

Antiretroviral Therapy

I. Introduction

The field of antiretroviral therapy has been explosive over the past 20+ 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. As of August 2008, there were 7 classes of FDA approved agents
 - Nucleoside analog reverse transcriptase inhibitors (NsRTI's)
 - Nucleotide analog reverse transcriptase inhibitor (NtRTI)
 - Non-nucleoside reverse transcriptase inhibitors (NNRTI's)
 - Protease inhibitors (PI's)
 - Fusion inhibitor
 - CCR5 antagonist
 - Integrase inhibitor
- D. Drugs must be used in combination to be effective.
 - This has led to dramatic reductions in morbidity and mortality in the developed world and clinical benefits in the developing world are now evident with the recent antiretroviral "rollout".
- E. Therapies are continuing to improve but remain imperfect due to
 - Toxicities
 - Drug resistance
 - Complexities of some regimens

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 anti-HIV 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)
- Etravirine (ETV)

- A. NNRTIs were the second class of anti-HIV agents developed. Nevirapine, delavirdine and efavirenz are considered “first generation” NNRTI's and demonstrate substantial cross-resistance. Etravirine was approved in January 2008 and is considered a “second generation” NNRTI, in part because it retains activity vs. HIV-1 isolates which harbor <3 NNRTI-associated mutations.
- 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. The most recently approved NNRTI, etravirine, is a substrate of CYP3A4, CYP2C9 and CYP2C19, an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19.
 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), now supplanted by fos-amprenavir (fos-APV)
- Lopinavir/ritonavir (LPV/r)
- Atazanavir (ATV)
- Tipranavir (TPV)
- Darunavir (DRV)

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 (e.g, saquinavir, indinavir, amprenavir, fosamprenavir, lopinavir, atazanavir, tipranavir, darunavir)
 - » 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 (ENF, 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. Chemokine Receptor Antagonists

In order for HIV-1 to enter cells, it must utilize a second cell surface receptor (in addition to the primary receptor, the CD4 molecule). These coreceptors are chemokine receptors with the major ones being CCR5 and CXCR4. HIV-1 strains that utilize CCR5 are termed “R5” viruses; those that utilize CXCR4 are termed “X4 viruses”. Most new infections are due to R5 viruses. Humans may harbor pure R5, pure X4, a mixture of R5 and X4, and viruses that can use both coreceptors. Maraviroc (MVC) is the lead compound in the sixth class of antiretroviral agents approved by the FDA and is a CCR5 antagonist. It is the first approved antiretroviral agent which targets a host cell molecule. It has been proven to be effective as part of combination regimens designed to treat patients with multidrug resistant HIV-1. Resistance to maraviroc can develop through either emergence of a pre-existent subpopulation of viruses which utilize the CXCR4 receptor or through the development of mutations in the viral gp120 which allow HIV-1 to utilize the CCR5 coreceptor even in the presence of bound maraviroc.

VIII. Integrase Inhibitors

The integrase enzyme of HIV-1 is essential for HIV-1 replication and is responsible for catalyzing the reaction which results in the integration of the proviral DNA copy of HIV into the host cell genome. Clinically effective integrase inhibitors interfere with the final step of integrase function, the strand transfer reaction. Raltegravir (RAL) is the lead compound in this 7th class of antiretroviral agents approved by the FDA and specifically inhibits this strand transfer reaction. It has been proven to be useful in the treatment of patients harboring multidrug resistant HIV-1. Raltegravir has a relatively low genetic barrier to resistance; therefore, the drug has to be used in combination regimens

designed to achieve maximal virologic suppression in order to avoid the rapid emergence of resistance to raltegravir.

IX. 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 fully 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. Accumulating evidence suggests that antiretroviral treatment should be started before the CD4 count falls below 350/mm³. 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. For example, plasma HIV-1 RNA levels >100,000 copies/ml have been shown to be independent predictors of disease progression in asymptomatic patients with CD4 cell counts >350/mm³. Additional considerations in the decision-making around initiating therapy include the presence of, or risk factors for, cardiovascular, hepatic and renal disease (so-called "non-AIDS" conditions).

X. 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, integrase inhibitor) 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 (or one nucleoside RTI and one nucleotide RTI) – most widely prescribed at present.
 - 1. PI sparing
- B. Protease inhibitor/low-dose RTV + 2 nucleoside RTI's (or one nucleoside RTI and one nucleotide RTI) – second most widely prescribed initial regimen.
 - 1. NNRTI sparing
- C. Protease inhibitor/low-dose RTV + 1 NNRTI + 1-2 NRTI's.
 - 1. Consideration in special circumstances
 - »e.g., primary acquisition of drug resistant virus
- D. Protease inhibitor/low-dose RTV + 1 NNRTI.
 - 1. NRTI sparing
- E. 3 Nucleoside RTI's + 1 NtRTI.
 - 1. PI and NNRTI sparing
 - 2. Used in special circumstances
 - » e.g., when one wants to avoid drug interactions with PI's or NNRTI's and other medications
- F. Integrase inhibitor + 2 nucleoside RTI's (or one nucleoside RTI and one nucleotide RTI)
 - 1. Under investigation

XI. 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.
 - a. This needs to be differentiated from the immune reconstitution inflammatory syndrome (IRIS) which can occur after the initiation of antiretroviral therapy in patients harboring subclinical opportunistic infections when antiretroviral therapy is started.
- 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 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.

XII. 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 HIV's 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, FTC, NNRTI's) 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.

XIII. 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 NNRTI's and PI's).
- 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 which may offer better pharmacokinetic profiles, activity against drug resistant virus and reduced toxicity. The availability of generic antiretrovirals and major funding opportunities (e.g., PEPFAR, the Global Fund to Fight AIDS, Tuberculosis and Malaria) are providing the opportunity to deliver these drugs to the developing world where >90% of the world's HIV-infected population lives.

