Antiretroviral Therapy

I. Introduction

The field of antiretroviral therapy has been explosive over the past 17 years as HIV targets have been identified, drugs developed and pathogenesis unraveled. A basic summary of this progress is as follows:

A. Every step in viral life cycle is a potential antiviral target.

B. Currently there are 5 classes of FDA approved agents
   - Nucleoside analog reverse transcriptase inhibitors (NsRTI’s)
   - Nucleotide analog reverse transcriptase inhibitors (NtRTI’s)
   - Non-nucleoside reverse transcriptase inhibitors (NNRTI’s)
   - Protease inhibitors (PI’s)
   - Entry (fusion) inhibitors

C. Drugs must be used in combination to be effective.
   - This has led to dramatic reductions in morbidity and mortality in the developed world.

D. Current therapies are imperfect due to
   - Complexities of some regimens
   - Toxicities
   - Drug resistance

II. Nucleoside Analog Reverse Transcriptase Inhibitors

The approved nucleoside analog reverse transcriptase inhibitors (NsRTIs) are:

- Zidovudine (ZDV, AZT)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

A. NsRTIs were the first class of anti-HIV agents developed and have activity vs. HIV-1 and HIV-2.

B. The parent compounds are not active. They need to undergo intracellular anabolic phosphorylation to the triphosphate (TP) form of the drug to be active vs. HIV.

C. Their mechanism of action is as follows:
1. NRTI-TP’s inhibit the HIV RT by competing with normal nucleoside triphosphates for incorporation into the growing proviral DNA chain.
2. Viral DNA chain elongation terminated.
   - Absence of 3’-OH group on sugar moiety prevents addition of another nucleotide.
3. Viral replication ceases.

III. Nucleotide Analog Reverse Transcriptase Inhibitor

There is currently one FDA approved member of this class, tenofovir disoproxil fumarate (TDF), which is a prodrug of tenofovir and the lead compound in the fourth class of antiretroviral agents approved for clinical use. Nucleotides contain a phosphate group so only need to be diphosphorylated intracellularly to be metabolized to their active forms. Tenofovir-diphosphate is the active moiety and acts as a competitive inhibitor of the HIV RT in a fashion similar to the nucleoside analog triphosphates.

IV. Non-Nucleoside Reverse Transcriptase Inhibitors

The FDA approved non-nucleoside RT inhibitors are:

• Nevirapine (NVP)
• Delavirdine (DLV)
• Efavirenz (EFZ)

A. NNRTIs were the second class of anti-HIV agents developed.

B. They are potent but subject to rapid emergence of resistance.

C. Active vs. HIV-1 only (except Group O).

D. Inactive vs. HIV-2 (important in areas of the world where this virus is seen – e.g., West Africa and in immigrants to Europe).

E. In contrast to NRTIs, the parent molecules are the active moieties so they are immediately active once they enter the cell.

F. The mechanism of action of NNRTIs is as follows:
   - NNRTI’s inhibit the HIV-1 RT by binding to a hydrophobic pocket on the enzyme close to the active site thereby locking the enzyme in an inactive conformation.

G. A major issue with NNRTIs is the potential for drug interactions.
   1. NNRTIs are metabolized by the CYP3A4 isozyme of the hepatic p450 system.
   2. Adding to the complexity of predicting possible drug interactions, NVP and EFZ are inducers of CYP3A4 while DLV is an inhibitor of CYP3A4.
3. Thus, there is the potential for major drug interactions with numerous HIV (esp. PI’s) and non-HIV agents which are also metabolized by the same hepatic pathway.

4. Maxim to follow: do not prescribe without first checking for potential drug interactions.
   - May be contraindications or need for dose adjustment(s).

V. Protease Inhibitors

The FDA approved protease inhibitors are:

- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Amprenavir (APV)
- Lopinavir/ritonavir (LPV/r)
- Atazanavir (ATV)

A. Protease Inhibitors were the third class of anti-HIV agents developed. They are highly potent vs. HIV and revolutionized therapy following their introduction in 1996.

B. They are active vs. HIV-1 and HIV-2.

C. Their mechanism of action is as follows:
   1. PI’s inhibit the HIV protease by binding to the active site of the enzyme thus preventing the cleavage of gag and gag-pol precursor polyproteins at a late stage of viral replication.
   2. Virions are produced but they are incomplete and non-infectious.

D. Similar to NNRTIs, drug interactions are a major issue for PIs.
   1. They are metabolized by the CYP3A4 isozyme of the hepatic p450 system.
   2. They inhibit CYP3A4 to varying degrees.
      a. Ritonavir is one of the most potent CYP3A4 inhibitors known.
         » Basis for using low-dose RTV as pharmacoenhancer of other PIs.
         » Lopinavir is coformulated with ritonavir to enhance the former’s pharmacokinetic profile.
   3. There is the potential for major drug interactions with numerous HIV (esp. NNRTI’s) and non-HIV agents.
   4. Maxim to follow: do not prescribe without first checking for potential drug interactions.
      - May be contraindications or need for dose adjustment(s).
VI. Fusion Inhibitor

A fusion inhibitor, enfuvirtide (T-20), is representative of the fifth class of antiretroviral agents approved by the FDA. This is a 36 amino acid peptide that binds to a region of the gp41 transmembrane glycoprotein of HIV and prevents virus – cell fusion. It must be given by subcutaneous injection and its major toxicity is injection site reactions. Resistance to enfuvirtide can develop and is characterized by the development of amino acid substitutions in the gp41 protein that prevents proper binding of the inhibitor.

VII. Initiation of Therapy in Established HIV Infection

When to initiate antiretroviral therapy in the course of HIV infection is one of the biggest questions facing patients and clinicians. The factors to be taken into account are:

A. Patient’s disease stage as measured by
   1. Symptomatic status.
      a. All symptomatic patients should be offered treatment irrespective of the CD4 count or plasma HIV-1 RNA level.
   2. CD4 cell count – measure of immune status.
   3. Plasma HIV-1 RNA level – reflective of the productively infected cell population in the body.

B. Patient’s commitment to therapy as drug adherence is critical to treatment success.

C. Philosophy of treatment. Since there is room for decision making, how aggressive the patient and physician wish to be with treatment – i.e., starting earlier vs. later – is an important third factor.

The question of ‘When to Start Therapy?’ in an asymptomatic person has not been answered by randomized controlled clinical trials so the field has relied on a number of population based, cohort studies. The summary of these studies has shown consistently that delaying therapy until the CD4 count falls below 200/mm³ compromises ultimate outcome with respect to the development of an AIDS defining illness or death. However, these studies have not been able to definitely answer the question of what CD4 level above 200/mm³ should be used as a guidepost for starting therapy. Consensus guidelines generally favor considering therapy when the CD4 count falls below 350/mm³ in order to provide a safety margin for the patient. When the CD4 count is above 350/mm³, the level of plasma HIV-1 RNA (viral load) is also factored into the decision because it predicts the rate of CD4 cell count decline.
VIII. Antiretroviral Regimens

When discussing antiretroviral therapy, one speaks in terms of combination regimens rather than individual drugs. Regimens are described by which drug classes they contain (NsRTI, NtRTI, NNRTI, PI) and by which drug classes they spare. Sparing drugs is important to avoid toxicities and to have effective alternative regimens in reserve. This is important because treatment, at present, is lifelong once it starts. Regimens that are considered at present include:

A. Non-nucleoside RTI + 2 nucleoside RTI’s – most widely prescribed at present.
   1. Newer options
      » NNRTI + 1 NsRTI + 1 NtRTI
      » NNRTI + 3 NsRTI’s
   2. PI sparing

B. Protease inhibitor (+/low-dose RTV) + 2 nucleoside RTI’s.
   1. NNRTI sparing

C. 3 Nucleoside RTI’s (including abacavir).
   1. PI and NNRTI sparing
   2. No longer a first line option
      » Recent data from ACTG study A5095 have shown ZDV/3TC/ABC to be virologically inferior to two other EFZ containing study arms which were combined for analysis purposes (EFZ/ZDV/3TC, EFZ/ZDV/3TC/ABC). The study is still ongoing.
         - 21% vs. 10% virologic failure rate, respectively, at 32 wks.

D. 3 Nucleoside RTI’s + 1 NtRTI.
   1. PI and NNRTI sparing
   2. Under investigation

E. 1-2 Protease inhibitors + 1 NNRTI + 1-2 NRTI’s.
   1. Consideration only in special circumstances
      » e.g., acquisition of drug resistant virus

F. Protease inhibitor/low-dose RTV + 1 NNRTI.
   1. NRTI sparing
   2. Currently in clinical trials

IX. Antiretroviral Failure

Antiretroviral failure is common as current regimens are imperfect and it is difficult for patients to maintain the level of drug adherence necessary to prevent viral breakthrough. The definitions of treatment failure are:

A. Clinical failure as measured by disease progression.
B. Immunologic failure as measured by CD4 cell count decline.

C. Virologic failure as measured by a rise in plasma HIV-1 RNA level above a certain threshold – e.g., detectability above a 50, 200 or 400 copy/ml threshold depending upon the assay used and the stringency of the definition of virologic failure employed.

The reasons for drug failure are potentially numerous and include:

A. Development of drug resistance.

B. Incomplete or poor drug adherence.

C. Pharmacologic factors leading to diminished drug levels.

D. Insufficiently potent regimens.

E. Tissue or cell sanctuaries that allow the virus to escape drug inhibitory effects.

F. Cellular mechanisms of resistance which may lead to drug efflux from cells.

G. Compromised host immune status which may facilitate higher degrees of virus replication.

X. Drug Resistance

HIV drug resistance is an increasing problem and should be thought about on a pathogenetic level. The principles and implications to consider are:

A. Genetic variants of HIV are continuously produced as a result of the high viral turnover and the inherent error rate of reverse transcriptase. Therefore, mutations at each base position occur daily. The survival of the resulting viral mutants depends on the replication competence of the mutants and the presence of drug or immune selective pressure.

B. The implications of this for treatment are that resistance mutations may (and do) exist before drug exposure and may emerge quickly after it is introduced. Therefore, drugs which develop high level resistance with a single mutation are at greatest risk (e.g., 3TC, NNRTIs) and resistance to agents which require multiple mutations will evolve more slowly (e.g., ZDV, protease inhibitors). In order to combat this effectively, potent combination regimens need to be constructed that pose a high ‘genetic barrier’ for the virus to overcome.
XI. Remaining Challenges

Despite the remarkable progress that has resulted from the currently available antiretroviral agents which have markedly reduced HIV-related morbidity and mortality in the developed world, they still possess significant limitations. These include:

A. Some regimens remain complex, particularly for treatment experienced patients.

B. Drugs have negative effects on quality of life even if no toxicities are apparent.

C. Toxicities, particularly metabolic
   1. Hyperlipidemia, fat redistribution, insulin resistance, decreased bone density, and mitochondrial dysfunction have become a major focus of clinical concern and one of the reasons patients and clinicians are waiting to start treatment until the risk:benefit ratio is acceptable.

D. Drug class cross resistance.

E. Drug interactions (esp. for NNRTIs and PIs).

F. Logistics and cost of delivering this life saving therapy to the developing world.

To meet these challenges, a number of new drugs are in development in both existing drug classes and new drug classes (e.g., integrase inhibitors, entry inhibitors) which will offer better pharmacokinetic profiles, activity against drug resistant virus and reduced toxicity. Price reductions from major pharmaceutical firms, the availability of generic antiretrovirals, and new funding opportunities (e.g., the Global Fund) are providing the opportunity to deliver these drugs to the areas of the world where >90% of the infected people live.