table>

NON-Nucleoside Reverse Transcriptase Inhibitors

- First drug available: Viramune® Nevirapine 1996
- Mechanism: NNRTIs are highly selective, noncompetitive inhibitors of HIV-1 reverse transcriptase. Binds directly to enzyme.
- Sustiva (efavirenz) most commonly used, unless patient is pregnant.
- Long half lives. Stop NNRTI first. Wait 1 week, then NRTI.

Class Effect of NNRTI

- Metabolized by liver. NO renal dosage adjustment needed.
- Class resistance. A single mutation (K103N) confers resistance to entire class
- Cytochrome P450 drug interactions. Efavirenz & Etravirine are INDUCERS.
- Sustiva: Preg Cat-D; Caution in psych disorder. Vivid dreams. Empty stomach.
- Intelenza: high pill burden. CYP1A4 inducer. Works in patient with K103N resistance. Take with food to maximize absorption.
NNRTI

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Abb</th>
<th>Dosage</th>
<th>COST (AWP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viramune®</td>
<td>Nevirapine</td>
<td>NVP</td>
<td>200mg daily x14 days, then 200q12</td>
<td>$570.00</td>
</tr>
<tr>
<td>Sustiva® (low pill burden)</td>
<td>Efavirenz</td>
<td>EFZ</td>
<td>600mg HS</td>
<td>$627.06</td>
</tr>
<tr>
<td>Rescriptor®</td>
<td>Delavirdine</td>
<td>DLV</td>
<td>400-600 mg every 8 hours</td>
<td>$344.83</td>
</tr>
<tr>
<td>Intelence®</td>
<td>Etravirine</td>
<td></td>
<td>200mg (2x100mg) BID pc</td>
<td>$861.65</td>
</tr>
</tbody>
</table>

Integrase Inhibitor

- NO CYP450 drug interactions. No dosage adjustments needed.
- Well tolerated
- May take with or without food.
- Currently recommended for treatment experienced patients.
- May become what the PI’s were in the mid-1990’s
- May see: headache, diarrhea nausea muscle pain, CK elevation.
Protease Inhibitors

Mechanism: reversible inhibitors of HIV aspartyl protease, a viral enzyme responsible for the cleavage of the viral polyprotein into a number of essential enzymes and several structural proteins.

Adverse reactions: Lipodystrophy, hyperglycemia, lipid metabolism, osteonecrosis, osteopenia, osteoporosis, avascular necrosis of the hips. Diarrhea.

Class Effect of Protease Inhibitors

- Lots of drug interactions.
- Most effective, most toxic of anti-retrovirals. Rapid reduction in viral load.

ARV Components in Initial Therapy: PIs

<table>
<thead>
<tr>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher genetic barrier to resistance</td>
<td>Metabolic complications (fat maldistribution, dyslipidemia, insulin resistance)</td>
</tr>
<tr>
<td>PI resistance uncommon with failure (boosted PI)</td>
<td>GI intolerance</td>
</tr>
<tr>
<td>NNRTI options preserved for future use</td>
<td>Potential for drug interactions (CYP450), especially with RTV</td>
</tr>
</tbody>
</table>

Protease Inhibitors

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Abbr</th>
<th>Dosage</th>
<th>COST (AWP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viracept</td>
<td>Nelfinavir</td>
<td>NFV</td>
<td>1250mg q12</td>
<td>$830.28</td>
</tr>
<tr>
<td>Norvir</td>
<td>Ritonavir</td>
<td>RTV</td>
<td>100-400mg with other PI for boosting</td>
<td>$321.46</td>
</tr>
<tr>
<td>Crixivan</td>
<td>Indinavir</td>
<td>IDV</td>
<td>800mg q 8 hrs</td>
<td>$570.96</td>
</tr>
<tr>
<td>Lexiva</td>
<td>fosamprenavir</td>
<td>1.4gm BID</td>
<td>$855.20</td>
<td></td>
</tr>
<tr>
<td>Invirase</td>
<td>Saquinavir (hard cap)</td>
<td>SQV/HGC</td>
<td>400mg q12 with 400mg Ritonavir</td>
<td>$1037.96</td>
</tr>
<tr>
<td>Reyataz</td>
<td>Atazanavir</td>
<td>TAZ</td>
<td>400mg daily</td>
<td>$1,069.69</td>
</tr>
<tr>
<td>Kaletra</td>
<td>Lopinavir/Ritonavir</td>
<td>LPV/r</td>
<td>200mg/50mg BID</td>
<td>$876.98</td>
</tr>
<tr>
<td>Aptivus</td>
<td>Tipranavir</td>
<td>TAZ</td>
<td>500mg BID give with ritonavir</td>
<td>$1,236.74</td>
</tr>
</tbody>
</table>
Indications for Initiating HAART: Chronic Infection

<table>
<thead>
<tr>
<th>Clinical Category and/or CD4 Count</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of AIDS-defining illness</td>
<td>Initiate HAART</td>
</tr>
<tr>
<td>CD4 count of &lt;350 cells/µL</td>
<td></td>
</tr>
<tr>
<td>Pregnant women</td>
<td></td>
</tr>
<tr>
<td>HIV-associated nephropathy</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B coinfection, when HBV treatment is indicated*</td>
<td></td>
</tr>
</tbody>
</table>

* Treatment with fully suppressive drugs active against both HIV and HBV is recommended.

Indications for HAART

Treat all (regardless of CD4 count):

- **Pregnant women**
  - To treat maternal infection and reduce risk of perinatal transmission
- **HIV-associated nephropathy (HIVAN)**
  - Not clearly related to CD4 decline; ART may preserve renal function
- **HBV coinfection, if HBV treatment is needed**
  - TNF + 3TC or FTC is recommended
  - If ART is not started, HBV therapy should not include agents that may select for resistance to ARVs

Initial Treatment: Choosing Regimens

- 2 main categories:
  - 1 NNRTI + 2 NRTIs
  - 1 PI + 2 NRTIs
- Combination of NNRTI or PI + 2 NRTIs preferred for most patients
- Fusion inhibitor, CCR5 antagonist, integrase inhibitor not recommended in initial ART
- Few clinical end points to guide choices
- Advantages and disadvantages to each type of regimen
- Individualize regimen choice

Initial Treatment: Preferred Components

**NNRTI Option**

- **Sustiva®**

**NRTI Option**

- **Truvada®**
- **Epzicom®**
  (each contains 2 NRTIs)

**PI Options** (alphabetical order)

- **Reyataz® + Norvir**
- **Prezista® + Norvir**
- **Lexiva® + Norvir**
- **Kaletra®**

OR:

- **Atripla®**
  (Truvada + Sustiva) in a single pill
Treatment of Pregnant Women
(expert consultation mandatory)

- An HIV-infected pregnant woman can transmit the virus to her infant during pregnancy, at labor and delivery, or through breastfeeding. Risk of infection is 30%, if untreated. Risk drops to between 0.7%-2% if treated.

- Treatment options:
  - Zidovudine plus Lamivudine are preferred (Combivir®) BID; also add neviripine (Viramune®) BID or potent protease inhibitor lopinavir/ritonavir (Kaletra®) 2BID. Efavirenz is contraindicated.
  - For newborn of untreated mother, offer Zidovudine (Retrovir) as soon as possible and continue for 6 weeks.

POST EXPOSURE PROPHYLAXIS

- PEPLINE: 1-888-448-4911

- Average risk for HIV transmission after percutaneous exposure of HIV infected blood is 0.3%

- Average after a mucous membrane exposure risk is about 0.09%

- CDC recommends prophylaxis if source is HIV positive.

PEP – Less Severe Exposure

- Less severe examples: solid needle and superficial injury; source has low viral load; or HIV status unknown (sharps container)

- Two drug combination therapy can be used
  - Combivir® (zidovudine/lamivudine)
  - Truvada® (tenofovir/emtricitabine)

PEP – Severe Exposure

- Deep puncture, or if source has high viral load, symptomatic HIV infection, or acute seroconversion.

- Additional drugs: add Kaletra® (lopinavir/ritonavir)

- Follow up testing: 6 weeks, 12 weeks and 6 months.
Predictors of Inadequate Adherence

- Regimen complexity and pill burden
- Low literacy level
- Active drug use or alcoholism
- Stigma
- Mental illness (especially depression)
- Cognitive impairment
- Lack of patient education
- Medication adverse effects
- Treatment fatigue

Predictors of Inadequate Adherence (2)

- Age, race, sex, educational level, socioeconomic status, and a past history of alcoholism or drug use do NOT reliably predict suboptimal adherence
- Higher socioeconomic status and education levels and lack of history of drug use do NOT reliably predict optimal adherence

Predictors of Good Adherence

- Emotional and practical supports
- Convenience of regimen
- Understanding of the importance of adherence
- Belief in efficacy of medications
- Feeling comfortable taking medications in front of others
- Keeping clinic appointments
- Severity of symptoms or illness

Improving Adherence

- Establish readiness to start therapy
- Provide education on medication dosing
- Review potential side effects
- Anticipate and treat side effects
- Use educational aids including pictures, pillboxes, and calendars
- Simplify regimens, dosing, and food requirements
- Engage family, friends
- Utilize team approach with nurses, pharmacists, and peer counselors
- Provide accessible, trusting health care team
Pill Box Reminders

- Use of a pillbox increased adherence to HIV therapy by more than 4%
- Use of pillbox increased the probability of achieving a viral load of less than 400 copies/ml by 15%

Source: APhA DrugInfoLine (Oct-2007)

Profile of HIV Patient “TE”

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Prescriber</th>
<th>Copay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam 1mg</td>
<td>GP</td>
<td>0.00</td>
</tr>
<tr>
<td>Atenolol 25mg</td>
<td>GP</td>
<td>0.00</td>
</tr>
<tr>
<td>Hydrocod/APAP 10/500</td>
<td>GP</td>
<td>1.00</td>
</tr>
<tr>
<td>Trazodone 50mg</td>
<td>GP</td>
<td>0.00</td>
</tr>
<tr>
<td>Androgel 1% 5GM</td>
<td>SP</td>
<td>3.00</td>
</tr>
<tr>
<td>Norvir 100mg</td>
<td>SP</td>
<td>0.00</td>
</tr>
<tr>
<td>Truvada</td>
<td>SP</td>
<td>0.00</td>
</tr>
<tr>
<td>Invirase 500mg</td>
<td>SP</td>
<td>0.00</td>
</tr>
</tbody>
</table>

QUESTIONS???