An Update On HIV Pharmacotherapy

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Outline

• Review
  – HIV epidemiology
  – HIV natural history
  – Viral Dynamic and three compartment model of HIV infection

• Current Antiretrovirals
  – Nucleoside/Nucleotide Analogs
  – NNRTI
  – PI
  – Fusion Inhibitors
  – Once daily dosing

• Highlight important toxicities and drug interactions

• DHHS guidelines for the use of antiretrovirals

• Treatment failure
  – Compliance and barriers to adherence
Estimated Incidence of AIDS and Deaths of Adults and Adolescents with AIDS*, 1985 - 2001, United States

No. of Cases and Deaths (in thousands)

Year of Diagnosis or Death

*Adjusted for reporting delays
Natural History of HIV Infection I

Figure 1: Typical Course of HIV Infection.

Pantaleo NEJM 1993;328:327
Viral Dynamics -- Summary

- 10 billion new virions created and cleared daily

- 200 million CD4 cells destroyed daily (twice the rate of replacement by the hematopoietic system)

Ho et al, Nature 1995;373:123
Likelihood of Developing AIDS Within 3 Years

Antiretroviral Therapy: 2004
Antiretroviral Drugs: 2004

nucleoside RTIs
- zidovudine (ZDV)
- didanosine (ddI)
- zalcitabine (ddC)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)

nucleotide RTIs
- tenofovir (TFV)

NNRTIs
- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)

protease inhibitors
- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- amprenavir (APV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)

fusion inhibitors
- enfuvirtide (T-20)
Life Cycle of HIV

[Diagram showing the life cycle of HIV, including steps such as adsorption, penetration, reverse transcriptase, RNA to DNA, integration, transcription, mRNA, transactivation, assembly, budding, and dsDNA complex formation.]
Life Cycle of HIV

- Adsorption
- Reverse transcriptase
- DNA Complex
- Integration (Uncoating)
- Transcription
- Transactivation
- Assembly
- Budding
- Protease inhibitors
- Entry inhibitors
- Reverse transcriptase inhibitors
Nucleoside/tide Analogs: Toxicity

- zidovudine – GI, anemia, leukopenia, myositis
- didanosine – PN, pancreatitis, diarrhea
- zalcitabine – PN, aphthous ulcers
- stavudine – PN
- lamivudine, emtricitabine – (uncommon)
- abacavir – GI, hypersensitivity reaction, rash
- tenofovir – (uncommon)
- nucleosides as a class – lactic acidosis with hepatic steatosis

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
Nucleoside/tide Analogs: Toxicity

• **Lactic Acidosis/hepatic steatosis**
  – Chronic compensated hyperlactatemia
  – Incidence of severe, decompensated lactic acidosis with hepatomegaly and steatosis is rare
    • 1.3 cases/1,000 person years of NRTI exposure
      – Must correlate blood lactate level with clinical presentation

• **Treatment**
  – Cessation of HAART
  – Supportive management
Newer formulations and once daily dosing.

• Didanosine EC - once daily dosing
• Stavudine XR - once daily dosing
• Lamivudine - 300 mg po qd
• Nevirapine - 400 mg po qd
• Atazanavir - 400 mg po qd
• Tenofovir - 300 mg po qd
• Emtricitabine - 200 mg po qd
Emtricitabine (Emtriva)

- One Capsule, Once daily
  - 200mg po qd

- Chemically structure similar to Epivir (3TC)
  - Clinical trials suggest that efficacy is similar to Epivir in treatment naive patients
    - Likely not effective on lamivudine resistant virus
  - Clinical activity against hepatitis B virus.

- Common side effects include headache, diarrhea, nausea and rash
Nucleoside/tide Analogs: Selected Drug Interactions

- ZDV and ganciclovir: leukopenia
- ZDV and ribavirin: antagonism \textit{in vitro}
- ZDV and d4T: antagonism, decreased CD\textsubscript{4}
- ddI, ddC, d4T: PN-causing agents
- ddI and other pancreatitis-causing agents
- ddI and d4T: methadone decreases levels
- ddI and tenofovir: increased ddI levels
- tenofovir and atazanavir: decreased atazanavir levels must ‘boost’ 300mg of atazanavir with 100mg of ritonavir

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
Structures of NNRTI - NVP, DLV, EFV

nevirapine (NVP)  efavirenz (EFV)  delavirdine (DLV)
NNRTI: Toxicity

- **Rash**
  - Majority are mild to moderate in severity, occurring within the first several weeks of therapy
  - Most are confined to cutaneous reactions only - do not involve mucous membranes.
  - NVP 7%, DLV 4%, EFV 2% require discontinuation
  - Stevens-Johnson syndrome reported

- **Hepatic transaminase elevations – NVP (EFV, DLV)**
  - Nevirapine 400mg po qd
    - Greater incidence of hepatotoxicity than 200 mg po bid dosing

- **CNS symptoms (~50%) -- EFV**

- **Teratogenicity in monkeys -- EFV**

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
NNRTI:

Selected Drug Interactions

- CYP 3A4 effects (NVP + EFV inducers; DLV inhibitor): rifampin/(rifabutin), ketoconazole, anticonvulsants, simvastatin/lovastatin, astemizole/tefenadine, midazolam/triazolam, ergotamines

- NVP, EFV decrease methadone levels

- NNRTI-PI interactions
  - NVP decreases SQV, IDV, LPV
  - DLV increases SQV, IDV
  - EFV decreases SQV, IDV, APV, LPV
  - Efavirenz decreases atazanavir: must ‘boost’ 300mg of atazanavir with 100mg of ritonavir

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
Life Cycle of HIV: Later Steps

Immature Virion

HIV Protease Activity

Mature HIV Virion

CD4 Lymphocyte
HIV Protease Inhibitors

Saquinavir

Ritonavir

Indinavir

Nelfinavir
HIV Protease Inhibitors (2)

amprenavir (APV)  lopinavir (LPV)

atazanavir (ATV)
PI: Toxicity

- SQV: GI
- RTV: GI, circumoral paresthesias
- IDV: nephrolithiasis, incr. indirect bilirubin
- NFV: diarrhea
- APV: GI, rash
- LPV: GI, diarrhea
- ATV: increased indirect bilirubin
- PIs as a class: increased hepatic transaminases, hyperglycemia, lipodystrophy and lipidemia, increased bleeding in hemophiliacs

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
New PI formulation: fosamprenavir

- **Lexiva**: fosamprenavir
  - ‘prodrug’ of agenerase (amprenavir)
  - Likely will not be effective in patients who are resistant to agenerase
  - For PI experienced patient
    - 700 mg fosamprenavir and 100mg ritonavir bid
  - Advantage over amprenavir
    - Easier dosing
    - Decreased incidence of nausea, diarrhea, abdominal pain and *rash*
New PI: Atazanavir

- Indicated both for PI naïve and PI experienced patients
- Once daily dosing; preferably taken with food to increase absorption
- Dosing
  - PI naive: 400mg po qd
  - PI experienced: 300mg atazanavir/100mg norvir
  - Boosted 300mg atazanavir/100mg norvir when administered with either efavirenz or tenofovir
- Side effects
  - Increased indirect bilirubin
  - May not increase triglycerides and LDL as do other protease inhibitors
    - Impact on lipodystrophy and CAD not well known yet
PI: Selected Drug Interactions

- CYP 3A4 effects (RTV>>other PIs): rifampin/(rifabutin), ketoconazole, anticonvulsants, simvastatin/lovastatin, astemizole/tefenadine, midazolam/triazolam, ergotamines, St. John’s Wort
- RTV increases levels of other PIs (1.5-40X)
- RTV, NFV, APV lower oral contraceptive levels
- APV lowers methadone levels

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
Fuzeon: enfuvirtide (T-20)

- **Enfuvirtide (T-20)**
  - **New Category**
    - Fusion Inhibitors/entry inhibitors
      - Fuzeon binds to gp41 protein thus preventing viral binding and entry into T-cells
  - **Indication**
    - For HAART experienced patient with resistant virus
    - Injectable formulation with bid dosing
  - **Side effects:**
    - Skin irritation at injection site is most common
    - Fatigue, insomnia and peripheral neuropathy
DOUBLE BLIND STUDY...
## Combination Therapy: 3 vs. 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimens</th>
<th>Results (1 yr f/u)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG 320 (N=1156)</td>
<td>ZDV/3TC vs. ZDV/3TC/IDV</td>
<td>3-drugs reduced AIDS/death by ~50%</td>
</tr>
<tr>
<td><em>Hammer, NEJM 1997</em></td>
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</tr>
<tr>
<td>Merck 035 (N=97)</td>
<td>ZDV/3TC vs. IDV vs. ZDV/3TC/IDV</td>
<td>3-drugs: ~80% HIV RNA &lt;500 cps/ml (compared to 30-45%)</td>
</tr>
<tr>
<td><em>Gulick, NEJM 1997</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agouron 511 (N=297)</td>
<td>ZDV/3TC vs. ZDV/3TC/NFV</td>
<td>3-drugs: ~75% HIV RNA &lt;400 cps/ml (compared to 37%)</td>
</tr>
<tr>
<td><em>Saag, AIDS 2001</em></td>
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Combination three drug management (HAART) is the standard of care.
Population based data correlates HAART -PI use with decreased HIV mortality

Palella et al NEJM 1998;338:853
## When To Start Treatment? – Summary of Current Guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>symptoms or CD4 &lt;200</th>
<th>CD4 200-350</th>
<th>CD4 &gt;350</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHHS: 7/14/03 update &lt;www.aidsinfo.nih.gov&gt;</td>
<td>treat</td>
<td>offer treatment</td>
<td>defer if VL &lt;55K; treat or defer if VL &gt;55K</td>
</tr>
<tr>
<td>IAS-USA: JAMA 2002</td>
<td>treat</td>
<td>consider treatment</td>
<td>consider if VL &gt;50-100K</td>
</tr>
</tbody>
</table>
Early vs Late Treatment

**EARLY RX:**
- HIV disease is progressive
- Rx decreases HIV RNA (and resistance) and increases CD4 (and immune function)
- 6+ years of virologic suppression demonstrated
- ? Decrease transmission

**DELAYED RX:**
- Risk of clinical progression low in early disease
- Practical factors (adherence, toxicity, quality of life outweigh benefits in early-disease)
- Long term effects unknown
- Preserve rx options

Based on DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
Goal of Antiretroviral Therapy

• 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
DHHS Treatment Guidelines: Recommended Initial ART

- **NNRTI-based regimens**
  - Preferred: ZDV (or TDF or d4T) + 3TC + EFV (except for pregnant women)
  - Alternatives:
    - ddI + 3TC + EFV (except for pregnant women)
    - ZDV or d4T or ddI + 3TC + NVP

- **PI-based regimens**
  - Preferred: ZDV (or d4T) + 3TC + LPV/r
  - Alternatives:
    - ZDV (or d4T) + 3TC + APV/r, IDV, IDV/r, NFV, or SQV/r

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
DHHS Treatment Guidelines: Triple NRTI Regimen

• A 3 NRTI regimen
  – Abacavir + Zidovudine + (or Stavudine) + Lamivudine
    • Should only be used when an NNRTI-based or PI-based regimen cannot or should not be used as initial Rx
      – eg.- drug-drug interactions; regimen complexity
    • Randomized clinical trial comparing triple NRTI vs PI-based regimens:
      – Substantially higher rate of early virologic non-response was seen in the 3-NRTI arm.
    • Tenofovir/abacavir/lamivudine or tenofovir/didanosine/lamivudine should not be used as a sole antiretroviral agent for naïve or treatment experienced patients
      – early virologic non-response
DHHS Treatment Guidelines: Not Recommended

- Single-drug therapy (monotherapy): not potent, rapid resistance
- Two-drug therapy: rapid development of resistance
- Certain nucleoside pairs and antiretroviral components:
  - d4T + ZDV: antagonistic
  - d4T + ddC: additive peripheral neuropathy
  - d4T + ddI: additive peripheral neuropathy
  - Emtricitabine + lamivudine: similar resistance profile; no potential benefit
- Protease inhibitors
  - Atazanavir + indinavir: potential additive hyperbilirubinemia
  - Saquinavir hard gel capsule; poor bioavailability (4%)
- 3–NRTI regimens containing
  - abacavir + tenofovir + lamivudine or didanosine + tenofovir + lamivudine
- Hydroxyurea: promotes toxicity of didanosine, increased peripheral neuropathy and pancreatitis
- In pregnancy: d4T + ddI (lactic acidosis); EFV (teratogenic); APV solution

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
What about Once Daily Dosing?

<table>
<thead>
<tr>
<th>Nucleoside/Nucleotide Analogues</th>
<th>Nonnucleoside Reverse Transcriptase Inhibitors</th>
<th>Protease Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didanosine (enteric-coated)</td>
<td>Efavirenz</td>
<td>Amprenavir/ritonavir</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Nevirapine</td>
<td>Atazanavir</td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td>Saquinavir/ritonavir</td>
</tr>
<tr>
<td>Stavudine (extended-release)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
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</tbody>
</table>

Most of these medications have been studied in combination with twice-daily drugs, but have not been studied as components of an entirely once-daily regimen.

One triple nucleoside regimen, abacavir + lamivudine + tenofovir has recently been found to have a high rate of virologic failure and should be avoided.
What about Once Daily Dosing?

- few efficacy studies of once-daily antiretroviral combinations have been conducted
- most are small and nonrandomized and must therefore be interpreted with caution
- regimens most thoroughly studied contain didanosine, efavirenz, and lamivudine or emtricitabine

<table>
<thead>
<tr>
<th>didanosine + emtricitabine** + efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>ddl 400 mg (wt &gt;= 60 kg), FTC 200 mg, EFV 600 mg QD</td>
</tr>
</tbody>
</table>

**virtually all patients were treatment naive**

- Viral load 4.9 log10 copies/mL; CD4 = 288 cells/mm³
- 60 weeks
- At 24 weeks, viral load <50 in 81%, compared to 70% in d4T arm. At 60 weeks, virologic failure in 7% versus 15% of d4T arm (by KM probability).

163 Better virologic and CD4 response and fewer adverse events in FTC-containing regimen

Largest RCT of a once-daily regimen

**Once Daily Dosing has not been extensively studied and these are not regimens of choice by DHHS guidelines.**
Once Daily Dosing Caveats:

- Paucity of long-term clinical trials with comparison to potent twice daily regimens

- **Caveat** - consequences of a missed dose:
  - May result in inadequate drug exposure over a defined time period
  - Consequent higher probability for development of drug resistance
Monitoring CD$_4$ cell counts

• When to measure
  – baseline (at time of diagnosis, 2 specimens)
  – ongoing evaluations every 3-6 months

• Treatment decisions
  – based on trend over time (at least 2 values)

• Significant change is >30% of absolute CD$_4$ value (or >3% of CD$_4$ percentage)

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
DHHS Monitoring Guidelines

Monitoring viral load

• **When to measure**
  – at baseline (2 specimens, 1-2 weeks apart)
  – prior to initiation of antiretroviral rx
  – 2-8 weeks after initiation of rx
  – ongoing evaluations every 3-4 months

• **Do not measure within 2-4 weeks of acute illness or immunization**

• **Minimum sign. change is 3-fold or 0.5 log**

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
Clinical Cohort Studies: Virologic Failure Rates

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>(% above LD, time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam</td>
<td>271</td>
<td>40%, 48 wks</td>
</tr>
<tr>
<td><em>Wit, JID 99</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleveland</td>
<td>310</td>
<td>53%, 1 yr</td>
</tr>
<tr>
<td><em>Valdez, Arch IM 99</em></td>
<td></td>
<td></td>
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<tr>
<td>Hopkins</td>
<td>273</td>
<td>63%, 1 yr</td>
</tr>
<tr>
<td><em>Lucas, Ann IM 99</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swiss</td>
<td>1517</td>
<td>38%, 2 yrs</td>
</tr>
<tr>
<td><em>Ledergerber, Lancet 99</em></td>
<td></td>
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</tr>
<tr>
<td>UCSF</td>
<td>337</td>
<td>50%, 48 wks</td>
</tr>
<tr>
<td><em>Deeks, AIDS 99</em></td>
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</table>

Incidence of virologic failure is not trivial!
Clinical Cohort Studies: Virologic Failure Rates 2002

ART Cohort collaboration

13 HIV clinical cohort studies
10 Europe, 2 Canada, 1 US
12574 individuals starting ≥3 drug ART
73% had HIV RNA <400 cpm at 6 months

Chene, et al., TuOrB1140, XIV AIDS Conf. 2002
Treatment Regimen Failure

- **Virologic failure**
  - Not achieving HIV RNA <400 cpm by wk 24 or <50 cpm by wk 48
  - After virologic response, repeated detection of viremia

- **Immunologic failure**
  - Failure to increase CD4 count by 25-50 cells over the first year of therapy or decrease to below baseline

- **Clinical failure**
  - Occurrence or recurrence of HIV-related events

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
Why Does Treatment Fail Patients?

- Adherence
  - Complicated regimens, heavy pill burden, toxicity
- Baseline resistance or cross-resistance
- Use of less potent antiretroviral regimens
- Sequential monotherapy
- Drug levels and drug interactions
- Tissue reservoir penetration
- Patient ‘not ready’ to take antiretrovirals
HIV Drug Resistance Pre-exists

- HIV genome contains 10,000 nucleotides
- Mutation rate of HIV is \( \sim 3 \times 10^{-5} \)
- 10 billion virions produced daily
- Therefore all single (and many double) mutations are produced daily
- Leads to extensive viral diversity
HIV Drug Resistance

- **Clinical resistance**
  - Follow HIV RNA on antiretroviral therapy

- **Genotypic resistance**
  - Perform *in vitro* assay to assess substitutions in viral genetic sequence; correlate with drug resistance

- **Phenotypic resistance**
  - Perform *in vitro* assay to assess growth of viral strain in the presence of antiretroviral drugs
## Prospective Resistance Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Design</th>
<th>Change in VL (log cps/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIRADAPT</td>
<td>108</td>
<td>24 wks</td>
<td>geno vs SOC</td>
<td>−1.2 vs −0.7*</td>
</tr>
<tr>
<td><em>Durant Lancet 1999</em></td>
<td></td>
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<tr>
<td>GART</td>
<td>153</td>
<td>8 wks</td>
<td>geno vs SOC</td>
<td>−1.2 vs −0.6*</td>
</tr>
<tr>
<td><em>Baxter AIDS 2000</em></td>
<td></td>
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</tr>
<tr>
<td>NARVAL</td>
<td>541</td>
<td>12 wks</td>
<td>geno vs pheno vs SOC</td>
<td>−1.0 vs −1.0 vs −0.7</td>
</tr>
<tr>
<td><em>Meynard AIDS 2002</em></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>VIRA3001</td>
<td>271</td>
<td>16 wks</td>
<td>pheno vs SOC</td>
<td>−1.2 vs −0.9*</td>
</tr>
<tr>
<td><em>Cohen, AIDS 2002</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAVANNA</td>
<td>274</td>
<td>12 wks</td>
<td>geno vs SOC</td>
<td>−1.5 vs −1.2*</td>
</tr>
<tr>
<td><em>Tural, AIDS 2002</em></td>
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</table>

*SOC = standard of care*

* = p < 0.05
Reduced Susceptibility (>10 Fold)

Primary HIV infection / 10 U.S. cities

The proportion of non-susceptible HIV isolates is increasing.


---|---|---|---|---|---
N | 32 | 106 | 88 | 71 | 15

NRTI | NNRTI | PI

DHHS Monitoring Guidelines

Use of drug resistance assays

- **Recommended**
  - virologic failure on rx
  - suboptimal HIV RNA suppression after starting rx
  - acute HIV infection

- **Consider**
  - chronic HIV infection prior to starting rx

- **Not usually recommended**
  - after discontinuation of drugs
  - HIV RNA <1000 copies/ml

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
Current Approach to Salvage Rx

- Review antiretroviral history; assess adherence, tolerability, and PK issues
- Distinguish first/second from multiple failures
- Perform resistance testing while on drugs
- Identify susceptible drugs/drug classes
- Consider novel strategies (PK enhancement with RTV; multidrug regimens)
- Consider newer agents through expanded access or clinical trials
- Design a regimen with $\geq 3$ active drugs (if possible)

DHHS Guidelines 11/10/03 <www.aidsinfo.nih.gov>
Antiretroviral Rx: Conclusions

• Antiretroviral rx suppresses HIV RNA, improves immune fx, decreases disease progression and prolongs survival.

• The optimal time to begin therapy is not clear.

• The optimal initial rx is not clear, but there are effective combination regimens available.

• First-line rx fails in 10-60% of patients.

• Resistance testing demonstrates benefits in selecting antiretroviral therapy.

• There are a number of new drugs in development.

• Further research is needed.
SAFE SEX
Question 1

• Emtricitabine (FTC) is similar in both structure and efficacy to which antiretroviral?
  – A. Stavudine
  – B. Nelfinavir
  – C. Tenofovor
  – D. Lamivudine
Question 2

• Which would be a DEFINITE indication for initiating antiretroviral therapy as per DHHS guidelines?
  – A. Asymptomatic, CD4>250 but <350, VL > 55,000
  – B. Asymptomatic, CD4<200, VL=30,000
  – C. Asymptomatic, CD4>350, VL>55,000
  – D. Asymptomatic, CD4>350, VL<55,000
Question 3

- The most common side effect of the fusion inhibitor T-20 (enfuvirtide) is:
  - A. Diarrhea
  - B. CNS side effects - vivid dreams
  - C. Skin irritation at injection site
  - D. Hepatic steatosis and lactic acidosis
Question 4

- As per the DHHS guidelines, when is HIV resistance testing not recommended?
  - A. virologic failure while on treatment
  - B. suboptimal HIV RNA suppression after starting rx
  - C. acute HIV infection
  - D. HIV RNA <1000 copies/ml
Question 5

- Which most accurately describes the class level TOXICITY of protease inhibitors?
  - A. Bone marrow suppression, anemia
  - B. Increased hepatic transaminases, hyperglycemia, lipodystrophy and lipidemia, increased bleeding in hemophiliacs.
  - C. Lactic acidosis and hepatic steatosis
  - D. Rash and CNS side effects (vivid dreams)
Answers

- Question 1: D
- Question 2: B
- Question 3: C
- Question 4: D
- Question 5: B