Anti-retroviral Therapy of HIV-1 Infection

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Introduction

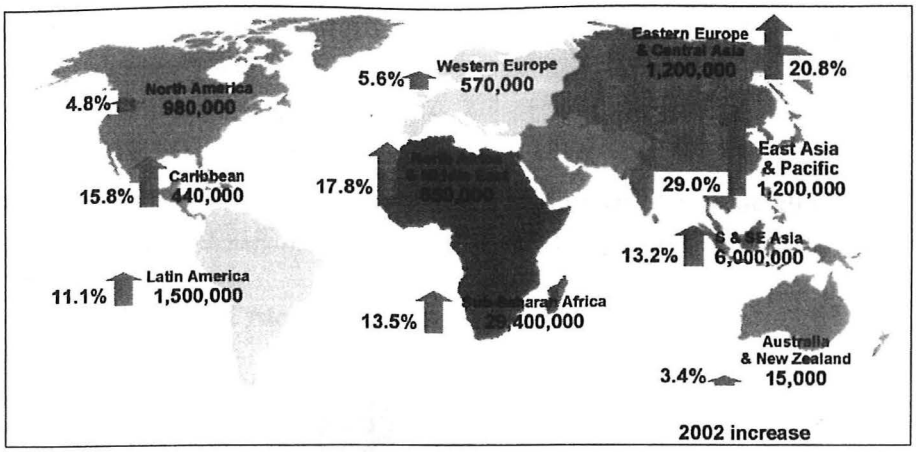
Anti-retroviral therapy has made a dramatic impact on the lives of individuals infected with the Human Immunodeficiency Virus. Therapy with combination of ant-retroviral drugs (often referred to as highly active anti-retroviral therapy or HAART) can reduce HIV-1 viral replication to undetectable levels. This results in improved immune functioning, decreased opportunistic infection and prolonged survival. However, HAART is not without costs. Many regimens are poorly tolerated and require taking large numbers of pills. There are also long term toxicities which can change the appearance of individuals on therapy and can place the patient at risk for cardiovascular disease and diabetes mellitus. A high portion of patients treated with HAART experience virologic failure. The most common reasons for treatment failure are the emergence of resistance and poor adherence. Resistance, when it occurs, may severely limit the use of other agents because of broad cross-resistance between agents.

Despite these downsides, patients continue to achieve better results with HAART. Newer agents with low pill burdens now allow for prescribing as little as 3 pills per day. Many of these agents have better toxicity profiles and are better tolerated by the patients. Newer drugs also have unique resistance profiles, which allow for patients with resistance viruses to be successfully treated.

Epidemiology

The HIV-1 pandemic is the largest and longest epidemic in the history of the world. Currently there are over 40 million individuals infected. While most of these individuals live in southern Africa, there are high rates of infection in south-east Asia an in the Caribbean basin. The infection continues to grow at an alarming rate. There has been as much as a 30% increase in the incidence of HIV-1 over the past year in regions as diverse as eastern Europe, India and the states of the former Soviet Union. As many a 100 million people may die from this disease within the next century.

Figure 1: Distribution of HIV-1 Infection and Percent Increase in 2002



In the United States, there are an estimated 900,000 cases of HIV-1 infection. The number of cases has been relatively steady over the past 10 years, with an estimated 40,000 new cases replacing the 40,000 deaths to AIDS each year. Last year, however, there was a 4% increase in the number of reported cases of HIV.

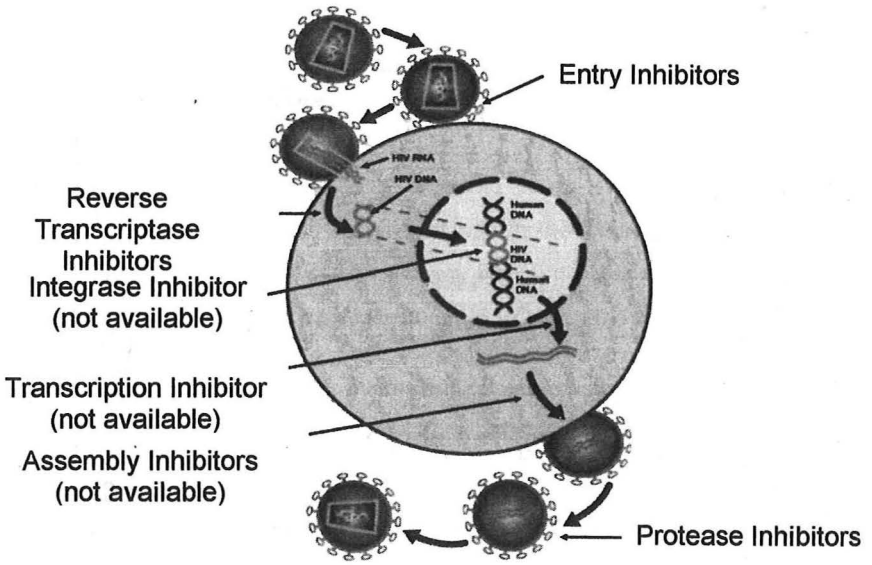
Demographically the epidemic in the US has shifted from gay white men to women and people of color. While much of this shift has been associated with drug abuse, an increasing number of individuals are acquiring HIV through heterosexual contact without other associated risk factors.

HIV Pathogenesis

HIV-1 is a lentevirus and consists of a lipoprotein envelope, core structure proteins, two strands of RNA which encode the genetic information and functional proteins including an RNA directed DNA polymerase known as reverse transcriptase. HIV-1 primarily infected CD4 bearing lymphocytes but can infect a variety of other cells including macrophages and dendrocytes. Expressed on the surface of the virus are two proteins that are essential for infection of the CD4 bearing cells, gp120 and the gp41. HIV-1 gp120

binds to the cellularly expressed CD4 molecule. The HIV-1 gp41 then interacts with adjacent cellular co-factors, such as the CCR5 molecule, fusing the viral envelope with the cell membrane and inserting the HIV-1 RNA and regulatory proteins into the cellular cytoplasm. HIV-1 reverse transcriptase then synthesized two strands of DNA, using the HIV-1 RNA as a template. The HIV-1 RNA is then transported into the nucleus of the cell and inserted into the cellular genome by and HIV-1 encoded integrase. HIV-1 takes over the cellular machinery and synthesizes genomic HIV-1, and HIV-1 encoded.

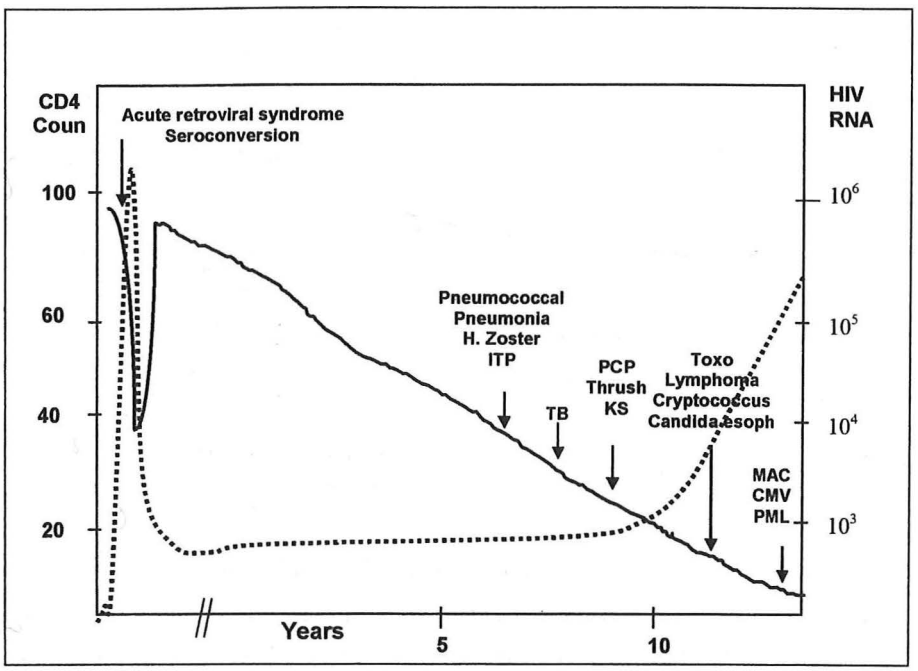
Figure 2: HIV-1 Life Cycle and Targets for Therapy.



proteins. These proteins are made as a long, single proto-protein that is ligated into component proteins by an HIV-1 encoded protease inhibitor. Viral assembly occurs inside the cell and immature viral particle bud off of the cell membrane. Post-budding maturation occurs and the virus is then able to infect other cells.

HIV infection is characterized by persistent viral replication. Budding of HIV-1 through the CD4 cell membrane causes cell lysis and death of the cell. Six to eight weeks after infection by HIV-1, there is a burst of viremia. There is a robust immune response to this viremia that is associated with a mononucleosis like illness. There is an initial drop in CD4 cell count but CD4 cell production increases in response to CD4 loss. An equilibrium develops between viral replication and CD4 cell loss, resulting in a stable rate of viral replication known as a viral set-point. Viral set-points vary widely between infected individuals with those with the highest set-point progressing most rapidly.

Figure 3: Changes in HIV-1 Plasma RNA and CD4 Count Over Time.



Individuals with viral set-points below the levels of detection have very slow loss of CD4 cells and may not develop symptomatic HIV infection. While there is a great deal of variation between the rates of viral replication between individuals, on average, the average time from infection to the development of AIDS is about 11 years.

Targets for Anti-retroviral Agents.

Currently, there are 5 classes of anti-retroviral drug representing 19 particular agents. The newest class of drugs are entry inhibitors of which only one is available for patient care. This drug, known as enfuvirtide, binds to the HIV-1 gp41 protein, blocking the interaction between this protein and cellular co-factors. This results prevents the fusion of the HIV-1 envelop with the cellular membrane, preventing infection of the cell by the

Table 1. Available Anti-retroviral Agents by Target and by Class

Class	Nuceloside Reverse Transcriptase Inhibitors	Non-nucleoside Reverse Transcriptase Inhibitor	Protease Inhibitors	Entry Inhibitors
Target	HIV-1 Reverse Transcriptase	HIV-1 Reverse Transcriptase	HIV-1 Protease	HIV-1 gp41
Agents	Zidovudine	Efavirenz	Saquinavir	Enfuvirtide
	Lamivudine	Nevirapine	Ritonavir	
	Didanosine	Delavirdine	Indinavir	
	Stavudine		Nelfinavir	
	Zalcitibine		Amprenavir	
	Abacavir		Lopinavir	
	Emtricitabine		Atazanavir	
	Tenofovir			

See Appendix 1 for a more complete description

virus. There are two major classes of reverse transcriptase inhibitors. Nucleoside reverse transcriptase inhibitors are analogues of naturally occurring nucleosides. They are competitively incorporated in to HIV-1 DNA by HIV-1 reverse transcriptase. Once in the HIV-1 DNA chain, these agents act as chain terminators. They also sterically inhibit the movement of reverse transcriptase down the RNA template. There are eight nucleoside analogues available. Tenofovir, is technically a nucleotide analogue and this a different class. The mechanism of action and clinical characteristics of this drug is so similar to the nucleoside analogues, that it is generally considered a member of this class. Non-nucleoside reverse transcriptase inhibitors directly bind to the HIV-1 reverse transcriptase

enzymes active site, irreversibly inhibiting it. There are three members of this class available, but only two, efavirenz and nevirapine, have widespread usage. Protease inhibitors bind to the active site of the HIV-1 protease enzyme, blocking proteolytic cleavage of HIV-1 proteins. This results in the formation of immature viral particles that are non-infectious.

History of Anti-retroviral Therapy

Anti-retroviral therapy was introduced in 1986 with the release of zidovudine, commonly call AZT. This medication was given as a single agent and was associated with 20-30 cell increase in CD4 cell count. Patients treated with zidovudine had decreased rates of opportunistic infections and improved survival of about 18 months. Because zidovudine did not fully suppress viral replication, resistance rapid develop and the effects of this drug were short lived. Newer agents in this class were used in a sequential fashion after zidovudine failure with predictable results; an initial response followed by further disease progression. In the early 1990s use of two nucleoside analogues provided better results than mono-therapy but patients ultimately failed their regimens.

Introduction of HIV-1 protease inhibitors in 1995 resulted in a revolution in the treatment of HIV infection. Protease inhibitors, in combination with two nucleoside analogues, could reduce viral replication to undetectable levels and sustain this suppression for as long as patients maintained taking the drugs. Subsequently, three drug combinations that do not include protease inhibitors have demonstrated similar efficacy as protease containing regimens. Because of the dramatic effects of these combinations on viral replication, use of three or more anti-retroviral agents has been referred to as Highly Active Anti-retroviral Therapy or HAART.

Benefits of HAART

Therapy with HAART is associated with a suppression of anti-retroviral replication to below the level of detection of this assay. First generation tests of viral replication have a lower level of detection of 400 copies of HIV-1 RNA per cubic milliliter of human blood. Newer generation tests have a lower limit of detection of 50 copies of HIV-1 RNA per

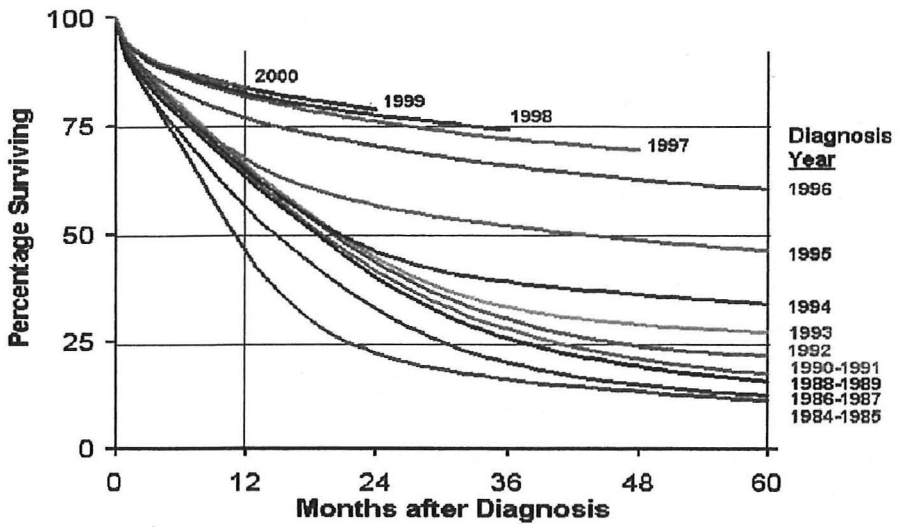
cubic milliliter while experimental assays can detect as little as 2 copies per milliliter. HAART has been able to suppress viral replication below the levels of detection of each of these generations of assays for as long as 5 years in clinical trials

Suppression of HIV-1 viral replication is associated with marked increases in CD4 cell count. Within several months of initiation of HAART, CD4 cell counts rise by as much as 200 cells per ml. This increase is primarily an expansion of the pool of pre-existing CD4 cells that have already been exposed to antigens. A second phase of CD4 cell increase occurs over a about an 18 month period that is primarily due to formation of new, naïve CD4 cells that have not been exposed to antigens.

The increase in CD4 cell counts has been associated with decreased rates of all opportunistic infection including AIDS defining illnesses such a Pneumocystis carinii pneumonia, cytomegalovirus infection, cryptococcal meningitis and other deep systemic fungal infection and mycobacterium avium complex infection. HIV-1 related neoplasms such as Kaposi's sarcoma and non-Hodgkins lymphoma occur at decreased frequency. Patients with these infection and or neoplasms often have better responses to therapy. Prior to the development of HAART, it was axiomatic that patients with opportunistic infections need life long therapy to prevent re-occurances. Since the widespread use of HAART, it has been demonstrated that therapy for opportunistic infections can be discontinued once a an acceptable CD4 cell count is achieved.

HAART therapy has been associated with a marked increase in survival in patients with AIDS. The HOPS study, a Center for Diseases Control cohort study of HIV infection, observed a 70% reduction in AIDS deaths between 1995 ad 1997 that was associated with protease inhibitor use. Other studies in the United States and in Europe have confirmed this finding. These effects continue to be seen. As of 2002, the CDC reported that 75% of AIDS cases reported in 1997 remained alive. Long term survival data is limited by fact that HAART has been widely used for only the last 7 years. Ultimately, the survival benefit from HAART may not been know for years.

Figure 4. Survival Benefit Associated with Anti-retroviral Therapy



Anti-retroviral therapy is very expensive, costing as much as $14,000 per patient per year. Newer agents are more costly and add to the expense of these regimens. Despite their high costs, anti-retroviral therapy has been shown to be cost effective. The decreased rates of opportunistic infection and death result in fewer emergency room visits and fewer and shorter hospitalizations. This has resulted in a shifting of costs from in-patient hospitalizations to the out-patient pharmacy, with a resulting net savings in overall HIV related care. In addition, utility based measures of effectiveness such as cost of quality of life year gained associated with HAART are lower than other those observed in other interventions such as dialysis in renal failure and coronary artery bypass surgery for atherosclerotic heart diseases.

Challenges to Providing HAART

Despite the benefits of HAART, taking these medications is no panacea. Initial regimens required a patient to take as many as 12 pills on a Q 8 hour schedule. Patients would also have to adhere to complex schedules of eating and drinking several liters of water per day. Some pills are very large and are difficult to swallow. Newer medications have

smaller pill burdens and longer high lives, allowing for a HAART regimen that can be administered in as little as 3 pills, once a day.

Short-Term Toxicites

Anti-retroviral drugs have a wide array of short term toxicities. Nausea, vomiting and diarrhea associated with almost all of the medications. Specific drugs have specific toxicities: Zidovudine causes anemia and neutropenia; didanosine, stavudine and zalcitibine can cause severe and painful peripheral neuropathy; abacavir is associated with a idopathic hypersensitivity reaction; non-nucleoside reverse transcriptase inhibitors frequently cause a rash and efavirenz is associated with central nervous system symptoms of dizziness and very vivid dreams. A large proportion of anti-retroviral agents can cause hepatitis, particularly in patients that are co-infected with Hepatitis B or Hepatitis C.

Hypercholesterolemia

Hypercholesterolemia has been associated with all classes of anti-retroviral medications.. As many a 30 % of patients treated with protease containing regimens have elevations of total cholesterol, LDL-cholesterol and trigycerides. Efavirenz, a non-nucleoside reverse transcripates inhibitor is associated with increases in total cholesterol that is primarily HDL cholesterol. A recent study has demonstrated that the nucleoside stavudine, is associated with increases in cholesterol. The implications of the cholesterol elevation is not clear. The mechanism by which this occurs has not been well elucidated. There have been as host of case reports of myocardial infarctions associated with anti-retroviral therapy. Cohort studies to date have yielded conflicting results; some show an association between anti-retroviral medications age adjusted rates of cardiovascular disease while others do not. Interpretation of these studies must be tempered by the realization that time frame examined is often less that seven years. Thus as patients are treated for longer period of time, the rates of cardiovascular disease may increase.

Treatment of hypercholesterolemia involves the use satins or fibrates. These medications must be used with caution as there is an interaction between protease inhibitors and some

statins that increases the levels of the latter drugs. There have been case reports of rabdomyalysis in patients receiving HIV-1 protease inhibitors and statins. A second strategy is to change medications to remove the anti-retroviral drug causing hypercholesterolemia. Abacavir ,a nucleoside analogue that is not associated with hypercholesterolemia, has been successfully substituted for protease inhibitors, resulting in an average 30% drop in total cholesterol levels. There have been high rates of virologic failures in subsets of patients who were changed to abacavir, however. Atazanavir, a new protease inhibitor, also has no effect on cholesterol. Switching patients from other protease inhibitors to atazanavir is also associated with decreases in cholesterol but maintains virologic suppression.

Mitochondrial Toxicity

Nucleoside analogues are associated with toxicity to mitochondrial DNA. Mitochondria have DNA that is separate from the cellular DNA and replicate independently of cellular DNA. Nucleoside analogues are inhibitors of DNA synthesis and can inhibit cellular mitochondria, causing the cell to use anaerobic glycolysis to produce energy. This inhibition has clinical implications: about 1% of patients treated with nucleoside analogues have clinical lactic acidosis. This syndrome is characterized by abdominal pain, nausea, vomiting and weakness. Lactic acidosis has been associated with decreased serum levels of mitochondrial DNA. Discontinuation of the nucleoside analogues results in resolution of symptoms, and a normalization of lactate and of mitochondrial DNA. While all of the nucleoside analogues can cause mitochondrial toxicity and lactic acidosis, stavudine has been the drug most associated with this syndrome and, not incidentally, has the highest affinity to human mitochondrial DNA.

Lipodystrophy-Lipoatrophy Syndrome.

The lipodystrophy/ lipoatrophy syndrome is a major long term toxicity of HAART that limits the use of these medications. Soon after the advent of protease inhibitor therapy, patients began complaining of abnormal fat distributions. Soon two distinct syndromes were identified: a lipodystrophy syndrome characterized by large fat deposits in the

abdomen and at the base of the neck; and a lipoatrophy syndrome characterized by wasting of fat in the arms, legs and face. There is also an overlap syndrome where individuals have components of both syndromes. Each of the syndromes can be highly disfiguring. The etiology of this fat mal-distribution is complex and unclear. Individuals with lipodystrophy/lipoatrophy typically are older, have had HIV for longer periods of time, have a lower nadir CD4 cell count and lower nadir weight than those who do not develop fat redistribution. Protease inhibitors are typically associated with the lipodystrophy syndrome. Nucleoside analogues, particularly stavudine, have been associated with lipoatrophy. While the etiology of these syndromes is unclear, it has been postulated that damage to the mitochondrial DNA of the peripheral fat cells by drugs like stavudine, results in the lost of peripheral fat. Complicating this explanation is the fact that fat ma-distribution has been observed in HIV patients who have never been treated with anti-retroviral medications.

Resistance

A final barrier to long term HAART therapy is the emergence of resistance. HIV-1 reverse transcriptase is highly error prone and has no proof reading ability. Thus the virus daily introduces mutations into its genome. Under the selective pressure of anti-retroviral medications, mutant viruses that are resistant to the drugs quickly arise and virologic failure ensues. Emergence of resistance can be avoided by complete suppression of viral replication that is accomplished by maintaining adequate levels of ant-retrovirals in the serum. When levels of drug fall below the threshold necessary to suppress viral replication, resistance emerges and the drugs loose their effectiveness.

The emergence of resistance limits the subsequent use of anti-retroviral medications. There is broad cross resistance in each of the classes of anti-retroviral drugs. A major pathway of resistance for the nucleoside analogues are the thymidine analogue mutations or TAMS. These mutations accumulate over time in a step wise fashion as virus replicates. The addition of each mutation increases the levels of resistance to nucleoside analogues including those to which the virus has not been exposed. In addition to TAMS, there are individual mutations that confer resistance across the class. Non-nucleoside

reverse transcriptase inhibitors, on the other hand, can quickly induce resistance with a single amino acid substitution (e.g. the K103N mutation in the HIV reverse transcriptase genome). Unlike the nucleoside analogues, this mutation confers resistance across the class. Protease inhibitors develop resistance in a similar manner to nucleoside analogues, that is, through the progressive accumulation of mutations. Some protease inhibitors have so called signature mutations or single amino acid substitutions that confer resistance to only that drug. The development of these signature mutations allows for sequencing of protease inhibitors. For example, viruses exposed to nelfinavir often have a single D30N substitution in the protease inhibitor genome, leading to nelfinavir resistance. Subsequent treatment with other protease inhibitors can suppress viruses with this mutation. Other protease inhibitors such as amprenavir or atazanavir also have signature mutations.

Resistance severely limits the ability to treat HIV-1 infection. Seventy five percent of patients who fail their first regimen have resistance to one or more agents. Ninety-five percent of people who fail a second regimen have resistance. In addition, HIV-1 infected patients with resistance are transmitting virus at high rates. A recent Center for Diseases Control Sponsored study have found that up to 12 % of new HIV infections in the United States are infected with resistance virus. While there are 19 agents that can be used in the treatment of HIV infection, cross resistance to these drug effectively limits these drug to two or three sequences of regimens.

Excellent adherence to anti-retroviral medication is critical to maintain virologic suppression and prevent resistance. Numerous studies have shown that 85-90% adherence to medications is required in order to prevent virologic rebound. Interestingly, those patients who take 70- 80 % of their drugs are the most likely to develop resistance, because they have persistent levels drug in the face of replicating virus. Because of the high rates of resistance associated with poor adherence, it is important to assess the potential for adherence prior to initiation of anti-retroviral therapy. Patients who are judged poor adherence risks should have therapy delayed as long as medically appropriate or until the patient the patient demonstrates readiness to take medication

Factors that can improve adherence include education of patient of benefits and side effects of anti-viral therapy; anticipation and treatment of side effects, and treatment of depression and substance abuse. Organization helps such as reminders and pill boxes can improve the patients ability to take medications. Finally, simpler regimens including Qday regimens can improve adherence to anti-retroviral therapy.

When to start- balancing treatment benefits and risks.

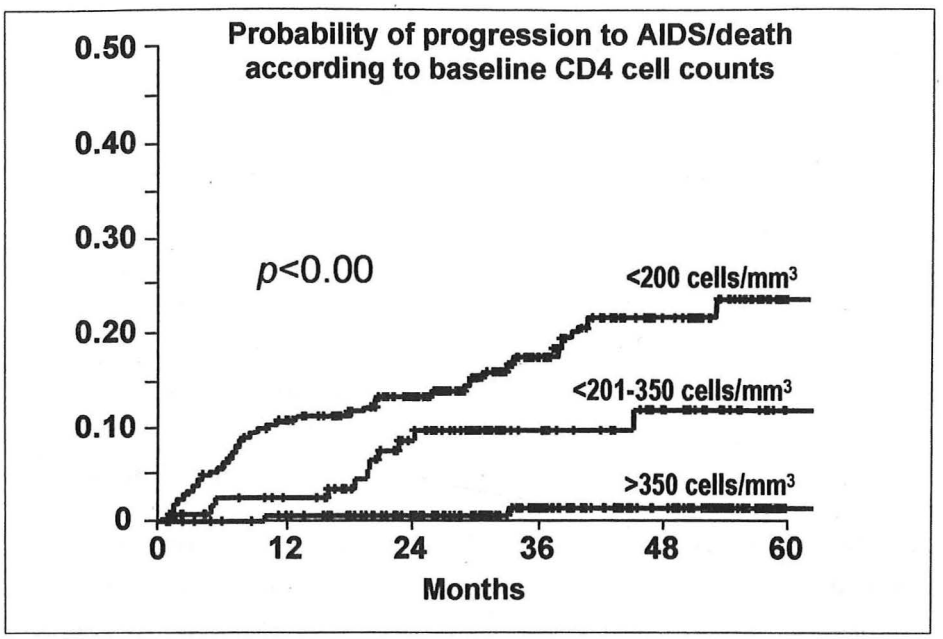
Timing of the initiation of HAART requires balancing the benefits of these drugs with the risks of toxicity and resistance. Treatment of an individual in early stages of HIV infection can produce dramatic virologic and immunologic results. Waiting for the development of an opportunistic infection or other AIDS related illness to begin therapy, exposes the patient to unnecessary morbidity and mortality. Unfortunately, early treatment also exposes a patient to toxicity of medication at a time when that person is unlikely to become sick from HIV-1 infection. In addition, resistance to anti-retroviral drugs may also develop, leaving few treatment options when that individual becomes sick from HIV-1.

Numerous studies have been done to try to determine the optimal time to initiate HAART. Observational databases in the United States and Europe have followed cohorts of HIV infection patients over time. In each of these studies, progression of HIV-1 disease to AIDS as measured by a new opportunistic infection or death was stratified CD4 cell count and plasma HIV-1 RNA at which therapy was initiated. There is remarkable consistency between these studies: the greatest benefit of HAART occurs in individuals with CD4 counts less than 200 cells/ml. There is an incremental benefit of therapy in those with CD4 cell counts between 200 and 350 cells, particularly in those with an HIV-1 RNA that is greater than 55,000 copies. There is little benefit to initiation of therapy in those individuals with CD4 cell counts greater than 500 copies/ml.

Based on these data, numerous organizations have developed treatment guidelines for the treatment of HIV infection. The various guidelines generally agree but have slightly

different nuances based on the authors interpretation of the data regarding initiation of therapy. The Department of Health and Human Services Treatment Guideline strongly

Figure 5: Time to AIDS Based on CD4 Count at HAART Initation



Based on these data, numerous organizations have developed treatment guidelines for the treatment of HIV infection. The various guidelines generally agree but have slightly different nuances based on the authors interpretation of the data regarding initiation of therapy. The Department of Health and Human Services Treatment Guideline strongly recommend therapy for individuals with clinical AIDS or a CD4 count less than 200 cells/ml. They also recommend therapy for asymptomatic individuals with CD4 counts between 200 and 350 cells/ml who also have an HIV-1 RNA greater than 55,000 copies/ml. Other treatment guidelines, such as the those from International AIDS Society –USA or the British HIV Association are influenced more by the patients symptoms than CD4 count thresholds. Patients with clinical AIDS should receive therapy; those with symptoms of HIV infection without an AIDS diagnosis may be treated and those without

an symptoms may have therapy deferred. All of the treatment guidelines emphasize the need for patient to be ready to meet the demands of adhering to HAART.

Table 2. Recommended Treatment Initiation Parameters

Clinical Syndrome	CD4 Cell Count	HIV-1 RNA	Recommendation
Symptomatic AIDS	Any	Any	Treat
Asymptomatic HIV	CD4 < 200 cells/mm3	Any	Treat
Asymptomatic HIV	CD4 between 200 and 350 cells/mm3	Any	Treat
Asymptomatic HIV	> 350 cells/mm3	> 55,000	Treat
Asymptomatic HIV	< 350 cells/mm3	< 55,000	Do not Treat

Initiation of Therapy

Two major strategies for the treatment of HIV infection have emerged. The first is to use two nucleosides plus the non-nucleoside reverse transcriptase inhibitor efavirenz. Efavirenz has been performed as well or better than protease containing regimens in a variety of studies. For example, in the DMP006 study, anti-retroviral naïve patients treated with efavirenz plus zidovudine and lamivudine had longer time to virologic failure that those treated with indinavir, zidovudine and lamivudine. Similar comparisons to other protease inhibitors such as nelfinavir and amprenavir have yielded similar results. Efavirenz containing regimens have performed better than triple nucleoside based HAART regimens such as zidovudine, lamivudine and abacavir. Efavirenz is supplied as a single pill that can be given once a day. Careful choice of a two nucleosides with efavirenz allows for a once daily regimen. The initial choice of efavirenz allows for sequencing of therapy. Patients who fail an efavirenz based regimen develop resistance to class of non-nucleoside reverse transcriptase inhibitors. However, virus from such individuals retain sensitivity to protease inhibitors and thus should have a good response protease containing regimen.

Table 3. List of Preferred and Alternative Initial Regimens

Preferred Regimens	Active Agent	Nucleoside Analogues	Qday Regimen/Pill Count
	Efavirenz	TNF + 3TC Or D4T + 3TC Or AZT + 3TC	Yes/ 3 No/4 or 5 No/3
	Kaletra	D4T + 3TC Or AZT + 3TC	No/ 9-10 No/9-10
Alternative Regimens	Efavirenz	DDI + 3TC	Yes/3
	Nelfinavir	D4T + 3TC Or ZDV + 3TC	No/13-14 No/12
	Indinavir + Ritonavir	D4T + 3TC Or AZT + 3TC	No/9-10 No/8
	Saquinavir + Ritonavir	D4T + 3TC Or AZT + 3TC	No/15-16 No/14
	Nevirapine	D4T + 3TC or DDI + 3TC Or AZT + 3TC	No/5-6 No/4 No/4

A second strategy is to use the combination of the protease inhibitors lopinavir/ritonavir. This is a fixed dose combination of these two drugs that is marketed under the brand name Kaletra. Lopinavir/ritonavir plus stavudine and lamivudine had a better time to

treatment failure that a nelfinavir plus stavudine and lamivudine. Lopinavir/ritonavir regimens have longer response rates than those seen with other protease containing regimens. In addition, there is a low rate of emergence of resistance to lopinavir/ritonavir regimens. The ability to sequence therapy after a lopinavir/ritonavir containing regimen is less well defined than in patients who have failed an efavirenz containing regimen. Although the rates of resistance in lopinavir/ritonavir failures in naïve patients are low, there is potential for broad cross resistance, limiting future treatment options. However, such patient should have virus that is sensitive to a non-nucleoside reverse transcriptase inhibitor.

Other popular treatment strategies have recently been shown to be less effective and should not be used. Combinations of three nucleosides have been used in an effort to avoid the toxicities associated with protease inhibitors and to reduce the pill burden associated with HAART. The appeal of this strategy was so strong that the combination of zidovudine-lamivudine-abacavir is marketed as a single pill that is administered twice daily. A recent comparative trial of this regimen and zidovudine-lamivudine-efavirenz demonstrated a superior time to treatment failure in the subjects treated with efavirenz. Several other trials that included triple nucleoside analogues as treatment arms have shown consistently higher failure rates in associated with these combinations compared to other protease or non-nucleoside containing regimens. Because of these results, triple nucleoside regimens are rarely indicated as therapy for HIV infection.

It is important to recognize that these recommendations are dynamic and change as new data and new agents are available. For example, a new protease inhibitor, atazanavir, has compared favorably to each of the preferred active (efavirenz and lopinavir/ritonavir) in two clinical trials. This agent can be given once daily and is not associated with lipid abnormalities associated with protease inhibitors. In addition, it can be given with other once daily regimens to construct a truly once daily regimen for HIV infection. As newer agents are developed, their use will be incorporated into therapeutic recommendations with the result being simpler, less toxic regimens for HIV.

Once a patient has been started on anti-retroviral therapy, close monitoring is required to insure a sustained response to therapy. CD4 counts and HIV-1 RNA should be monitored every 3 months. Most HIV- experts will see the patient at one month after starting therapy to assess toxicity, adherence and HIV-1 RNA decline. HIV-1 RNA should decrease by 1 log in 12 weeks and should be below levels of detection by 24 weeks. Specific toxicities for particular anti-retrovirals should be monitored by selected testing. Typically, CBC, electrolytes, BUN, creatinine, LFTs and glucose are monitored every 3 months. Lipids should be monitored every 6 months.

Patients who fail to achieve an undetectable HIV-1 RNA or who have a rebound in HIV-1 RNA should be considered for a change in therapy. Viral rebound should be confirmed by a second HIV-1 RNA test. Once virologic failure has been confirmed, potential reasons for failing should be assessed. The most common reason for failure is poor adherence the anti-retroviral regimen. Other possibilities include insufficient drugs levels due to malabsorbtion or dues to a drug-drug interaction. Adherence and toxicity issues should be addressed prior to considering changing medication.

Resistance testing is key to choosing a successful subsequent regimen. Currently there are two major methods of HIV-1 resistance testing. Genotype testing is performed by sequencing the HIV-1 genome from viral isolates from a particular patient. Identification of key mutations that have been associated with resistance indicate drugs that are no longer effective. Phenotype testing involves growing the virus in the presence of therapeutic levels of drugs. While traditionally time intensive, recombinant techniques and robotics have decreased the time required to perform phenotype testing so that it can have clinical applications. Resistance testing, either genotype or phenotype, have been shown to improve outcomes in patients changing anti-retroviral medications. In addition, both assays are cost effective: the increased cost associated with resistance is off-set by decreased costs of anti-retroviral medications. There is little data to recommend one method of testing over another. Currently, genotype testing is used most often because it is cheaper than phenotype testing.

Choice of new drugs should be based on results of resistance tests and past anti-retroviral therapy. Generally patients should be treated with at least 3 new drugs to which the patients virus is susceptible. For patients who had toxicity to a particular agent, new drugs with overlapping toxicity should be avoided. Monitoring of patients should be as described above. After 2 regimen sequences, broad cross resistance typically occurs, diminishing treatment options.

Although the concept of sequencing is integral to anti-retroviral strategies, there is little data, to support using one sequence of anti-retroviral. The ACTG 384 study is the only large trial to date that compares two sequencing strategies. Subjects were randomized to either an efavirenz based regimen or a nelfinavir based regimen. Subjects who failed their initial regimen were crossed over to the other drug class in the trial as a second regimen. Overall, there was no difference in time to failure of the second regimen regardless of the initial therapy. Other sequencing trials are underway. Ultimately, it may take many years before the optimal sequence of anti-retroviral drugs are delineated.

Summary

In summary, anti-retroviral therapy has seen dramatic advances in the past 10 years. Combination therapy has resulted in dramatic improvements in morbidity and mortality associated with HIV-1 infection. These medications are not without costs; there are long term toxicities and emergence of resistance represents a substantial barrier to long term success of anti-retroviral therapy. Newer agents provide simpler regimens that may be as toxic. Optimal use of these drugs remains undefined but ongoing studies are seeking to define the best sequences of these drugs. New classes of drugs may provide additional opportunities to improve care of HIV-1 infected patients.

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Appendix 1. Listing of Currently Available Anti-retroviral Drugs by Class, Dosage and Common Toxicities.

Class	Generic Name	Brand Name	Common Abbreviation	Formulation	Preferred Dosage	Common Toxicities
Nucleoside Analogue	zidovudine	Retrovir	AZT, ZDV	300 mg tablet	300 mg bid	GI intolerance, neutropenia, anemia
	didanosine	Videx	ddI		200 mg bid	
		Videx-EC	ddI	250 mg or 400 mg enteric capsule	400 mg qday or 250 mg qday + tenofovir	GI intolerance, diarrhea, pancreatitis, peripheral neuropathy
	zalcitibine		ddC	0.375 mg or 0.75 mg tablet	0.75 mg tid	Peripheral neuropathy, stomatitis
	lamuvidine	Epivir	3TC	150 mg or 300 mg capsule	150 mg bid or	Generally well tolerated

					300 mg qday	
	stavudine	Stavudine	D4T	20 mg, 30 mg or 40 mg tablets	< 60 kg 30 mg bid > 60 kg 40 mg bid	Peripheral neuropathy, pancreatitis
	abacavir	Ziagen	ABC	300 mg tablet	300 mg bid	Hypersensitivity
	emtricitabine		FTC			
Nucleotide Analogue	tenofovir	Viread	TNF	300 mg tablet	300 mg qday	Minimal toxicity Lactic acidosis Rare renal toxicity
Non-Nucleoside Reverse Transcriptase Inhibitor	efavirenz	Sustiva	EFV	200 mg or 600 mg tablet	600 mg q day	Vertigo, difficulty sleeping and vivd dreams in 1st month Rx., rash, hepatitis
	nevirapine	Viramune	NVP	200 mg	200 mg bid	Rash, Stevens-Johnson Syndrome, hepatitis
	delavirdine	Rescriptor	DLV	100 mg or 200 mg tablets	600 mg bid	Rash, hepatitis

Protease Inhibitors	saquinavir	Invirase	SQV	200 mg	400 mg bid plus ritonavir 400 mg bid	GI intolerance, hepatitis, hyperglycemia
		Fortovase	SQV	200 mg	400 mg bid plus ritonavir 400 mg bid	"
	ritonavir	Norvir	RTV	100 mg	Generally only used to enhance levels of other protease inhibitors. Not recommended as a single PI	GI intolerance, aesthenia, cholesterol abnormalities
	indinavir	Crixivan	IDV	200 mg or 400 mg	800 mg bid plus 100 mg of ritonavir bid	GI intolerance, cholesterol abnormalities, nephrolithiasis, hyperbilirubinemia, hyperglycemia
	nelfinavir	Viracept	NLF	250 mg	1250 mg bid	Diarrhea
	amprenavir	Agenerase	AMP	150 mg	600 mg bid	Nausea, vomiting,

					plus ritonavir 100 mg bid or 1200 mg bid plus ritonavir 200 mg qday	rash, lipid abnormalities
	lopinavir/ritonavir	Kaletra	LPV/r	133 mg plus ritonavir 33.3 mg in a combination capsule	400 mg bid	GI intolerance, aesthenia, hepatitis, cholesterol abnormalities, hyperglycemia
	Atazanavir	Reyataz	TAZ	150 mg or 200 mg	400 mg qday or 300 mg qday plus ritonavir 100 mg q day	hyperbilirubinemia

Entry Inhibitors	Enfuvirtide	Fuzeon	T-20	108 mg vials to be reconstituted with 1.1 ml sterile water	90 mg SQ bid	Injection site reaction, hypersensitivity, increased rates of bacterial pneumonia