Arch Pharm Res Vol 23, No 5, 425-437, 2000 Review

Antiretroviral Therapy 2000

Rafik Samuel and Byungse Suh

Section of Infectious Diseases, Temple University Hospital, Philadelphia, USA

(Received July 20, 2000)

As we enter the new millennium, there have been dramatic improvements in the care of patients with HIV infection. These have prolonged life and decreased morbidity and mortality. There are fourteen currently available antiretrovirals approved in the United States for the treatment of this infection. The medications, including their pharmacokinetic properties, side effects, and dosing are reviewed. In addition, the current approach to the use of these medicines is discussed.

Key words: HIV, Antiretroviral therapy, Viral load, CD4 count, Nucleoside reverse transcriptase Inhibitors, Non nucleoside reverse transcriptase inhibitors, Protease inhibitors

INTRODUCTION

As we enter the third decade of the HIV epidemic, we have seen dramatic improvements in outcomes of people with this infection. The reasons are not completely clear, but undoubtedly they are multiple. These include better understanding of the disease, earlier diagnosis, better therapies for HIV, as well as better prophylaxis and treatment of opportunistic infections (Detels *et al.*, 1998; Mocroft *et al.*, 1998; Ledergerber *et al.*, 1999). In recent years, the implementation of antiretroviral therapy has dramatically reduced mortality and morbidity. Patients with "end stage" disease (CD4 counts less than 100) had mortality rates decreased four fold and morbidity rates reduced almost eight fold (Palella *et al.*, 1998).

However, we are not seeing these trends across the world (UNAIDS/WHO, 1999). These are seen pre-dominantly in North America and Western Europe. The estimated number of people infected with HIV at the end of 1999 in North America and Western Europe was only 1.4 million, while the rest of the world's infection rate was 32.2 million. The HIV epidemic is devastating the social and economic cultures of Sub Saharan Africa, where 23.3 million individuals are infected (MAP, 1998; UNAIDS/WHO, 1998). HIV infection is increasing at an alarming rate in Asia, India, and the former Soviet Union where 7 million people are currently infected (MAP, 1997). The reasons we are seeing this devastation is likely the lack of resources that were mentioned above.

We would like to review the currently available antiretrovirals, how they are being used in combination, and the approach to specific cases such as the pregnant patient and post exposure prophylaxis.

HIV Life Cycle

HIV is a retrovirus, which is so named because it carries RNA. The virus enters the host cell by binding the CD4 receptor and either the CCR5 or CXCR4 co-receptor. It then binds the gp 41 protein which initiates its fusion. Upon entry into the cell, the virus is uncoated, and the viral reverse transcriptase transcribes the RNA into DNA. With the help of the enzyme integrase, the viral DNA integrates into the cell genome. The viral DNA is transcribed into mRNA and then translated into protein precursors by the host machinery. The protein precursors are then cleaved by the virus enzyme protease and are packaged into a virion particle. This cycle begins again and continues at incredible levels. There are approximately 10 billion particles of HIV generated per day (Folks and Hart, 1997).

Currently Available Antiretrovirals

There are fourteen medications currently available, and three that will be approved in the next year for the treatment of HIV. These medicines fall into three major classes: the nucleoside reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors and the protease inhibitors. There are also two other agents currently used which are not antiretrovirals: hydroxyurea and interleukin 2.

Correspondence to: Byungse Suh, MD, PhD, Section of Infectious Diseases, Temple University School of Medicine, 3401 N Broad St, Philadelphia, PA 19140, USA
E-mail: bsuh@nimbus.ocis.temple.edu

The Nucleoside Reverse Transcriptase Inhibitors (NRTI) (Table I)

These agents are nucleoside analogs which become phosphorylated by the host enzymes. After phosphorylation, they are incorporated into the newly forming viral DNA. The transcription ceases, thus halting replication of virus before incorporating into the host genome. There are six currently available NRTIs: zidovudine, didanosine, zalcitabine, stavudine, lamivudine and abacavir.

Zidovudine (Retrovir) was the first antiretroviral agent approved in the mid 1980's (Hirsch 1988). It is a synthetic thymidine analog. It is rapidly absorbed from the gastrointestinal tract. Its area under the curve is not affected by food. Zidovudine is rapidly metabolized and eliminated by the kidneys in about 1 h (Acosta *et al.*, 1996). Common toxicities seen with zidovudine include headache, fatigue, malaise, myalgia, anorexia, nausea, anemia and neutropenia. Chronic toxicities include nail hyper pigmentation, hepatotoxicity, and muscle toxicity (Fischl, 1999). The usual dose is 300 mg twice daily (Hilts and Fish, 1998).

Didanosine (Videx) is an adenosine analog approved in 1991. Didanosine is highly acid labile, and is degraded rapidly in acid pH. The oral preparation is buffered with calcium carbonate and magnesium hydroxide. It is packaged as a chewable/dispersable tablet. The bioavailability is decreased by fifty percent with food and therefore must be administered on an empty stomach. Didanosine is rapidly excreted by the kidneys in 2 to 3 h. The most common toxicities include peripheral neuropathy which is a symmetric distal polyneuropathy in 9 to 15% of individuals as well as pancreatitis which occurs in 4 to 7% of patients. The usual dose is 400 mg once daily (Perry and Noble, 1999).

Zalcitabine (Hivid) is a cytosine analog approved in 1992. It has a 70 to 90% bioavailability which is significantly decreased by food. It has a half life of 1 to 3 h and it is excreted unchanged by the kidneys. The most common toxicity is peripheral neuropathy in up to 23% of patients. Other less common toxicities include stomatitis (2 to 4%), rash and pancreatitis (1%). The usual dose is 0.75 mg three times daily (Bartlett, 1999).

Stavudine (Zerit) is a synthetic analog of thymidine (similar to zidovudine) approved in 1995. It has a bioavailability of 82% and its absorption is not affected by food. It has a half life of 3 to 4 h and is excreted unchanged by the kidneys (Rana and Dudley, 1997). Common toxicities include neuropathy in 2% of patients, and elevated hepatic transaminases less frequently. As with all the agents that cause peripheral neuropathy, this toxicity is unpredictable and usually not reversible. The usual dose is 40 mg twice daily (Hurst and Noble, 1999). Stavudine and zidovudine compete with the thymidine kinase which makes these two agents antagonistic in vitro (Katlama and Havlir, 1996).

Lamivudine (Epivir) is a synthetic analog of cytosine (similar to zalcitabine) approved in 1996. It has a bioavailability of 82 % and is not affected by food. Its half life is 3 to 4 h and it is excreted unchanged by the kidneys (Perry and Faulds, 1997). There are no significant toxicities to note. Mild toxicities including diarrhea, headache, fatigue, nausea and insomnia have been reported. Since lamivudine and zalcitabine are cytosine analogs, they compete for phosphorylation and may be antagonistic (Katlama and Havlir, 1996). The usual dose is 150 mg twice daily. Lamivudine has shown activity against hepatitis B in addition to its HIV activity.

Abacavir (Ziagen) is a guanosine analog approved in 1999. It is well absorbed, unaffected by food, and has a half life of 3.3 h. It is metabolized by glucuronidation and carboxylation in the liver. Abacavir is well tolerated with side effects including nausea and diarrhea which are self limited. However, an important clinical side effect is the abacavir hypersensitivity reaction which occurs in 3% of patients. A vast majority of this manifestation occurs within 11 days of initiating therapy. Findings include fever, rash, arthralgias and myalgias. The symptoms worsen as the medicine is continued. The drug should be discontinued after ascertaining that the symptoms are related to the medicine because if re-challenged, the symptoms are much more severe and may include death. Therefore, once a rash and flu symptoms develop in a patient on this medicine, it should be stopped and never re-introduced. The usual dose is 300 mg twice daily (Foster and Faulds, 1997; McDowell *et al.*, 1999; Wolback and Capoccia, 1999).

Table I. Currently available Nucleoside Reverse Transcriptase Inhibitors

Generic Names	Abbreviated Names	Brand Names	Chemical Structure	Dosage	Comments
Zidovudine	AZT	Retrovir	Fig. 1	300 mg twice daily	Headache, fatigue, anemia, leukopenia
Didanosine	ddI	Videx	Fig. 1	400 mg once daily	Pancreatitis, neuropathy
Zalcitabine	ddC	Hivid	Fig. 1	0.75 mg three times daily	Neuropathy, stomatitis
Stavudine	d4T	Zerit	Fig. 1	40 mg twice daily	Neuopathy
Lamivudine	3TC	Epivir	Fig. 1	150 mg twice daily	No significant side effects
Abacavir	ABC	Ziagen	Fig. 1	300 mg twice daily	Hypersensitivity reaction
Zidovudine and Lamivudine		Combivir	Fig. 1	1 tablet twice daily	Lowers pill burden

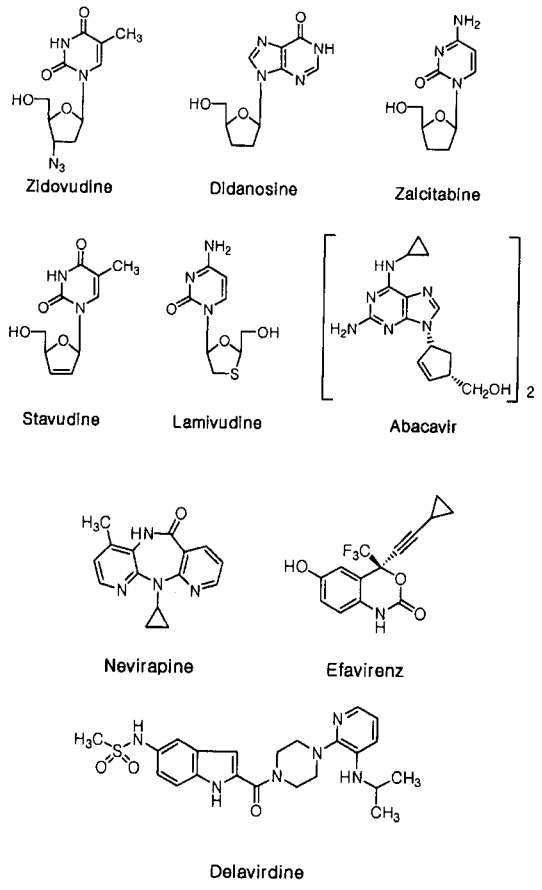

Fig. 1. Structures of nucleoside reverse transcriptase inhibitors.

The Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) (Table II)

These agents work by binding directly to the reverse transcriptase which causes a conformational change in the enzyme rendering it non functional (Miller *et al.*, 1997). There are currently three available agents in this class including nevirapine, delavirdine, and efavirenz.

Nevirapine (Viramune) was the first NNRTI approved in 1996. It is readily absorbed and is unaffected by food. Its half life is 25 to 30 h and it is metabolized by the cytochrome P-450 CYP-3A4. It is an inducer of the P-450 and induces its own metabolism. Toxicity associated with nevirapine is limited. The main adverse event is rash which occurs in 16% of patients. The rash is occasionally significant with reports of Stevens-Johnson Syndrome occurring. Elevated liver enzymes have been seen in 1.1 % of patients. It is given 200 mg once daily and then increased to 200 mg twice daily after two weeks to decrease the likelihood of rash (Pollard *et al.*, 1998).

Delavirdine (Rescriptor) was approved in 1997. Its absorption is decreased significantly with food, therefore it must be given on an empty stomach. Its pharmacokinetics are nonlinear, and its half life cannot accurately be determined. It is metabolized by the cytochrome P-450 CYP-3A4. It is also a P-450 CYP-3A4 inhibitor. The most common side effect is a maculo-papular rash which occurs in 18 to 36% of patients. The rash occurs within 1 to 3 weeks and usually resolves without discontinuation of the drug (Friedland *et al.*, 1999). The usual dose is 400 mg three times daily (Demeter and Reichman, 1999).

Efavirenz (Sustiva) was approved in 1998 for the treatment of HIV. It is absorbed quickly and its levels are increased significantly with high fat meals. Its half life is 40 to 55 h and it is metabolized by the P-450 CYP-3A4 and also CYP-2B6. In addition, it is an inducer of the CYP-3A4. Common side effects include headache and dizziness, impaired concentration, and abnormal dreaming which resolve in weeks (11%). The other side effect seen is rash which occurs in the second week of therapy in 19% of patients. Efavirenz therapy can continue with supportive care and the rash resolves in about 4 weeks (Adkins and Noble, 1998; Bossi *et al.*, 2000). The usual dose is 600 mg daily.

Protease Inhibitors (PI) (Table III)

These antiretrovirals work by preventing cleavage of the protein precursors by inhibiting the protease enzyme. The resultant proteins that are formed cannot be packaged into mature virus and are therefore not virulent (Flexner 1998). These medicines include saquinavir, ritonavir, indinavir, nelfinavir, amprenavir and lopinavir.

Saquinavir hard gel (Invirase) was the first PI approved in 1995. The oral bioavailability of saquinavir hard gel was only 4%, even with a high fat meal (Vella and Floridia, 1998). For this reason, a new formulation was developed and released in 1997 (saquinavir soft gel). The oral bioavailability of the soft gel formulation is 3 times that of the hard gel form and food increases its absorption another 6 fold. The half life of saquinavir is 2 h and it is metabolized by the P-450 CYP-3A4. The most frequent side effects include diarrhea, nausea and headache (2 to

Table II. Currently Available Non-nucleoside Reverse Transcriptase Inhibitors

Generic Name	Abbreviated Name	Brand Name	Chemical Structure	Dosage	P450 effect	Comments
Nevirapine	NVP	Viramune	Fig. 1	200 mg twice daily	Inducer	Rash
Delavirdine	DVD	Rescriptor	Fig. 1	400 mg three times daily	Inhibitor	Rash
Efavirenz	EFV	Sustiva	Fig. 1	600 mg once daily	Inducer	Rash, dizziness, insomnia

Table III. Available Protease Inhibitors

Generic Name	Abbreviated Name	Brand Name	Chemical Structure	Dosage	P 450 Effect	Comments
Saquinavir	SQV-HG SQV-SG	Invirase Fortovase	Fig. 2	1600 mg twice daily	+++	Only use the soft gel form, taken with high fat meal
Ritonavir	RTV	Norvir	Fig. 2	600 mg twice daily	+++++	Stored in refrigerator Dose escalate
Indinavir	IDV	Crixivan	Fig. 2	800 mg three times daily	++++	Must be taken on empty stomach and with 6 glasses of water
Nelfinavir	NFV	Viracept	Fig. 2	1250 mg twice daily	+++	Can cause diarrhea
Amprenavir	APV	Agenerase	Fig. 2	1200 mg twice daily	++++	Rash, diarrhea
Lopinavir	LPV	Approved on Sep. 16, 2000	Fig. 2	ABT-378 (133 mg)+ritonavir (33.3 mg) three tablets twice daily	unavailable	Diarrhea, nausea

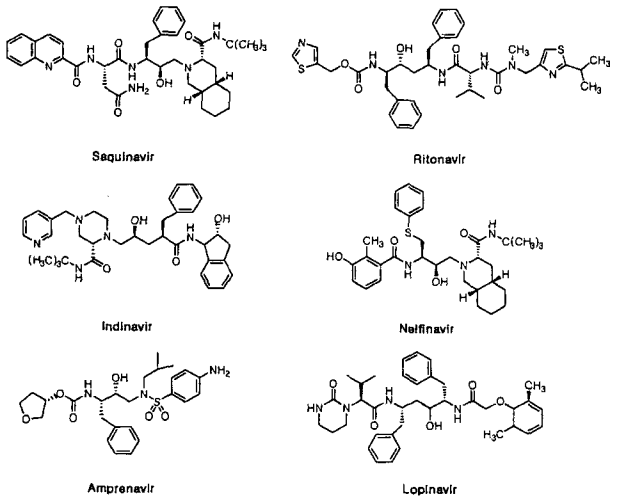

Fig. 2. *Structures of protease inhibitors.*

5%). The hard gel form is administered as three 200 mg tablets three times a day and the soft gel form is given as eight 200 mg tablets twice daily (Perry and Noble, 1998).

Ritonavir (Norvir) was the second PI approved in 1995. It is well absorbed and minimally affected by food. Its half life is 3 to 5 h and it is metabolized by the P-450 CYP-3A4. It has significant affinity for several P-450 enzymes and is a potent inhibitor of the CYP -3A4 in particular. It is also an inducer of the P-450 enzymes and induces its own metabolism (Lea and Faulds, 1996). It is very important to note that this drug has multiple and often significant drug interactions. The most common adverse events include nausea, diarrhea, vomiting, anorexia, abdominal pain, peripheral paresthesias and peri-oral paresthesias. To decrease these side effects, the drug is dose escalated from 300 mg twice daily to 600 mg twice daily over 10 to 14 days. Because it is unstable at room temperature, it must be stored in a refrigerator (Hsu *et al.*, 1998a).

Since these were the first two protease inhibitors available, and the hard gel saquinavir had very poor absorption, they were used in combination. The combination of hard gel saquinavir 400 mg and ritonavir 400 mg was shown to achieve very good levels of both drugs. At present time there is no other use for the hard gel saquinavir, and if using saquinavir alone, the soft gel preparation must be used despite the significant cost difference (Hsu *et al.*, 1998b).

Indinavir (Crixivan) was the third PI approved in 1996. It is well absorbed on an empty stomach or low fat meal, but its absorption is decreased by 86% with a high fat meal. Its half life is 1.9 h and is metabolized by the P-450 CYP-3A4. Its most common side effects include gastrointestinal disturbances (4 to 12%). Its most noted toxicity is nephrolithiasis secondary to crystallization of indinavir in the renal tubules (9%). The nephrotoxicity can be decreased with substantial water intake (six glasses). The usual dose is two 400 mg tablets three times a day on an empty stomach (Plosker and Noble, 1999).

Nelfinavir (Viracept) was the fourth PI approved in 1997. It is well absorbed and has no food interactions. Its half life is 3.5 to 5 h. As the other PIs, it is metabolized by the cytochrome P-450 CYP-3A4. It too, is an inhibitor of the same enzyme, but to a much lower degree than ritonavir or indinavir. The side effects of nelfinavir include diarrhea (21%), and nausea (2 to 4%). Antimotility agents such as loperamide or calcium can be used to decrease the side effects. The diarrhea usually resolves over time. The usual dose is three 250 mg tablets three times a day or five 250 mg tablets twice daily (Jarvis and Faulds 1998; Haubrich and Havlir, 1999).

Amprenavir (Agenerase) was the last PI approved in 1999. This is considered a second generation PI, designed to be active against virus resistant to the previously released PIs. It is absorbed well but its concentration decreases 46% with food. Its half life is 7 to 9.5 h, and it undergoes limited hepatic metabolism followed by biliary secretion. It is also a potent P-450 CYP-3A4 inhibitor similar to indinavir, but less than ritonavir. Adverse events include rash (10 to 20%), diarrhea and headache (10%). The usual dose is six 200 mg tablets twice daily (Adkins and Faulds, 1998).

Lopinavir (Kaletra) is in expanded access and has just been approved. It is considered a second generation PI which is active against virus resistant to the previously released PIs, including amprenavir. Its design is unique in that it was developed to be effective against viral isolates known to be resistant to ritonavir. Lopinavir is a combination of 2 PIs-ABT-378 (133 mg) and ritonavir (33 mg) which inhibits the metabolism of the parent compound. It is well absorbed and is not affected by food. The level of ABT-378 is near undetectable if given alone, but it is increased by 14 fold with the addition of ritonavir. ABT-378 is metabolized by the P-450 CYP-3A4 (Sham *et al.*, 1998). The most common side effects include diarrhea, nausea and abnormal stool (21%). It is admini-stered as 3 tablets twice daily (Deeks *et al.*, 2000; Gulick *et al.*, 2000).

Unfortunately, the use of these antiretroviral agents has long term side effects which are now being noted. Over the last two years, people have reported a group of findings now termed the lipodystrophy syndrome. This syndrome includes three distinct problems including fat redistribution, glucose intolerance and lipid abnormalities. The fat redistribution includes central obesity, muscle wasting, buffalo hump formation, associated with normal ACTH/cortisol levels. Glucose intolerance ranges from elevated sugars to frank diabetes. The lipid abnormalities include elevated triglycerides, elevated total cholesterol and LDL, but decreased HDL (Carr, *et al.*, 1998).

The etiology of this syndrome is not clear, but it is believed to be secondary to multiple factors including the PI inhibition of the P-450 system and its interactions with lipid metabolism. There is also a possible contribution from the NRTI effects including mitochondrial toxicity and lactic acidosis (Carr, *et al.*, 1998).

Long term effects of these complications such as cardiovascular disease are being studied. Therapy at present is controversial. Changing therapy from a PI to a NNRTI may have some benefit, however this is not clear. Addition of oral hypoglycemic agents, lipid lowering agents, and growth hormone, have been investigated with variable efficacy (Bersconi, 1999).

Other Agents Used In The Treatment of HIV

Hydroxyurea (Hydrea), an antimetabolite, has been used in the treatment of HIV. It has no activity against HIV, but inhibits ribonucleotide reductase which phosphorylates the nucleosides. The nucleoside affected most significantly is adenosine. Since adenosine is not phosphorylated, its analog, didanosine is. With subsequent high levels of phosphorylated didanosine as compared to adenosine, it is selectively used allowing inhibition of the HIV DNA transcription (Sherman and Fish, 1999). Therefore, this agent should be used with didanosine. Hydroxyurea is well absorbed, it has a half life of 2.6 h, it is metabolized by the liver and excreted in the urine. The primary side effects of hydroxyurea include nausea, vomiting, diarrhea and constipation. The most concerning side effect includes bone marrow suppression, predominantly leukopenia (Luzzati *et al.*, 1998). There are a few studies which show minimal efficacy (Hellinger *et al.*, 2000; Havlir *et al.*, 2000), and one recent report on toxicity including pancreatitis and death (Havlir *et al.*, 2000). The usual dose is 500 mg given twice daily.

Interleukin 2 has been studied extensively in the treatment of HIV. It has no activity against HIV but it activates dormant CD4 cells. The benefit of activating these cells is two fold. An increase in CD4 cells would theoretically bolster the immune system as well as activate dormant virus which would then be killed by the antiretrovirals being concurrently used (Williams 1998; Chun *et al.*, 1999). Interleukin 2 is given subcutaneously. Its common adverse effects are fevers, chills, rigors, sweats, muscle and joint pains and vomiting (45%). Elevated bilirubin, stomatitis and hypotension occurred in 7% of patients (Arno *et al.*, 1999).

Under investigation at present is an agent called T-20. This is a fusion inhibitor which binds the gp 41 which is a surface glycoprotein of the virus. When the CD4 and the viral gp 120 bind, the gp 41 acts like a drill that injects the viral genetic materials into the CD4 cell. By binding the gp 41, the virus is unable to enter the host cell. There are multiple studies underway looking at its efficacy and tolerability (Kilby *et al.*, 1998). It will most likely be available in 2001.

Treatment Options

It was clear early in the HIV epidemic that the etiology of the immune deficiency was a result of the loss of the CD4 cells. It was shown very nicely by multiple investigators that the best predictor of the CD4 decline and thus the progression to AIDS and AIDS related illnesses was the amount of virus replicating. The amount of virus could be checked by measuring the amount of RNA in the blood. Furthermore, the virus reaches a set point where a steady amount of virus is replicated each day. This set point is directly related to the rate of progression to AIDS (Saksela *et al.*, 1995; Mellors *et al.*, 1996; Saag *et al.*, 1996; Hughes *et al.*, 1997; Mellors *et al.*, 1997; OBrien *et al.*, 1997; Vlahov *et al.*, 1998; Yerly *et al.*, 1998; Miller *et al.*, 1999).

There are currently two types of tests to quantify amount of virus present in a patients blood. These include PCR and branched chain DNA. The PCR test is done by amplifying the RNA present in the blood. This test is sensitive to a lower limit of fifty copies (Van Gemen *et al.*, 1994). The branched chain DNA test is not as sensitive with a lower level of detection of five hundred. The results are not interchangeable between the two tests. They are roughly twice as high using the branched chain

DNA test when compared to the PCR (Pachl *et al.*, 1995).

Based on the premise that the lower the viral RNA, the slower the progression to AIDS and death, it was believed that antiretrovirals could be used to decrease the viral set point and slow the progression of the disease. This goal was not attainable for long periods of time by using any one drug or two drugs, but has been accomplished with the use of three agents. In studies where 2 NRTIs are used in combination with a PI, 2 PIs or an NNRTI, the ability to decrease viral load and obtain durability of this goal were shown (Collier *et al.*, 1996; DAquila *et al.*, 1996; Hammer *et al.*, 1997; Gulick *et al.*, 1997; Gulick *et al.*, 1998; Montaner *et al.*, 1998; Murphy *et al.*, 1999; Staszewski *et al.*, 1999). There have been studies that have shown two PI's used alone could accomplish this goal as well (Moyle *et al*, 2000). Survival benefit has only been shown by using PIs in combination with 2 NRTIs (Cameron *et al.*, 1998). As of yet, NNRTI studies have not been shown to increase survival. In addition, the response to therapy only occurs when maximum suppression is being used. In two studies where medications were decreased in number, the viral load increased and failure occurred (Havlir *et al.*, 1998; Pialoux *et al.*, 1998). These results tell us that all medicines must be continued as long as therapy is administered.

With the knowledge that the antiretrovirals available at this time can prolong life and decrease the progression to AIDS, therapy appears to be very promising. However these medicines carry a significant cost, high risk of complications and cannot cure HIV infection (Pomerantz, 1998). There are many ways to approach therapy, thus guidelines for the use of antiretroviral therapy have been published (DHHS, 2000).

The first question in antiretroviral therapy is when should therapy be initiated. There is no clear answer. Most importantly, however, is the patient must be willing to take medicines for a long time and be very compliant. Antiretroviral therapy should be recommended if any of the following are present.

1. CD4 count < 500.
2. HIV RNA >10-20,000.
3. Opportunistic Infection
4. Symptomatic disease such as thrush or unexplained fever.

However, antiretroviral therapy can be justified at any stage of HIV infection. Although all patients could be expected to benefit from antiretroviral therapy, the need to begin treatment can be viewed as a continuum. Patients with low CD4 counts and high viral loads are in need of immediate and aggressive therapy. Therapy is less urgent and more optional for patients with low viral loads and high CD4 cell counts (DHHS, 2000). There are significant disadvantages that patients and clinicians must be aware of, especially when early intervention is being considered. Patients beginning antiretroviral therapy are committing themselves to lifelong polypharmacy, with its associated costs, inconvenience and significant side effects. Also, treating early could compromise patients' ability to benefit from future therapies when resistance develops (DHHS, 2000). On the other hand, there has been a recent study which has shown that the lower the CD4 count nadir before antiretroviral therapy, the higher the morbidity and mortality even after they reach a similar CD4 count as one who had a higher nadir CD4 count (Miller *et al.*, 1999). Thus the rate of decline of CD4 counts should be another feature in the decision making process of initiating antiretroviral therapy.

Once the decision to start therapy is made, the next question is to decide what medications to initiate. Goals of therapy include maximal and durable suppression of virus, restoration of immune function, improvement of quality of life and reduction of HIV related morbidity and mortality. To achieve this goal, adherence, rational sequencing of drugs, preservation of future options and use of resistance testing must be considered. Based on available data from clinical trials, two NRTIs in addition to either efavirenz, indinavir, nelfinavir or saquinavir/ritonavir should be used as first line agents. Further details of these regimens

Table IV. Strongly Recommended Antiretroviral Regimens–1 From Column A+1 From Column B

NRTI	Potent Arm
Zidovudine/Lamivudine	Nelfinavir
Zidovudine/Didanosine	Indinavir
Zidovudine/Zalcitabine	Saquinavir/Ritonavir
Stavudine/Didanosine	Efavirenz
Stavudine/Lamivudine	

Table V. Antiretroviral Recommendations- Alternative regimens

Potent Arm	Reason
Ritonavir	Significant side effects
Saquinavir soft gel	Large number of pills
Amprenavir	Large number of pills
Nevirapine	Not compared to other 3 drug regimens
Delavirdine	Not compared to other 3 drug regimens
Abacavir	Not proven for high Viral loads

Table VI. Contraindicated combinations

Zalcitabine with didanosine, or stavudine	Toxicity
Zalcitabine with lamivudine	antagonistic
Stavudine with zidovudine	antagonistic
Two non-nucleoside reverse transcriptase inhibitors	antagonistic
Indinavir with saquinavir	antagonistic
Amprenavir with efavirenz	Pharmacokinetics

are in Table IV, V, and VI.

Once antiretroviral therapy is initiated, treatment must be monitored carefully. Evaluating efficacy is accomplished using CD4 counts and viral load. The viral load is used to monitor antiretroviral therapy and the CD4 count is used to monitor immune restoration and prophylaxis of opportunistic infections (OI's). The virologic goal is to suppress virus below the level of detection. Virologic response to antiretroviral therapy follows a 2 phase pattern. A quick drop of virus which is a result of the immediate destruction of circulating virus which takes approximately 4 to 8 weeks. This is followed by a second phase which is the slow decline of virus resulting from a turnover of slowly growing cells which can take up to 4 to 6 months. These times vary based on initial viral load (DHHS, 2000).

The CD4 counts are used to follow immune restoration. The CD4 counts increase in a 3 phase pattern which consists of a rapid increase during the first 3 weeks of suppressive therapy, a gradual increase for 72 weeks, then no further increase followed by stabilization (Nottermans *et al.*, 1999). The possible explanation for this pattern is the return of naive CD4 cells, followed by a slow recovery of memory helper cells (Nottermans *et al.*, 1999). The rate and degree of the CD4 response is variable. Some contributing factors noted include age, thymic activity, level of base line viral load and previous antiretroviral therapy (Sabin *et al.*, 2000).

If a person who is started on antiretroviral therapy does not respond as expected, then the medicines should be changed. If the viral load does not decrease by 0.5 log in 4 weeks or 1 log in 8 weeks; if viral load does not become undetectable in 6 months; if virus detection is noted after suppression was obtained; declining CD4 counts despite viral suppression; or clinical deterioration are noted, then change of therapy is indicated (DHHS, 2000).

When changing antiretroviral therapy, it is important to understand resistance patterns that occur and the options available for sequencing these medicines. There are two approaches that can be used, best guess based on previous experience with sequencing medicines or by using resistance testing (DHHS, 2000). Previous clinical experience has brought some clinical points to the forefront. When sequencing NRTI, the resistance patterns found suggest that these can be used in any combination or sequence with the following exceptions: zidovudine should not be combined with stavudine; zalcitabine should not be combined with stavudine, didanosine or lamivudine; abacavir is more likely to be effective if used early in a patient's therapy; and lamivudine causes a structural alteration in the reverse transcriptase increasing susceptibility to zidovudine (DHHS, 2000).

NNRTI cannot be sequenced, usually resistance is across the whole class of agents (DHHS, 2000).

PI's have the most complicated resistance patterns, but in general the following points can be made. Nelfinavir is not very effective in patients failing other PI's, therefore it is best used as the first PI. Following nelfinavir, all the other PIs are likely to be active. Indinavir and ritonavir are very similar in resistance patterns and could be included in the second protease regimens. Third protease regimens could either include amprenavir, lopinavir or the combination of ritonavir and saquinavir (Fatkenheuer *et al.*, 1999; Gallant 1999; Martinez-Picado *et al.*, 1999; Falloon *et al.*, 2000).

In addition to the above basics, there are two HIV resistance tests currently available to help in the sequencing of antiretrovirals. The first test made available was the genotypic resistance test which involves obtaining the virus from the individual in question and checking the genome for mutations. The results are reported to the physician as alterations of the protease and reverse transcriptase genes. It is up to the physician to decide if resistance is present based on known mutations conferring resistance (usually with the help of a chart with the mutations listed). This test has some faults including inability to detect small clones of viral mutations, long turn around time (2-4 weeks), and the difficulty in interpreting the test results (Hirsch *et al.*, 1998; Martinez-Picado and DAquila, 1998; Hanna and DAquila, 1999).

The other resistance test is the phenotypic test which involves obtaining the virus from the individual and growing it in vitro. The isolate is then tested against the antiretrovirals at varying concentrations followed by identifying growth. Unfortunately this takes a very long time to get results, it is very expensive, and also misses small clones of virus. The benefit of this test as compared to the genotype is interpretation is easier. It is still unclear how much of an increase of in vitro resistance indicates in vivo resistance (Hirsch *et al.*, 1998).

There have been 2 studies which show genotypic tests may be of benefit in people who have failed many regimens (Baxter *et al.*, 1999; Durant *et al.*, 1999). There is one study that showed the efficacy of phenotypic resistance in experienced patients (Cohen *et al.*, 2000). There are no studies yet addressing the use of these tests in the care of the naive patient. In addition, there is little information on the use of these two tests together, or if one is more efficacious than the other. The latest US DHHS guidelines from January 2000 recommend that genotypic testing be used when a regimen fails, or if a person does not respond as expected to a particular therapy (DHHS, 2000).

Special Considerations

Occupational exposure: These recommendations were published in the MMWR in May 15, 1998. Briefly, chemoprophylaxis is recommended based on the type of bodily fluids involved and the route and severity of exposure. For needle sticks with HIV infected blood, chemopro-

phylaxis is recommended. For low risk exposures such as mucous membrane involvement, chemoprophylaxis is considered. For negligible risk exposures such as blood contact with intact skin, chemoprophylaxis is not recommended. For human bites, if blood exposure is involved, consideration of chemoprophylaxis is recommended (CDC, 1998a; Gerberding 1996).

If chemoprophylaxis is used, it should be started within hours of the exposure. Animal studies suggest that post exposure prophylaxis is not effective if started after 24 to 36 h, however it should still be offered in that setting since there is no data in humans. The duration of therapy is not actually known, but 4 weeks is recommended. Choice of medications include lamivudine and zidovudine and the addition of a protease inhibitor in high risk exposure. However individualization is recommended based on the source patient's history of antiretrovirals and possible resistant patterns (CDC, 1998a; Gerberding 1996).

Non-occupational exposure: There is lack of efficacy data for the use of antiretroviral agents to reduce HIV transmission after a Non-occupational exposure. There are no recommendations for Non-occupational exposure prophylaxis. If this therapy is started, it probably should be limited to those who had unprotected receptive anal or vaginal intercourse with a KNOWN HIV positive person. The medicines should be the ones described in the last section (CDC, 1998b; Lurie *et al.*, 1998).

Care of the pregnant patient

There are no differences in recommendations for the care of the HIV infected pregnant woman as compared to other adults. However, the impact of therapy on the fetus is unknown. If a woman discovers she is HIV positive while pregnant, therapy might be delayed until after the first trimester, after the embryo is at greatest risk for teratogenic effects of the medicines. There is limited data on the effect of the antiretrovirals on humans. At present, didanosine, saquinavir, ritonavir, and nelfinavir are class B, while all others are class C (DHHS, 2000).

In addition to the care of the mother, is the prevention of transmission of the virus to the newborn. The risk of transmission from mother to child is about 15 to 35% (Pecham and Gibb, 1995). The timing of transmission of HIV is believed to be peripartum. In addition, multiple factors influence transmission of virus, they include maternal viral load, mode of delivery, low CD4 counts, chorioamnionitis, premature delivery and premature rupture of the placental barrier (Pecham and Gibb, 1995).

Multiple studies have been done addressing peripartum therapy and its effect on transmission of HIV. These studies look at the use of zidovudine at various doses and intervals at the time of delivery. Even though the timing is different, they all show significant decrease in transmission. These decreases in transmission range from 38% to 50% (Sperling *et al.*,1996; Mandelbrot *et al.*, 1998; Shaffer *et al.*, 1999; Wiktor *et al.*, 1999). The addition of zidovudine to the infant increased the reduction to 68% (Wade *et al.*, 1998). The other medication studied at the time of delivery, nevirapine given as 200 mg and then given to the neonate at birth (2mg/kg), showed similar efficacy as zidovudine (Guay *et al.*, 1999).

Mode of delivery has been evaluated as a factor in transmission as well. In one study in Europe, caesarean section decreased the risk of transmission by 60% in non treated mothers and by 30% in those receiving zidovudine (EMDC, 1999). It appears that caesarean section adds protective benefit to those mothers receiving zidovudine (IPHC, 1999).

Two studies address viral load in the mother as a factor in transmission. In these, undetectable viral load decreased the risk of transmission to nearly zero, and the need of caesarean section may not be needed in this setting (Mofenson, *et al.*, 1999; Garcia, *et al.*, 1999).

CONCLUSION

HIV medicine is an area which is continually changing and growing. The advances made in the last two decades have changed this disease from a certain death sentence to a chronic infection. Since patients will be on these medications for an extended period of time, side effects and complications of therapy will play more important roles in the future. The increase in glucose intolerance, lipid abnormalities and redistribution of lipids may lead to premature cardiovascular disease. In addition, resistance issues and loss of active agents effective in the treatment of HIV may occur.

Therefore, there will be a need for newer medications in the current three classes with better pharmacokinetics and safety profiles, as well as totally new classes. We have seen advances in development of compounds that are active against the chemokine receptors, the gp 41 protein, the enzyme integrase, and nucleotide analogues. We have also seen advances in newer protease inhibitors and reverse transcriptase inhibitors which could improve our treatment options as we enter the new millennium. However, we do not have a cure or a vaccine; we do know that the best approach is prevention of HIV infection.

These resources and technologies are available in North America and Western Europe. The antiretroviral medications as well as the supportive care necessary to treat this infection are not available in all areas of the world. We clearly are not making much of an impact in the spread of this infection in Sub Saharan Africa, Southeast Asia, India and the former Soviet Union. In order to contain this epidemic in the new millennium, we must get these resources to these countries.

REFERENCES

Acosta E. P., Page L. M., and Fletcher C. V. Clinical pharmacokinetics of zidovudine. *Clin. Pharmacokinet.*, 30, 251-262 (1996).

Adkins, J. C., and Faulds, D. Amprenavir. *Drugs*, 55, 837-842 (1998).

Adkins, J. C. and Noble, S. Efavirenz. *Drugs*, 56, 1055-1064 (1998).

Arno, A., Ruiz, L., Juan, M., Jou, A., Balague, M., Zayat, M. K., Marfil, S., Martinez-Picado, J., Martinez, M. A., Romeu, J., Pujol-Borrell, R., Lane, C., and Clotet, B. Efficacy of low-dose subcutaneous interleukin-2 to treat advanced human immunodeficiency virus type 1 in persons with <250/μl CD4 T cells and undetectable plasma virus load. *J. Infect. Dis.*, 180, 56-60 (1999).

Bartlett JA. Zalcitabine, p 49-59. In Dolin R, Masur H, and Saag MS (ed), *AIDS Therapy*. Churchill Livingstone, Philadelphia. (1999).

Baxter, J. D., Mayers, D. L., Wentworth, D. N., Neaton, J. D., and Merigan, T. C. A pilot study of the short-term effects of antiretroviral management based on plasma genotypic resistance testing (GART) in patients failing antiretroviral therapy. In: *6th Conference on Retroviruses and Opportunistic Infections*. Chicago: Abstract LB8, (1999).

Bernasconi, E. Metabolic effects of protease inhibitor therapy. *AIDS Reader* 9, 254-269 (1999).

Bossi, P., Colin, D., Bricaire, F., and Caumes, E. Hypersensitivity syndrome associated with efavirenz therapy. *Clin. Infect. Dis.*, 30, 227-228 (2000).

Cameron, D. W., Heath-Chiozzi, M., Danner, S., Cohen, C., Kravcik, S., Maurath, C., Sun, E., Henry, D., Rode, R., Potthoff, A., and Leonard, J. Randomized placebo-controlled trial of ritonavir in advanced HIV-1 disease. *Lancet*, 351, 543-549 (1998).

Carr, A., Samaras, K. Chisholm, D. J., and Cooper, D. A. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. Lancet, 352, 1881-1883 (1998).

CDC. Public Health Service guidelines for management of health-care worker exposures to HIV. *MMWR.*, 47, (RR-7), 1-28 (1998).

CDC. Public Health Service statement management of possible sexual, injecting-drug-use, or other Non-occupational exposure to HIV, Including considerations related to antiretroviral therapy. *MMWR.*, 47, (RR-17), 1-14 (1998).

Chun, T. W., Engel, D., Mizell, S. B., Hallahan, C. W., Fischette, M., Park, S., Davey, R. T., Dybul, M., Kovacs, J. A., Metcalf, J. A., Mican, J. M., Berrey, M. M., Corey, L., Lane, H. C., and Fauci, A. S. Effect of Interleukin-2 on the pool of latently infected, resting CD4+ T cells in HIV-1-infected patients receiving highly active antiretroviral therapy. *Nature Med.*, 3, 651-655 (1999).

Cohen, C., Hunt, M., Sension, C., Farthing, C., Conant, M., Jacobson, S., Nadler, J., Verbiest, W., Hertogs, K., Ames, M., Rinehart, A., and Graham, N. Phenotypic resistance testing significantly improves response to therapy: a randomized trial (VIRA3001). Abstract *7th Conference on Retroviruses and Opportunistic Infections*, San Francisco, USA, (2000).

Collier, A. C., Coombs, R. W., Schoenffeld, D. A., Bassett, R. L., Timpone, J., Baruch, A., Jones, M., Facey, K., Whitacre, C., McAuliffe, V. J., Friedman, H. M., Merigan, T. C., Reichman, R. C., Hooper, C., and Corey, L. Treatment of human immunodeficiency virus infection with saquinavir, zidovudine, and zalcitabine. *N. Engl. J. Med.*, 334, 1011-1017 (1996).

DAquila, R. M., Hughes, M. D., Johnson, V. A., Fischl, M. A., Sommadossi, J. -P., Liou, S. -H., Timpone, J., Myers, M., Basgoz, N., Niu, M., and Hirsch, M. S. Nevirapine, zidovudine, and didanosine compared with zidovudine and didanosine in patients with HIV-1 infection. *Ann. Intern. Med.*, 124, 1019-1030 (1996).

Deeks, S., Brun, S., Xu, Y., Real, K., Benson, C., Kessler, H., Murphy, R., Wheeler, D., Hicks, C., Eron, J., Feinberg, J., Gulick, R., Glesby, M., Sax P., Stryker, R., Riddler, S., Thompson, M., King, M., Potthoff, A., Hsu, A., Bertz, R., Molla, A., Mo, H., Kempf, D., Japour, A., and Sun, E. ABT-378/ritonavir suppresses HIV RNA to <400 copies/ml in 86% of PI-experienced HIV+ patients at 48 weeks. Abstract *7th Conference on Retroviruses and Opportunistic Infections*, San Francisco, USA, (2000).

Demeter LM and Reichman RC. Delavirdine, p 97-105. In Dolin R, Masur H, and Saag MS (ed), *AIDS Therapy*. Churchill Livingstone, Philadelphia. (1999).

Detels, R., Munoz, A., McFarlane, G., Kingsley, L. A., Margolick, J. B., Giorgi, J., Schrager, L. K., and Phair, J. P. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. *JAMA.*, 280, 1497-1503 (1998).

Durant, J., Clevenbergh, P., Halfon, P., Delgludice, P., Porsin, S., Simonet, P., Montagne, N., Boucher, C. A. B., Schapiro, J. M., and Dellamonica, P. Drug resistance genotypic in HIV-1 therapy: the VIRADAPT randomized controlled trial. *Lancet*, 353, 2195-2199 (1999).

European mode of delivery collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomized clinical trial. *Lancet*, 353, 1035-1039 (1999).

Falloon, J., Piscitelli, S., Vogel, S., Sadler, B., Mitsuya, H., Kavlick, M. F., Yoshimura, K., Rogers, M., LaFon, S., Manion, D. J., Lane, C., and Masur, H. Combination therapy with amprenavir, abacavir, and efavirenz in human immunodeficiency virus (HIV)-infected patients failing a protease-inhibitor regimen: pharmacokinetic drug interactions and antiviral activity. *Clin. Infect. Dis.*, 30, 313-318 (2000).

Fatkenheuer, G., Hoetelmans, R. M., Hunn, N., Schwenk,

A., Franzen, C., Reiser, M., Jutte, A., Rockstroh, J., Diehl, V., and Salzberger, B. Salvage therapy with regimens containing ritonavir and saquinavir in extensively pretreated HIV-infected patients. *AIDS*, 13, 1485-1489 (1999).

Fischl, M. A. Zidovudine, p17-31. In Dolin R, Masur H, and Saag MS (ed), AIDS Therapy. Churchill Livingstone, Philadelphia. (1999).

Flexner, C. HIV-protease inhibitors. *N. Engl. J. Med.*, 338, 1281-1292 (1998).

Folks, T. M., and Hart, C. E. The life cycle of human immunodeficiency virus type 1, p 29-44. In DeVita Jr VT, Hellman S and Rosenberg SA (ed), AIDS. Lippincott-Raven Publishers, Philadelphia. (1997).

Foster, R. H. and Faulds, D. Abacavir. *Drugs*, 55, 729-736 (1998).

Friedland, G. H., Pollard, R., Griffith, B., Hughes, M., Morse, G., Bassett, R., Freimuth, W., Demeter, L., Connick, E., Nevin, T., Hirsch, M., and Fischl, M. Efficacy and safety of delavirdine mesylate with zidovudine and didanosine compared with two-drug combinations of these agents in persons with HIV disease with CD4 counts of 100 to 500 cells/mm3. *J. AIDS*, 21, 281-292 (1999).

Gallant, J. E. Antiretroviral therapy in the treatment-experienced patient. *AIDS Reader*, 9, 284-291 (1999).

Garcia, P. M., Kalish, L. A., Pitt, J., Minkoff, H., Quinn, T. C., Burchett, S. K., Kornegay, J., Jackson, B., Moye, J., Hanson, C., Zorrilla, C., and Lew, J. F. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. *N. Engl. J. Med.*, 341, 394-402 (1999).

Gerberding, J. L. Prophylaxis for occupational exposure to HIV. *Ann. Intern. Med.*, 125, 497-501 (1996).

Guay, L. A., Musoke, P., Fleming, T., Bagenda, D., Allen, M., Nakabiito, C., Sherman, J., Bakaki, P., Ducar, C., Deseyve, M., Emel, L., Mirochnick, M., Fowler, M. G., Monfenson, L., Mioti, Paolo, Dransfierld, K., Bray, D., Mmiro, F., and Jackson, J. B. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomized trial. *Lancet*, 354, 795-802 (1999).

Gulick, R. M., Mellors, J. W., Havlir, D., Eron, J. J., Gonzalez, C., McMahon, D., Richman, D. D., Valentine, F. T., Jonas, L., Meibohm, A., Emini, E. A., and Chodakewitz, J. A. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N. Engl. J. Med.*, 337, 734-739 (1997).

Gulick, R. M., Mellors, J. W., Havlir, D., Eron, J. J., Gonzalez, C., McMahon, D., Jonas, L., Meibohm, A., Holder, D., Schleif, W. A., Condra, J. H., Emini, E. A., Isaacs, R., Chodakewitz, J. A., and Richman, D. D. Simultaneous vs sequential initiation of therapy with indinavir, zidovudine, and lamivudine for HIV-1 infection. *JAMA.*, 280, 35-41 (1998).

Gulick, R., King, M., Brun, S., Real, K., Murphy, R., Hicks, C., Eron, J., Thommes, J., Glesby, M., Thompson, M., White, C., Benson, C., Albrecht, M., Kessler, H., Hsu, A., Bertz, R., Kempf, D., Sun, E., and Japour, A. ABT-378/ritonavir in antiretroviral-naive HIV+ patients: 72 weeks. Abstract *7th Conference on Retroviruses and Opportunistic Infections*, San Francisco, USA, (2000).

Hammer, S. M., Squires, K. E., Hughes, M. D., Grimes, J. M., Demeter, L. M., Currier, J. S., Eron, J. J., Feinberg, J. E., Balfour, H. H., Deyton, L. R., Chodakewitz, J. A. and Fischl, M. A. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N. Engl. J. Med.*, 337, 725-733 (1997).

Hanna, G. J., and DAquila, R. T. Antiretroviral drug resistance in HIV-1 *Cur. Infect. Dis. Rep.*, 1, 289-297 (1999).

Haubrich, R. H., and Havlir, D. Nelfinavir p 177-187. In Dolin R, Masur H, and Saag MS (ed), *AIDS Therapy*. Churchill Livingstone, Philadelphia. (1999).

Havlir, D., Gilbert, P., Bennett, K., Collier, A., Hirsch, M., Tebas, P., Adams, E., Goodwin, D., Schnitman, S., Holohan, M. K., and Richman, D. Randomized trial of continued indinavir (IDV)/Zidovudine/3TC vs. switch to IDV/ddI/d4T or IDV/ddI/d4T+hydroxyurea in patients with viral suppression. Abstract *7th Conference on Retroviruses and Opportunistic Infections*, San Francisco, USA, (2000).

Havlir, D. V., Marschner, I. C., Hirsch, M. S., Collier, A. C., Tebas, P., Bassett, R. L., Ioannidis, J. P. A., Holohan, M. K., Leavitt, R., Boone, G., Richman, D. D. Maintenance antiretroviral therapies in HIV-infected subjects with undetectable plasma HIV RNA after triple-drug therapy. *N Engl. J. Med.*, 339, 1261-1268 (1998).

Hellinger, J. A., Iwane, M. K., Smith, J. J., Fleishman, A. N., Torres, R. A., Schrader, S., Perez, G., Cohen, C. J., Skowron, G., Giordano, M. F., Accetta, G., Cooper, E. C., and Froxt, K. R. A randomized study of the safety and antiretroviral activity of hydroxyurea combined with didanosine in persons infected with human immunodeficiency virus type 1. *J. Infect. Dis.*, 181, 540-547 (2000).

Hilts, A. E., and Fish, D. N. Dosage adjustment of antiretroviral agents in patients with organ dysfunction. Am. J. Health-Syst. Pharm., 55, 2528-2533 (1998).

Hirsch, M. S. Azidothymidine. *J. Infect. Dis.*, 157, 427-430 (1998).

Hirsch, M. S., Conway, B., DAquila, R. T., Johnson, V. A., Brun-Vezitet, F., Clotet, B., Demeter, L. M., Hammer, S. M., Jacobsen, D. M., Kuritzkes, D. R., Loveday, C., Mellors, J. W., Vella, S., and Richman, D. D. Antiretroviral drug resistance testing in adults with HIV infection. *JAMA.*, 279, 1984-1991 (1998).

Hsu, A., Granneman, R., and Bertz, R. J. Ritonavir: Clinical pharmacokinetics and interactions with other anti-HIV agents. *Clin. Pharmacokinet.*, 35, 275-291 (1998).

Hsu, A., Granneman, G. R., Cao, G., Carothers, L., El-Shourbagy, T., Baroldi, P., Erdman, K., Brown, F., Sun, E., and Leonard, J. M. Pharmacokinetic interactions between two human immunodeficiency virus protease inhibitors, ritonavir and saquinavir. *Clin. Pharm. Ther.*, 63, 453-464 (1998).

Hurst, M., and Noble, S. Stavudine: an update of its use in the treatment of HIV infection. Drugs, 58, 919-949 (1998).

Hughes, M. D., Johnson, V. A., Hirsch, M. S., Bremer, J. W., Elbeik T., Erice, A., Kuritzkes, D. R., Scott, W. A., Spector, S. A., Basgoz, N., Fischl, M. A., and D'Aquila, R. T. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. *Ann. Intern. Med.*, 126, 929-938 (1997).

The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1. *N. Engl. J. Med.*, 340, 977-987 (1999).

Jarvis, B., and Faulds, D. Nelfinavir a review of its therapeutic efficacy in HIV infection. *Drugs*, 56, 147-167 (1998).

Katlama, C. and Havlir, D.V. Newer nucleosides: lamivudine and stavudine. *AIDS*, 10, (supple A), S135-S143 (1996).

Kilby, J. M., Hopkins, S., Venetta, T. M., DiMassimo, B., Cloud, G. A., Lee, J. Y., Alldredge, L., Hunter, E., Lambert, D., Bolognesi, D., Matthews, T., Johnson, M. R., Nowak, M. A., Shaw, G. M., and Saag, M. S. Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry. *Nature Med.*, 4, 1302-1307 (1998).

Lea, A. P., and Faulds, D. Ritonavir. *Drugs*, 52, 541-546 (1996).

Ledergerber, B., Egger, M., Erard, V., Weber, R., Hirschel, B., Furrer, H., Battegay, M.,Vernazza, P., Bernasconi, E., Opravil, M., Kaufmann, D., Sudre, P., Francioli, P., and Telenti, A. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy. *JAMA.*, 282, 2220-2226 (1999).

Lurie, P., Miller, S., Hecht, F., Chesney, M., and Lo, B. Postexposure prophylaxis after Non-occupational HIV exposure. *JAMA.*, 280, 1769-1773 (1998).

Luzzati, R., DiPerri, G., Fendt, D., Ramarli, D., Broccali, G., and Concia, E. Pharmacokinetics, safety, and anti-human immunodeficiency virus activity of hydroxyurea in combination with didanosine. *J. Antimicrob. Chemother.*, 42, 565-566 (1998).

Mandelbrot, L., LeChenadec, J., Berrebi, A., Bongain, A., Benifla, J. -L., Delfraissy, J. -F., Blanche, S., and Mayaux, M. -J. Perinatal HIV-1 transmission- interaction between zidovudine prophylaxis and mode of delivery in the french perinatal cohort. *JAMA.*, 280, 55-60 (1998).

Martinez-Picado, J., and DAquila, R. HIV-1 drug resistance assays in clinical management. *AIDS. Clin. Care*, 10, 81-88 (1998).

Martinez-Picado, J., Savara, A. V., Sutton, L., and DAquila, R. T. Replicative fitness of protease inhibitor-resistant mutants of human immunodeficiency virus type 1. *J. Virol.*, 73, 3744-3752 (1999).

McDowell, J. A., Chittick, G. E., Ravitch, J. R., Polk, R. E., Kerkering, T. M., and Stein, D. S. Pharmacokinetics of abacavir, a human immunodeficiency virus type 1 reverse transcriptase inhibitor, administered in a single oral dose to HIV-1-infected adults: a mass balance study. *Antimicrob. Agents. Chemother.*, 43, 2855-2861 (1999)

Mellors, J. W., Munoz, A., Giorgi, J. V., Margolick, J. B., Tassoni, C. J., Gupta, P., Kingsley, L. A., Todd, J. A., Saah, A. J., Detels, R., Phair, J. P., Rinaldo, C. R. Plasma viral load and CD4+ Lymphocytes as prognostic markers of HIV-1 infection. *Ann. Intern. Med.*, 126: 946-954 (1997).

Mellors, J. W., Rinaldo, C. R., Gupta, P., White, R. M., Todd, J. A. and Kingsley, L. A. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science*, 272, 1167-1170 (1996).

Miller, V., Mocroft, A., Reiss, P., Katlama, C., Papadopoulos, A. I., Katzenstein, T., Van Lunzen, J., Antunes, F., Phillips, A. N., and Lundgren, J. D. Relations among CD4 lymphocyte count nadir, antiretroviral therapy, and HIV-1 disease progression: results from the EuroSIDA study. *Ann. Intern. Med.*, 130, 570-577 (1999).

Miller, V., Staszewski, S., Boucher, C. A., and Phair, J. P. Clinical experience with non-nucleoside reverse transcriptase inhibitors. *AIDS*, 11, (suppl A), S157-S164 (1997).

Mocroft, A., Youle, M., Phillips, A. N., Halai, R., Easterbrook, P., Johnson, M. A. and Gazzard, B. The incidence of AIDS-defining illnesses in 4883 patients with human immunodeficiency virus infection. *Arch. Intern. Med.*, 158, 491-497 (1998).

Mofenson L. M., Lambert, J. S., Stiehm, E. R., Bethel, J., Meyer III, W. A., Whitehouse, J., Moye Jr, J., Reichelderfer, P., Harris, D. R., Fowler, M. G., Mathieson, B. J., and Nemo, G. J. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. *N. Engl. J. Med.*, 341, 385-393 (1999).

Montaner, J. S. G., Reiss, P., Cooper, D., Vella, S., Harris, M., Conway, B., Wainberg, M. A., Smith, D., Robinson, P., Hall, D., Myers, M., and Lange, J. M. A. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients. *JAMA.*, 279, 930-937 (1998).

Moyle, G., Pozniak, A., Opravil, M., Clumeck, N., DelFraissy, J. -F., Johnson, M., Pelgrom, J., Reynes, J., Vittecoq, D., DeLora, P., Salgo, M., and Duff, F. The SPICE study: 48-

week activity of combinations of saquinavir soft gelatin and nelfinavir with and without nucleoside analogues. *J. AIDS*, 23, 128-137 (2000).

Murphy, R. L., Gulick, R. M., DeGruttola, V., D'Aquila, R. T., Eron, J. J., Sommadossi, J. -P., Currier, J. S., Smeaton, L., Frank, I., Caliendo, A. M., Gerber, J. G., Tung, R., Kuritzkes, D. R. Treatment with amprenavir alone or amprenavir with zidovudine and lamivudine in adults with human immunodeficiency virus infection. *J. Infect. Dis.*, 179, 808-816 (1999).

Nottermans, D. W., Pakker, N. G., Hamann, D., Foudraine, N. A., Kauffmann, R. H., Meenhorst, P. L., Goudsmit, J., Roos, M. T. L., Schellekens, P. T. A., Miedema, F., and Danner, S. A. Immune reconstitution after 2 years of successful potent antiretroviral therapy in previously untreated human immunodeficiency virus type 1-infected adults. *J. Infect. Dis.*, 180, 1050-1056 (1999).

OBrien, W. A., Hartigan, P. M., Daar, E. S., Simberkoff, M. S., and Hamilton, J. D. Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. *Ann. Intern. Med.*, 126, 939-945 (1997).

Pachl, C., Todd, J. A., and Kern D. G. Rapid and precise quantification of HIV-1 RNA in plasma using a branched DNA signal amplification assay. *J. AIDS*, 8, 446-454 (1995).

Palella, F. J., Delaney, K. M., Moorman, A. C., Loveless, M. O., Fuhrer, J., Satten, G. A., Aschman, D. J., and Holmberg, S. D. Declining morbidity and mortality among patients with advanced human immunode-ficiency virus infection. *N. Engl. J. Med.*, 338, 853-60 (1998).

Panel on clinical practices for the treatment of HIV infection-Department of Health and Human Services. *Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents.* (2000).

Peckham, C., and Gibb, D. Mother-to-child transmission of the human immunodeficiency virus. *N. Engl. J. Med.*, 333, 298-302 (1995).

Perry, C. M. and Faulds, D. Lamivudine: a review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in the management of HIV infection. *Drugs*, 1997;53:657-680.

Perry, C. M. and Noble, S. Didanosine: An updated review of its use in HIV infection. *Drugs*, 58, 1099-1135 (1999).

Perry, C. M., and Noble, S. Saquinavir soft-gel capsule formulation a review of its use in patients with HIV infection. *Drugs*, 55, 461-486 (1998).

Pialoux, G., Raffi, F., Brun-Vezinet, F., Meiffredy, V., Flandre, P., Gastaut, J. -A., Dellamonica, P., Yeni, P., Delfraissy, J. -F., and Aboulker, J. -P. A randomized trial of three maintenance regiments given after three months of induction therapy with zidovudine, lamivudine, and indinavir in previously untreated HIV-1-infected patients. *N. Engl. J. Med.*, 339, 1269-1276 (1998).

Plosker, G. L., and Noble, S. Indinavir: a review of its use in the management of HIV infection. *Drugs*, 58, 1165-2003 (1999).

Pollard, R. B., Robinson, P., and Dransfield, K. Safety profile of nevirapine, a nonnucleoside reverse transcriptase inhibitor for the treatment of human immunodeficiency virus infection. *Clin. Therap.*, 20, 1071-1092 (1998).

Pomerantz, R. J. How HIV Resists Eradication. *Hosp. Pract.*, 87-101 (1998).

Provisional Report: The status and trends of the HIV/AIDS epidemics in the world. Monitoring the AIDS pandemic (MAP) network, (1998).

Rana, K. Z., and Dudley, M. N. Clinical pharmacokinetics of stavudine. *Clin. Pharmacokinet.*, 33, 276-284 (1997).

Saag, M. S., Holodniy, M., Kuritzkes, D. R., O'Brien, W. A., Coobs, R., Poscher, M. E., Jacobsen, D. M., Shaw, G. M., Richman, D. D., and Volberding, P. A. HIV viral load markers in clinical practice. *Nature Med.*, 6, 625-629 (1996).

Sabin, C., Staszewski, S., Phillips, A. Rabenau, H., Cozzi Lepri, A., Weidman, E., and Miller, V. Discordant immnological and virological responses to HAART. Abstract *7th Conference on Retroviruses and Opportunistic Infections*, San Francisco, USA, (2000).

Saksela, K., Stevens, C. E., Rubinstein, P., Taylor, P. E., and Baltimore, D. HIV-1 messenger RNA in peripheral blood mononuclear cells as an early marker of risk for progression to AIDS. *Ann. Intern. Med.*, 123, 641-648 (1995).

Shaffer, N., Chuachoowong, R., Mock, P. A, Bhadrakom, C., Siriwasin, W., Young, N. L., Chotpitayasunoundh, T., Chearskul, S., Roongpisuthipong, A., Chinayon, P., Karon, J., Mastro, T. D., and Simonds, R. J. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomized controlled trial. *Lancet*, 353, 773-780 (1999).

Sham, H. L., Kempf, D. J., Molla, A., Marsh, K. C., Kumar, G. N., Chen, C. -M., Kati, W., Stewart, K., Lal, R., Hsu, A., Betebenner, D., Korneyeva, M., Vasavanonda, S., McDonald, E., Saldivar, A., Wideburg, N., Chen, X., Niu, P., Park, C., Jayanti, V., Grabowski, B., Granneman, C. R., Sun, E., Japour, A. J., Leonard, J. M., Plattner, J. J., and Norbeck, D. W. ABT-378, a highly potent inhibitor of the human immunodeficiency virus protease. *Antimicrob. Agents Chemother.*, 42, 3218-3224 (1998).

Sherman, D. S., and Fish, D. N. Hydroxyurea in the treatment of HIV infection. *AIDS. Reader*, 9, 18-19,23-24 (1999).

Sperling, R.S., Shapiro, D. E., Coombs, R. W., Todd, J. A., Herman, S. A., McSherry, G. D., O'Sullivan, M. J., Van Dyke, R. B., Jimenez, E., Rouzioux, C., and Flynn, P M. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. *N. Engl. J. Med.*, 335, 1621-1629 (1996).

Staszewski, S., Morales-Ramirez, J., Tashima, K. T., Rachlis,

A., Skiest, D., Stanford, J., Stryker, R., Johnson, P., Labriola, D. F., Farina, D., Manion, D. J., and Ruiz, N. M. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N. Engl. J. Med.*, 341, 1865-1873 (1999).

The status and trends of the HIV/AIDS epidemics of Asia and the Pacific: final report. Monitoring the AIDS pandemic (MAP) network, October (1997).

UNAIDS: *AIDS epidemic update*. December (1998).

UNAIDS/WHO. *Report on the Global HIV/AIDS Epidemic*. June (1998).

Van Gemen, B., Van Beuningen, R., and Nabbe A. A one tube quantitative HIV-1 RNA NASBS nucleic acid amplification assay using electrochemiluminescent (ECL) labeled probes. *J. Virolog., Meth.*. 49, 157-168 (1994).

Vella, S., and Floridia, M. Saquinavir: Clinical pharmacology and efficacy. *Clin. Pharmacokinet.*, 34, 189-201 (1998).

Vlahov, D., Graham, N., Hoover, D., Flynn, C., Bartlett, J. G., Margolick, J. B., Lyles, C. M., Nelson, K., E., Smith, D., Holmberg, S., and Farzadegan, H. Prognostic indicators for AIDS and infectious disease death in HIV-infected injection drug users- plasma viral load and CD4+ cell count. *JAMA.*, 279, 35-40 (1998).

Wade, N. A., Birkhead, G. S., Warren, B. L., Charbonneau, T. T., French, T., Wang, L., Baum, J. B., Tesoriero, J. M., and Savicki, R. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N. Engl. J. Med.*, 339, 1409-1414 (1998).

Wiktor S. Z., Ekpini, E., Karon, J. M. Nkengasong, J., Maurice, C., Severin, S. T., Roels, T. H., Kouassi, M. K., Lackritz, E. M., Goulibaly, I. -M., and Greenberg, A. E. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote dlvoire: a randomized trial. *Lancet*, 353, 781-785 (1999).

Williams, N. Can IL-2 smoke out HIV reservoirs. *Science*, 282, 1394-1395 (1998).

Wolbach, J. and Capoccia, K. A review of abacavir and efavirenz: new antiretroviral drugs to treat HIV-1 infection. *Nurse Practitioner*, 24, 81-92 (1999).

Yerly, S., Perneger, T. V., Hirschel, B., Dubuis, O., Matter, L., Malinverni, R., Furrer, H., and Perrin, L. A critical assessment of the prognostic value of HIV-1 RNA levels and CD4+ cell counts in HIV-infected patients. *Arch. Intern. Med.*, 158, 247-252 (1998).