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Antiretroviral Therapy 2006: Pharmacology, Applications, and Special Situations

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As we approach the completion of the first 25 years of the human immunodeficiency virus (HIV) epidemic, there have been dramatic improvements in the care of patients with HIV infection. These have prolonged life and decreased morbidity. There are twenty 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. We have included a section addressing common comorbid conditions including hepatitis B and C along with tuberculosis.

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

INTRODUCTION

As we approach the completion of the first 25 years of the HIV epidemic, we have seen profound outcome improvements in people with this infection. The reasons include better understanding of the disease, earlier diagnosis, better therapies for HIV, as well as better prophylaxis and treatment of opportunistic infections (Detels, 1998; Mocroft, 1998; Ledergerber, 1999). Over the last decade, the implementation of antiretroviral therapy has dramatically reduced mortality and morbidity. Patients with "end stage" disease had mortality rates decreased four fold and morbidity rates reduced almost eight fold (Palella, 1998).

However, we are not seeing these trends across the world (UNAIDS/WHO, 2006). These improvements are only seen predominantly in North America and Western Europe. The estimated number of people living with HIV at the end of 2005 in North America and Western Europe is only 1.9 million, while there are 40.3 million living with HIV around the world. The HIV epidemic is devastating the social and economic cultures of Sub Saharan Africa, where 25.8 million individuals are infected (UNAIDS/WHO, 2006). The rates are increasing at an alarming rate in Asia including Thailand, India, and the former Soviet Union countries where 9.8 million people are currently living with HIV (UNAIDS/WHO, 2006). Although there has been an increase in the care given in these countries, there is still a significant lack of resources available to deliver care in these countries.

Since this topic was last reviewed in 2000 (Samuel and Suh, 2000), a vast amount of advancements in antiretroviral therapy was achieved. We therefore 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. In addition we will discuss co-infections with hepatitis B, hepatitis C and tuberculosis.

HIV life cycle

HIV is a retrovirus, which is so named because its genetic information is encoded by RNA rather than DNA. The virus enters the host cell by binding to the CD4 receptor and either the CCR5 or CXCR4 co-receptor. It then binds the gp 41 protein that 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

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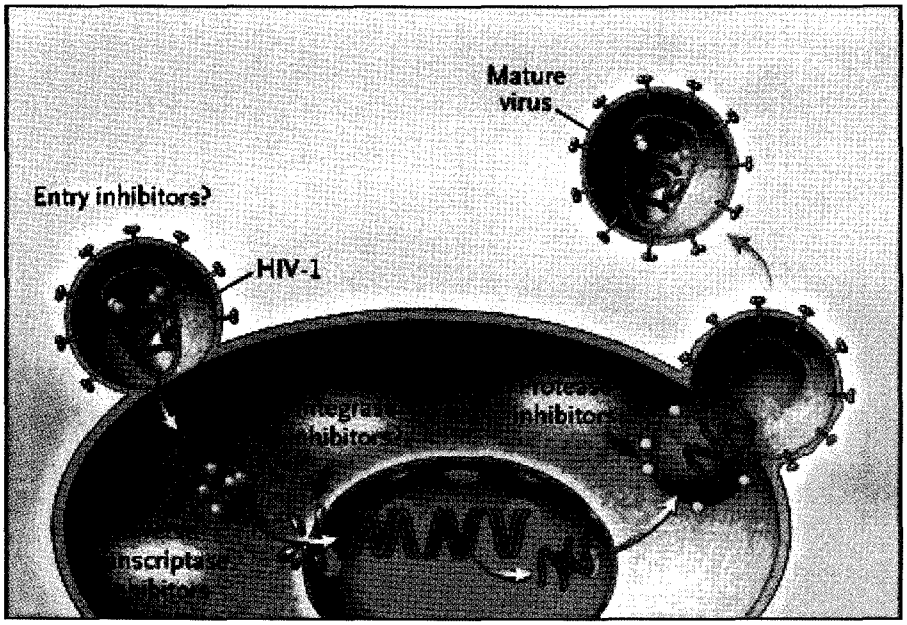

Fig. 1. HIV-1 binds to receptors on the cell surface, undergoes membrane fusion, and then releases copies of the RNA genome into the cytoplasm. After successful invasion of the cell, the viral reverse-transcriptase enzyme transcribes single-stranded viral RNA into double-stranded DNA that can be integrated into the genetic material of the human host. The viral integrase enzyme is required for the integration of proviral DNA into the host genome before replication. When the infected cell synthesizes new protein, integrated proviral DNA is also translated into the protein building blocks of new viral progeny. The viral components then assemble on the cell surface and bud out as immature viral particles. The final maturation of newly formed viruses requires the HIV-1 protease to digest larger components into the intricate pieces that make up an infectious virion. (Reprinted and adapted from Kilby and Eron, 2003).

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) (Fig. 1).

The nucleoside reverse transcriptase inhibitors (NRTI)

NRTI are nucleoside analogs that become phosphorylated by the host enzymes. After phosphorylation, they are incorporated into the newly forming viral DNA. Transcription ceases, thus halting replication of virus before it incorporates into the host genome. There are seven currently available NRTI's: zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and emtricitabine (Table I). There are currently 3 nucleoside combination tablets (zidovudine/lamivudine; zidovudine/lamivudine/abacavir; abacavir/lamivudine) and one combination nucleoside/nucleotide tablet (tenofovir/emtricitabine).

Zidovudine (Retrovir), the first antiretroviral agent, was 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, 1996). Common toxicities seen with zidovudine include headache, fatigue, malaise, myalgia, anorexia, nausea, anemia and neutropenia. Chronic toxicities include nail hyperpigmentation, hepatotoxicity, and muscle toxicity (Fischl, 1999). The usual dose is 300 mg twice daily (Hilts and Fish, 1998). Zidovudine is now available as a generic formulation.

Didanosine (Videx) is an inosine analog approved in 1991. It is highly acid labile, and is degraded rapidly in acid pH. The original preparation that was buffered with calcium carbonate and magnesium hydroxide is no longer being manufactured. Its newer formulation is an enteric capsule, which is much better tolerated than the original formulation. 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 that occurs in 4 to 7% of patients. The usual dose is 400 mg daily (Perry and Noble, 1999). Didanosine is currently available as a generic.

Didanosine has a few interactions worth noting. Because of lactic acidosis, pancreatitis and neuropathy, this agent should not be administered with stavudine, especially in pregnant individuals (Bonnett *et al.*, 2003). Didanosine has an interaction with tenofovir that is important to note as well. Didanosine levels are increased

Table I. Currently available Nucleoside Reverse Transcriptase Inhibitors

Generic Names	Abbreviated Names	Brand Names	Dosage	Comments
Zidovudine	AZT	Retrovir	300 mg twice daily	Headache, fatigue, anemia, leukopenia
Didanosine	ddI	Videx	400 mg once daily	Pancreatitis, neuropathy
Zalcitabine	ddC	Hivid	0.375 mg three times daily	Neuropathy, stomatitis
Stavudine	d4T	Zerit	40 mg twice daily	Neuropathy
Lamivudine	3TC	Epivir	150 mg twice daily or 300 mg once daily	No significant side effects
Abacavir	ABC	Ziagen	300 mg twice daily or 600 mg once daily	Hypersensitivity reaction
Tenofovir	TDF	Viread	300 mg once daily	
Emtricitabine	FTC	Emtriva	200 mg once daily	
Zidovudine/Lamivudine		Combivir	1 tablet twice daily	Lowers pill burden
Zidovudine/Lamivudine/Abacavir		Trizivir	1 tablet twice daily	Lowers pill burden
Abacavir/Lamivudine		Epzicom	1 tablet once daily	Lowers pill burden
Tenofovir/Emtricitabine		Truvada	1 tablet once daily	Lowers pill burden

by tenofovir, which requires decreasing the daily dose of didanosine to 250 mg once daily (Kearny *et al.*, 2004). In addition, this interaction allows didanosine to be given with food. Recently, the combination of tenofovir and didanosine has resulted in poor outcomes when used with efavirenz and is therefore not recommended to be used together (Maitland *et al.*, 2005). Also of note, the use of didanosine and tenofovir has resulted in decreased CD4 cell count when used in combination (Karrer *et al.*, 2005); therefore the use of didanosine, even when dose adjusted, must be used with caution when given with tenofovir.

Zalcitabine (Hivid) is a cytosine analog approved in 1992. It has a 70 to 90% bioavailability that is significantly decreased by food. It has a half-life of 1 to 3 h and is excreted unchanged by the kidneys. The most common toxicity is peripheral neuropathy, which may be seen in up to 23% of patients. Other less common toxicities include stomatitis (2 to 4%), rash and pancreatitis (1%). The usual dose is 0.375 mg three times daily (Bartlett, 1999). Production of this agent is going to be discontinued in 2006.

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. 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). As mentioned in the didanosine section, stavudine and didanosine should not be combined in the same regimen. Stavudine will soon become available in generic form.

Lamivudine (Epivir) is a synthetic analog of cytosine (similar to zalcitabine and emtricitabine) 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 except for rare pancreatitis and hepatitis. Mild toxicities including diarrhea, headache, fatigue, nausea and insomnia have been reported. Since lamivudine, emtricitabine and zalcitabine are cytosine analogs, they compete for phosphorylation and may be antagonistic (Katlama and Havlir, 1996). Although originally approved as a twice-daily agent, its pharmacokinetics allows it to be formulated as a 300 mg once daily agent (Bergshoeff *et al.*, 2005). Lamivudine will soon be available in generic formulation.

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 and its two main side effects, nausea and diarrhea, are self-limited. However, an important clinical side effect is the abacavir hypersensitivity reaction that occurs in 5-9% of patients. Manifestations occur at a mean of 11 days after initiating therapy. Findings include fever, rash, arthralgias and myalgias. A physician should verify that the symptoms are related to abacavir before discontinuing the drug. If the symptoms worsen as the medicine is continued, the drug should be discontinued by the physician after ascertaining that the symptoms are related to the abacavir. If re-challenged with the medication, a patient often develops much more severe symptoms that may include death (Hewitt, 2002). Therefore, once a rash and

flu-like symptoms develop in a patient on this medicine, it should be stopped and never re-introduced. The usual dose is 300 mg twice daily, but abacavir has recently been approved as a once daily 600 mg agent (Foster and Faulds, 1997; McDowell, 1999; Wolback and Capoccia, 1999).

Emtricitabine (Emtriva) is a cytosine analog approved in 2002. It is well absorbed, unaffected by food and has a half-life of 8-9 h. It is predominantly excreted in the urine. It is generally well tolerated with the main side effect being palmar discoloration. Mild toxicities including diarrhea, headache, fatigue, nausea and insomnia have been reported. Since this is a cytosine analog, it must not be combined with zalcitabine or lamivudine. It is given as 200 mg once daily (Saag, 2006).

The nucleotide reverse transcriptase inhibitors (NtRTI)

Tenofovir (Viread) (Table I) is currently the only nucleotide reverse transcriptase inhibitor and was approved in 2001. It is a monophosphorylated adenosine analog. It is well absorbed and its bioavailability is increased 40% when given with food. Its half-life is 17 h, which allows it to be administered once daily. It is cleared by the kidney. It is generally well tolerated but has mild side effects including diarrhea, and nausea (Gallant and Deresinski, 2003). Recently there have been reports of renal toxicity associated with this agent. These are not clearly defined but should warrant close monitoring of renal function (Malik *et al.*, 2005). It is given as 300 mg once daily.

Tenofovir has demonstrated drug interactions with other antiretrovirals. First, its interactions with didanosine are listed in the didanosine section. Second, its interactions with atazanavir are listed in the atazanavir section. Third, lopinavir/ritonavir increases the levels of tenofovir by 32% (Kearney *et al.*, 2003). Currently there is no recommendation to alter the dosing of either lopinavir/ritonavir or tenofovir when used together.

Nucleoside or nucleoside/nucleotide reverse transcriptase inhibitor combinations (Table I)

Zidovudine/lamivudine (Combivir) was approved in 1997. It is administered with 300 mg of zidovudine and 150 mg of lamivudine twice daily. Zidovudine/lamivudine/abacavir (Trizivir) was approved in 2001. It is administered with 300 mg of zidovudine, 150 mg of lamivudine and 300 mg of abacavir twice daily. Abacavir/lamivudine (Epzicom) was approved in 2004. It is administered as abacavir 600 mg and lamivudine 300 mg once daily. Tenofovir/emtricitabine (Truvada) was approved in 2004. It is administered as 300 mg of tenofovir and 200 mg of emtricitabine. These combination preparations are listed in Table I.

The non nucleoside reverse transcriptase inhibitors (NNRTI)

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

Nevirapine (Viramune), the first NNRTI, was 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 CYP-3A4 and induces its own metabolism. The main adverse event is rash which occurs in 16% of patients. The rash may be significant with Stevens-Johnson Syndrome being reported. Elevated liver enzymes including fulminant hepatic failure have been seen in less than 1.1% of patients. Recently, there have been recommendations to use nevirapine in women only if their CD4 counts are less than 250 or in men if their CD4 counts are less than 400. The change in recommendations is based on the hepatotoxicity noted with this agent. It is given 200 mg once daily and then increased to 200 mg twice a day after two weeks to decrease the likelihood of rash (Pollard, 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 is 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 maculopapular rash that occurs in 18 to 36% of patients. The rash occurs within 1 to 3 weeks and usually resolves without discontinuation of the drug (Friedland, 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

Table II. Currently Available Non-nucleoside Reverse Transcriptase Inhibitors

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

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 within 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, 2000). Efavirenz has been linked to neural tube defects in neonates after the mother was exposed to this agent. It is currently listed as a category D drug and therefore should not be used in women who are or may become pregnant (DHHS, 2005). The usual dose is 600 mg daily.

Currently under development is a co-formulation of efavirenz, tenofovir and emtricitabine. This would result in the first active antiretroviral combination given as one pill once daily. Also in development are newer NNRTI, which are active against virus resistant to currently approved NNRTI.

Protease inhibitors (PI)

Protease inhibitors (Table III) work by inhibiting proteolytic cleavage of structural proteins, which prevents the virus from maturing into an infectious virion. (Flexner, 1998; Clavel and Hance, 2004). Currently, there are 8 FDA approved protease inhibitors: saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, atazanavir, fosamprenavir, and tipranavir.

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 Fortovase). 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 hours and it is metabolized by the P-450 CYP-3A4. The most frequent side effects include diarrhea, nausea and headache (2 to 5%). In 2004, the hard gel (Invirase) was reformulated into a 500 mg tablet, to be taken with 100 mg of ritonavir within two hours of a meal. Due to the increased bioavailability with ritonavir boosting, this combination need only be taken twice daily (Dragsted, 2003). The soft gel capsule and the 200 mg hard gel formulation is to be discontinued.

Ritonavir (Norvir), the second PI, was 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). 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, 1998a). Due to its high incidence of side effects, this drug is rarely used at full dose. It is, however, used to boost the serum levels of other protease inhibitors due to its blockage of the CYP-3A4 enzyme (Cooper, 2003).

Indinavir (Crixivan), the third PI, was 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), the fourth PI, was approved in 1997. It is well absorbed and has no food interactions. Its half-life is 3.5 to 5 h. It is metabolized by the cytochrome P-450 CYP-3A4, as are other PI's, but it is also metabolized *via* the 2C19 (Kurowski, 2002). 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 original formulation of 250 mg tablets was given as five 250 mg tablets twice daily (Jarvis and Faulds, 1998; Haubrich and Havlir, 1999). It should be taken with food

Table III. Available Protease Inhibitors That Can be Given Without Ritonavir

Generic Name	Abbreviated Name	Brand Name	Dosage	P 450 Effect	Comments
Indinavir	IDV	Crixivan	800mg three times daily	++++	Must be taken on empty stomach and with 6 glasses of water
Nelfinavir	NFV	Viracept	1250 mg twice daily	+++	Can cause diarrhea
Fosamprenavir	fAPV	Lexiva	1400 mg twice daily	++++	Rash, diarrhea
Atazanavir	ATV	Reyataz	400 mg tablets once daily		Hyper-bilirubinemia No PPI or H2 blockers

(Jarvis, 1998). In 2004, the FDA approved a 625mg tablet formulation of nelfinavir to be taken as two pills twice daily.

Lopinavir/ritonavir (Kaletra) is a co-formulation of lopinavir and ritonavir that was originally approved in 2000. The level of lopinavir is nearly undetectable if given alone, but it is increased by 14 fold with the addition of ritonavir. Lopinavir/ritonavir was originally co-formulated as a capsule; however, it was discontinued after the 2005 approval of the lopinavir/ritonavir 200 mg/50 mg tablet. The tablet is well absorbed and is not affected by meals, but the oral solution should be taken with food. Lopinavir is metabolized by the P-450 CYP-3A4 (Sham, 1998). The most common side effects include diarrhea, nausea and abnormal stool (21%). The dose in treatment-experienced patients is 2 tablets twice daily or 5 mL liquid twice daily. In treatment of naïve patients, lopinavir may be taken twice daily as for experienced patients or it can be taken as four tablets or 10 mL daily. (Deeks, 2000; Gulick, 2000).

Atazanavir (Reyataz) was approved in 2003. It is the first PI approved for daily dosing in antiretroviral-experienced patients. Atazanavir has good oral bioavailability, but should be taken with a light meal. The half-life of atazanavir is 6 hours. Atazanavir undergoes metabolism by hepatic cytochrome CYP-3A4 (Havlir and O'Marro, 2004). The most frequent adverse events are diarrhea and nausea which are much less than with other protease inhibitors. The most common abnormality is hyperbilirubinemia, which occurs in over 25% of patients. This is reversible and not a result of hepatotoxicity but inhibition of bilirubin glucuronidation. Atazanavir is administered as two 200 mg tablets or, if boosted with ritonavir, as two 150 mg tablets with 100 mg of ritonavir (Hanna and Hirsch, 2003).

Atazanavir may be more tolerable than other protease inhibitors; however it has some notable drug interactions. Its levels are decreased by 25% when combined with tenofovir; therefore it must be given with ritonavir whenever they are used together (le Tiec *et al.*, 2005). It also increases tenofovir's serum levels by 25%; however no dose adjustment is necessary. Atazanavir also has significant interactions with H2 blockers and proton pump inhibitors. If given with H2 blockers, the 2 drugs must be given 12 h apart. Proton pump inhibitors should NOT be given with atazanavir, even if given with ritonavir (Le Tiec *et al.*, 2005).

Amprenavir (Agenerase) was approved in 1999; however, because of pill burden and tolerability issues, this formulation was underutilized. As a result, fosamprenavir became available in 2003. Fosamprenavir (Lexiva, Telzir) is the calcium phosphate ester prodrug of amprenavir. Fosamprenavir is more water-soluble and is readily absorbed (Chapman *et al.*, 2004). It is hydrolyzed in the gut epithelium to the parent drug amprenavir. Amprenavir is metabolized by the CYP-3A4. Common side effects include diarrhea, nausea, vomiting and rash. Fosamprenavir is administered as two 700 mg tablets twice daily. If combined with ritonavir, it is given one tablet twice daily with ritonavir 100 mg twice daily. It can be given in naïve patients once daily with ritonavir (1400 mg with 200 mg of ritonavir).

Tipranavir (Aptivus) is the newest protease inhibitor, approved in June 2005. This is the first non-peptidic protease inhibitor. Tipranavir's absorption is increased when given with food; however it cannot reach therapeutic levels without the concomitant use of ritonavir. Tipranavir is metabolized by the cytochrome CYP-3A4 and is an inducer of the same enzyme. Common side effects include nausea, vomiting and diarrhea. It is also associated with elevated liver enzymes and hyperlipidemia. It is given as two 250 mg tablets along with 200 mg of ritonavir twice daily. Because it is an inducer of the cytochrome P450, the correct doses when co-administered with other protease inhibitors or nonnucleosides are not yet determined and should not be used at this point (Croom and Keam, 2005).

Other non-peptidic protease inhibitors are under development. Darunavir, currently in expanded access in the US, is the PI furthest along in development. Similar to tipranavir, it must be given with ritonavir to achieve therapeutic levels (Katlama *et al.*, 2005). Other protease inhibitors are also in development.

Low dose ritonavir boosting

Oral bioavailability of most protease inhibitors is limited. The intestinal and hepatic cytochrome P-450 enzyme 3A4 is responsible for the clearance of the majority of PIs and it is extensively inhibited by ritonavir (Cooper, 2003). Pharmacokinetic enhancement or "boosting" of PI serum levels and prolongation of their half-life can be achieved with subtherapeutic doses of ritonavir (Table IV). Saquinavir 400 mg twice daily with ritonavir 400 mg twice daily along with 2 NRTIs was the first combination studied, showing 80% of patients with a viral load < 200 at week 48 by on treatment analysis (Cameron, 1999). Further experimentation found that lower doses of ritonavir could boost most PIs and increase bioavailability while decreasing dosing frequency and food restrictions (van Heeswijk, 1999; Kilby, 2000; Veldkamp, 2001). Metabolized mostly through the 2C19 enzyme, nelfinavir is the only PI not markedly boosted with ritonavir (Kurowski, 2002).

In addition to decreasing dosing frequency and food restrictions, boosting appears to maintain or even enhance PI potency and durability. Boosted indinavir twice daily appears to be virologically similar to unboosted indinavir thrice daily (Young, 2002). Ritonavir had to be increased to 200 mg twice daily in a regimen with indinavir 800 mg

Table IV. Protease Inhibitors when boosted with ritonavir

Generic Name	Abbreviated Name	Brand Name	Dosage	Comments
Saquinavir	SQV-HG	Invirase	1000 mg twice daily with ritonavir 100 mg twice daily	Cannot be given without ritonavir
Indinavir	IDV	Crixivan	800 mg twice daily with ritonavir 100 mg twice daily	Take with food
Lopinavir	LPV	Kaletra	Lopinavir (200 mg)/ritonavir (50 mg) 2 tablets twice daily	Diarrhea, nausea Co-formulated with ritonavir
Atazanavir	ATZ	Reyataz	Atazanavir 300 mg once daily with ritonavir 100 mg once daily	Increased risk for hyperbilirubinemia
Fosamprenavir	fAPV	Lexiva	Fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily	Can also be given once daily 1400 mg fAPV with 200 mg RTV
Tipranavir	TPV	Aptivus	Tipranavir 500 mg twice daily with ritonavir 200 mg twice daily	Can only be given with ritonavir Increased liver toxicity

bid in order to suppress patients who were otherwise failing unboosted regimens (Katner, 2002). Lopinavir achieves minimal serum levels and has a short half-life without boosting, and four-year follow-up data shows that this drug combination, along with 2 NRTIs, has excellent potency and durability (Murphy, 2002).

Ritonavir interacts with multiple other medicines and recreational drugs, and care must be taken when adding them to a patient taking ritonavir (Piscitelli, 2001; Clevenbergh, 2002; Antoniou, 2002).

Taste perversion and gastrointestinal symptoms remain an issue with even low dose ritonavir (Gerstoft, 2001). Ritonavir full dose is associated with lipid abnormalities, and it appears that low dose can cause elevations as well, although studies are somewhat confounded by the additional PI in the regimen (Youle, 1999; Gerstoft, 2002).

Entry inhibitors

Over the last 5-10 years the entry of HIV into the CD4 cell has been a target of antiretroviral agent development. The entry of the virus uses multiple steps. First, the GP-120 glycoprotein of the virus binds the CD4 receptor of the host cell. The GP-120 then must bind a co-receptor to gain entry into the cell. The co-receptors have been identified as the chemokine co-receptors- CCR5 and CXCR4. In the majority of the cases, the GP-120 uses the CCR5 co-receptor; in a minority of cases, usually in late disease, the virus uses the CXCR4 receptor. Rarely the virus can use either co-receptor. After binding the co-receptor a structural change occurs resulting in the GP-41 glycoprotein to be exposed. GP-41 contains a repeat domain which folds upon itself, which brings the two membranes in close proximity resulting in fusion (Kilby and Eron, 2003) (Fig. 2).

There have been multiple agents evaluated to target each of these steps. The agent enfuvirtide (Fuzeon) was approved in 2003. This agent targets the GP-41 repeat domain and prevents fusion (Cervia and Smith, 2003). Enfuvirtide is a 36 amino acid synthetic peptide that is administered 90 mg twice daily subcutaneously. It has a half-life of approximately 2 h (Kilby, 2003). The efficacy of this agent has been evaluated in multiple studies including 2 large randomized studies (Lalezari *et al.*, 2003; Lazzarin *et al.*, 2003). These studies demonstrated the added benefit of this agent to standard of care. The most important point learned from these studies is that the agent is best used with at least 1 other active agent.

Enfuvirtide has a few adverse events worth mentioning. First, the subcutaneous injection can lead to injection site reactions that can occur in up to 90 percent of individuals. These injection site reactions vary from erythema to nodules, which may last up to 7 days. Interestingly in the enfuvirtide studies, there was an increase in pneumonia in patients on enfuvirtide; there is no clear explanation for this finding (Lalezari *et al.*, 2003; Lazzarin *et al.*, 2003).

There are multiple agents in different classes targeting cell entry that are currently under development. Those that target the CCR5 receptor are the furthest along in development; however, hepatotoxicity may delay their development (Steel, 2005). CXCR4 receptor inhibitors, other fusion inhibitors, monoclonal antibodies targeting CD4, and other small molecules that inhibit entry into the cell are currently under development.

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 nicely by multiple investigators that the 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 viral RNA in the blood. After the acute infection transitions into chronic infection, the virus reaches a set point where a steady amount of virus is replicated

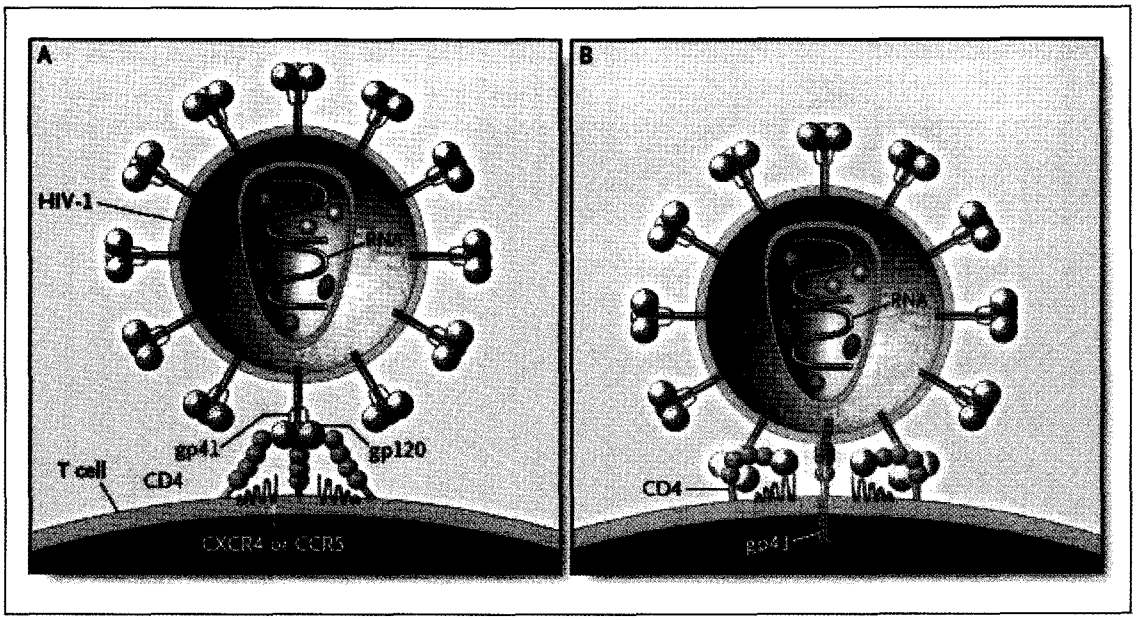

Fig. 2. Over the last 5-10 years the entry of HIV into the CD4 cell has been a target of antiretroviral agent development. The entry of the virus uses multiple steps. First, the GP-120 glycoprotein of the virus binds the CD4 receptor of the host cell (Panel A). The GP-120 then must bind a co-receptor to gain entry into the cell (Panel B). The co-receptors have been identified as the chemokine co-receptors- CCR5 and CXCR4. In the majority of the cases, the GP-120 uses the CCR5 co-receptor; in a minority of cases, usually in late disease, the virus uses the CXCR4 receptor. Rarely the virus can use either co-receptor. After binding the co-receptor a structural change occurs resulting in the GP-41 glycoprotein to be exposed. GP-41 contains a repeat domain which folds upon itself, which brings the two membranes in close proximity resulting in fusion (Reprinted and Adapted from Kilby and Eron, 2003).

each day. This set point is directly related to progression to AIDS (Saksela, 1995; Mellors, 1996; Saag, 1996; Hughes, 1997; Mellors, 1997; O'Brien, 1997; Vlahov, 1998; Yerly, 1998; Miller, 1999).

There are currently two types of tests to quantify the amount of virus present in a patient's blood. These include PCR and branched chain DNA. The PCR test is done by amplifying the RNA present in the blood. The currently available test is sensitive to a lower limit of fifty copies (Van Gemen, 1994). The branched chain DNA test is not as sensitive as the RNA PCR 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 as the RNA PCR (Pachl, 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 NRTI are used in combination with an NNRTI or one or two PI, the ability to decrease viral load and obtain durability of this goal were shown (Collier, 1996; D'aquila, 1996; Hammer, 1997; Gulick, 1997; Gulick, 1998; Montaner, 1998; Murphy, 1999; Staszewski, 1999). Studies have shown that two PI's used alone could accomplish this goal as well (Moyle *et al.*, 2000). In addition, a durable response to therapy only occurs when maximum suppression is being used. In early studies where fewer medications were used, the viral load increased and failure occurred (Havlir, 1998; Pialoux, 1998). More recently studies of monotherapy with boosted PI have been shown to be effective (Campo, 2005).

Antiretrovirals can prolong life and decrease the progression to AIDS; however these medicines are expensive, have a high risk of complications and cannot cure the infection (Pomerantz, 1998). There are many ways to approach therapy, thus guidelines for the use of antiretroviral therapy have been published and updated frequently (DHHS, 2005).

The first question in antiretroviral therapy is when therapy should be initiated. There are multiple cohorts that may start to answer this (Sterling *et al.*, 2003), however the duration of follow-up is not long enough to give a clear answer. Most important, however, is that the patient must be willing to take medicines for a long time and be adherent. Antiretroviral therapy should be offered if the CD4 count < 200/mm^3; opportunistic infection; or symptomatic disease such as weight loss, fevers, or malignancies.

Antiretroviral therapy should be considered in patients

with CD4 counts between 200-350 or if the viral load is greater than 100,000 copies (DHHS, 2005).

Guidelines aside, 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 for patients with low viral loads and high CD4 cell counts (DHHS, 2005). 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 a patient's ability to benefit from future therapies when resistance develops (DHHS, 2005). On the other hand, 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, 1999).

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 these goals, adherence, toxicity, tolerability and use of resistance testing must be considered. Based on available data from clinical trials, two NRTI and either an NNRTI or a PI are recommended as first line agents. The NRTI combinations of either zidovudine/lamivudine or tenofovir/emtricitabine are the first line agents for the NRTI backbone. Recently these agents have been studied in combination with efavirenz, demonstrating the superiority of tenofovir/emtricitabine over zidovudine/lamivudine when combined with efavirenz (Gallant *et al.*, 2006).

If using an NNRTI, efavirenz is suggested as the first line, but in women who may become pregnant, nevirapine is recommended if their CD4 is less than 250. Both NNRTIs were compared in a randomized prospective trial with the use of stavudine and lamivudine. There were no statistically significant differences between these two NNRTIs (van Leth *et al.*, 2004). The recommended protease inhibitor is lopinavir/ritonavir. This agent has been studied in the naïve setting versus nelfinavir in combination with stavudine and lamivudine. Lopinavir/ritonavir demonstrated superiority to nelfinavir in both virologic suppression and, as importantly, no protease resistance was demonstrated in the lopinavir failures (Walmsley *et al.*, 2002).

Other agents and combinations of agents have been studied in the naïve setting and are effective. These include fosamprenavir with or without ritonavir (Gathe *et al.*, 2004; Rodriguez-French *et al.*, 2004), atazanavir (Squires *et al.*, 2004), or saquinavir with ritonavir. These may be used, however they are not recommended as the first line by the DHHS.

Certain agents should not be used in combination because of toxicity, interactions, or inferiority to standard of care. The combinations of stavudine with didanosine, zalcitabine, or zidovudine; lamivudine with either zalcitabine or emtricitabine; tenofovir with didanosine; or tipranavir with any other currently available protease inhibitors are contraindicated because of interactions. The following combinations are inferior to standard of care and therefore should not be used: abacavir/lamivudine/tenofovir (Gallant *et al.*, 2005) or zidovudine/lamivudine/abacavir (Gulick *et al.*, 2004). Further details of these regimens are in Tables 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. The CD4 counts increase in a 3 phase pattern which consists of a rapid increase during the first 3 weeks of suppressive therapy, then a gradual increase for 72 weeks followed by a slow steady increase or stabilization (Nottermans, 1999). The

Table V. Antiretroviral Recommendations-Strongly recommended-Column A +Column B

NRTI	Potent Arm
Zidovudine/Lamivudine	Lopinavir/ritonavir
Tenofovir/emtricitabine	Efavirenz

Table VI. Contraindicated combinations

Zalcitabine with didanosine, or stavudine	Toxicity
Zalcitabine with lamivudine or emtricitabine	antagonistic
Stavudine with zidovudine	antagonistic
Tenofovir with didanosine	Increased failures, decreased CD4 counts
Stavudine with didanosine	Pancreatitis, lipoatrophy, neuropathy and lactic acidosis
Tenofovir, abacavir and lamivudine	Significantly increased failure
Two non-nucleoside reverse transcriptase inhibitors	Increased toxicity
Tipranavir and another Protease inhibitor	Tipranavir induces metabolism of other PI
Amprenavir with efavirenz	Pharmacokinetics

possible explanation for this pattern is the return of naive CD4 cells, followed by a slow recovery of memory helper cells (Nottermans, 1999). The rate and degree of the CD4 response vary. Some contributing factors noted include age, thymic activity, level of base line viral load and previous antiretroviral therapy (Sabin, 2000).

If a person who is started on antiretroviral therapy does not respond as expected, then the regimen 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, 2005).

Over the last 5 years or so, there has been a significant interest in structured treatment interruptions (STI) in therapy. First, there was an interest in STI in the acutely infected patient to improve immune function and possibly allow the patient's immune system to control the virus (Lisziewicz *et al.*, 1999). Second, STI were evaluated in patients with no therapeutic options to assess if allowing the original virus to grow and allow highly active antiretroviral therapy (HAART) to work (Lawrence *et al.*, 2003; Deeks *et al.*, 2003) Third, STI were evaluated in chronically controlled patients to either boost the immune system or to decrease the toxicity and cost of antiretrovirals (Molto *et al.*, 2004; El Sadr and Neaton, 2006). Each and every one of these approaches has failed. Currently available studies do not support this approach as an option for our patients.

Metabolic complications

Patients receiving HAART may have metabolic complications. Some of the side effects are directly a result of the medications, while others may be due to the virus itself. Originally termed the lipodystrophy syndrome, enough research has been done to demonstrate that these entities are not one syndrome, but multiple different ones that interconnect to lead to the myriad of symptoms: hyperlipidemia, decreased insulin sensitivity, peripheral fat atrophy and central fat deposition (Carr *et al.*, 1998).

Hyperlipidemia is noted with most of the antiretroviral drugs. In general, the protease inhibitors lead to an elevation of total cholesterol, LDL, and triglycerides, while decreasing the HDL (Dube *et al.*, 2003). Not all protease inhibitors act in a similar fashion. Ritonavir and tipranavir are the worst offenders, while atazanavir is the least likely to lead to these adverse events. The NNRTI also cause hyperlipidemia with their major effect being to raise all 3 lipids: total cholesterol, HDL, and LDL. The effect of nevirapine on the lipid profile is better than efavirenz (van Leth *et al.*, 2004). The NRTIs also contribute to hyperlipidemia with stavudine and zidovudine being much worse than tenofovir. Attempts to correct the abnormal lipids include switching from one agent that is causing the hyperlipidemia to one that does not (Martinez *et al.*, 2003). Another approach is to use agents that lower lipids such as HMG-CoA inhibitors, fibrates, or fish oils (Dube *et al.*, 2003).

New onset diabetes mellitus can affect 1-6% of HIV infected patients treated with protease inhibitors. An even a higher incidence of insulin resistance and impaired glucose tolerance can occur. In studies where protease inhibitors are switched to either an NNRTI or abacavir, insulin resistance decreases (Martinez *et al.*, 2003). In another study comparing stavudine and tenofovir, the patients in the stavudine arm had a higher glucose than tenofovir (Gallant *et al.*, 2004). In general, glucose intolerance may be a result of PI or certain NRTI (Dube, 2000). Treatment of established diabetes mellitus should follow guidelines for those that are not HIV infected (Dube, 2000).

One of the earliest noted metabolic findings was fat redistribution. There are two distinct events that occur: peripheral fat loss and central fat accumulation. The peripheral fat loss is related to the NRTI, mainly stavudine and zidovudine. The fat loss may or may not be treatable. Some switch studies replace the thymidine analogs with either abacavir or tenofovir with modest outcomes (Martin *et al.*, 2004). Lipid accumulation is a result of the protease inhibitors, first noted with indinavir, but can be seen with others as well (Grinspoon and Carr, 2005).

Obviously concerning are the possible long-term effects of these complications. Multiple cohort studies have reviewed the risk of cardiovascular disease with mixed results (Friis-Moller *et al.*, 2003; Bozzette *et al.*, 2003). When looking at the predictors of disease and the strength of the risk factors, the classic risk factors such as diabetes and tobacco use have a much higher risk than does HAART.

Other findings associated with antiretrovirals are related to mitochondrial toxicity. The NRTIs work by being incorporated in the newly forming DNA of HIV, however the NRTIs can have the same effect to a much lesser degree on the mitochondrial DNA. Over time, the mitochondrial destruction can lead to lactic acidosis, neuropathy and pancreatitis.

Lactic acidosis has been reported in people on HAART. The symptoms include fatigue, abdominal pain, nausea and vomiting. Laboratory findings include elevated transaminases, lactate and decreased bicarbonate. When a patient has these symptoms, all HAART must be stopped. Other methods to treat this syndrome are still controversial. The agents most often implicated in this syndrome are stavudine and zidovudine, and especially the combination of stavudine and didanosine. The newer agents abacavir

and tenofovir are much less likely to result in this syndrome.

Pancreatitis and peripheral neuropathy are likely linked to mitochondrial toxicity and are most likely seen with the use of stavudine and didanosine in combination or to a lesser degree when either is used alone. Treatment for pancreatitis is supportive with the discontinuation of the medication. Treatment for neuropathy includes discontinuation of the medication and the use of analgesics (Keswani *et al.*, 2002).

HIV Resistance testing: genotypes and phenotypes

HIV reverse transcriptase is an error prone enzyme, allowing for base pair substitutions at a rate of one per genome transcribed (Roberts, 1998; Preston, 1998). Certain mutations in the viral RNA confer resistance to antiretroviral agents *in vivo*, and information about an individual's particular virus is important to know when constructing a HAART regimen. Two methods are available for resistance testing: genotypes and phenotypes. HIV genotypic testing sequences the reverse transcriptase (*pol*) and protease (*pro*) genes of a patient's virus to find mutations known to confer resistance. By contrast, an HIV phenotype places these two genes into a viral construct and determines how well this hybrid will grow in varying concentrations of antiretroviral agents (Hirsch, 2003). A virtual phenotype matches a patient's genotype to a similar one in a database for which a phenotype is known (Clavel, 2004). This paper will review the basics of resistance testing; the reader is encouraged to consult with an HIV expert for interpretation of an individual patient's resistance test results.

Genotype

An HIV genotype will examine the *pol* and *pro* genes for nucleotide substitutions that have been associated with drug failure. Some agents require only a single mutation to lose activity against the virus, and others may become partially or completely inactive after only multiple sequential mutations. For instance, the replacement of methionine with valine at codon 184 (M184V) of *pol* gene leads to resistance to both emtricitabine and lamivudine (Schuurman, 1995; Gao, 2000). On the other hand, zidovudine and stavudine generally require three or more mutations. ([M41L, L210W, and T215Y] or [D67N, K70R, T215F, K219Q/E]) (Marcellin, 2004), commonly referred to as thymidine analog mutations (TAMs). NRTI mutations in *pol* tend to function by decreased incorporation of the drug or increased excision of a drug already added to the growing DNA chain. The M184V blocks incorporation of lamivudine or emtricitabine into the growing DNA, and the Q151M complex inhibits binding of most NRTIs to RT—lamivudine and tenofovir being notable exceptions (Iversen, 1996; Kosalaraksa, 1999; Feng, 2006). The K65R mutation can occur when a patient is on abacavir or tenofovir and it blocks the incorporation of most nucleosides except zidovudine (White, 2005).

The TAMS increase excision of the drug from the growing DNA chain and offer broad cross-reactivity with other NRTIs (Larder, 1989; Picard, 2001). Interestingly, the M184V and K65R mutations inhibit the ability of reverse transcriptase (RT) to excise the chain terminating compounds, and thus may somewhat increase the efficacy of zidovudine (Larder, 1995; Picard, 2001).

All currently available NNRTIs bind RT in the same hydrophobic site (Esnouf, 1997), and mutations generally incur resistance to the entire class. The K103N mutation confers resistance to all three NNRTIs. Nevirapine often selects for Y181C, and although efavirenz has activity against this mutation, subdetectable populations of K103N virus are thought to exist. Efavirenz has poor durability when replacing nevirapine during virologic failure (Hirsch, 2003).

Genotypic analysis of the *pro* is more complicated, as multiple mutations are usually required to confer increased resistance to the protease inhibitor drugs. Nelfinavir with its signature mutation D30N, atazanavir with its I50L, and fosamprenavir with the I50V are notable exceptions to this (Jarvis and Faulds, 1998; Arvieux and Tribut, 2005; Weinheimer, 2005). Ritonavir boosting of PIs adds another level of complexity, as the higher serum levels achieved may overcome some resistance. (Hirsch, 2003; Clavel, 2004). The recently approved tipranavir (to be taken with ritonavir) may have 31 different mutation sites conferring varying levels of resistance in different combinations (Kohlbrenner, 2004).

A genotype is recommended in cases of acute or recent (within 12 months) infection, pregnancy, and HAART regimen failures. Sexual transmission of resistant virus has been well documented (Hecht, 1998; Little, 2002a) and may impact the choice of a HAART regimen. A genotype in a patient with an established infection may be of use in regions where the incidence of transmitted resistance is high, as resistance mutations have been detected for > 2 years after initial infection (Little, 2002b). As the virus can lose its resistance *via* backward mutation, genotype should be obtained prior to switching a patient's failing antiretroviral regimen (Deeks, 2001). Several studies have verified improved outcomes when a genotype, along with expert interpretation, is used to assist in selecting a new regimen (Durant, 1999; Baxter, 2000; Tural, 2002).

Genotype resistance testing cannot detect minority viruses with different mutations, nor can it detect archived resistant genomes (Finzi, 1997; Resch, 2001). The structural *gag* protein, the natural substrate of the protease enzyme,

can also mutate and lend resistance to protease inhibitors (Doyon, 1996; Zhang, 1997). The *gag* gene is not examined by current commercially available genotypic or phenotypic tests, and thus this information cannot be used to predict protease susceptibility.

Phenotype

Viruses with multiple resistance mutations make a genotype difficult to interpret. Phenotypes, by actually growing a construct of the patient's virus in the presence of antiretrovirals, may better predict which agents remain active–analogous to a bacterial antibiogram. This test, however, is more expensive and has a longer turnaround time than an HIV genotype. Actual clinical cut-off points do not exist for many agents, and the test does not examine possible synergy between the multiple agents used in a regimen (Hirsch, 2003). Prospective studies on phenotypic testing versus standard of care did show a positive effect upon patient care, but the strength of the association was less strong than with genotypes (Cohen, 2002; Haubrich, 2005; Meynard, 2002). Phenotypic and genotypic tests for the fusion inhibitor enfuvirtide are commercially available (Menzo, 2004).

Pregnancy and HIV

As of December 2005, an estimated 17.5 million women worldwide are living with HIV, with an estimated 700,000 new mother to child transmissions (MCT) in 2005 (UNAIDS/WHO, 2005). A child born to an infected mother has an approximate 30% chance of acquiring HIV, which is higher than any other risk factor (Connor, 1994; Quinn, 2000; Scully, 2000; Colfax, 2002). Pregnancy alone, however, does not appear to worsen maternal HIV disease (Watts, 2002).

The AIDS Clinical Trials Group (ACTG) 076 was the first study to document the use of AZT to prevent vertical transmission of HIV. Mother/child pairs receiving antepartum and intrapartum zidovudine followed with 6 weeks of zidovudine to the newborn were compared with placebo. Approximately 8% of newborns in the zidovudine group were infected, as compared with 25.5% of children in the placebo group–a relative risk reduction of 67.5% (Connor, 1994).

Further studies have shown that multiple agents can lower transmission risk even further–down to 1.2% in women receiving HAART (Cooper, 2002; Dorenbaum, 2002). Although there is some controversy, there appears to be no increased risk of birth defects, premature deliveries, or low birth weight associated with HAART (Tuomala, 2002).

Mother to child transmission is believed to occur in the peripartum and intrapartum period (Kuhn, 1997; Mock, 1999). Maternal baseline HIV-1 viral load correlates strongly with transmission (Dickover, 1996), with few infections occurring with a viral load below 1,000 copies/mL (Mofenson, 1999; Garcia, 1999). Other factors must contribute as well, as there have been documented transmissions in the setting of an undetectable viral load (European Collaborative Study, 1999; Thea, 1997).

Since a significant amount of organogenesis occurs in the first trimester, it is recommended that antiretroviral therapy be held until 10-12 weeks into the pregnancy, unless maternal health requires it (Mofenson, 2002). All women with a viral load above 1,000 copies/mL should be offered HAART in the second and third trimester, preferably a regimen including zidovudine. As there is no absolute threshold below which perinatal transmission does not occur, all mother/child pairs should undergo the three-part zidovudine prophylaxis (Ioannidis, 2001; Public Health Service, 2005).

The NNRTI efavirenz was shown to cause birth defects--anencephaly, anophthalmia, and cleft palate–in 3 of 20 monkeys (15%) when given in the first trimester; it should be avoided in pregnant women (US Dept of Health and Human Services, 2002). Nevirapine is the most commonly used NNRTI in pregnancy (Watts, 2002), and intrapartum single dose of nevirapine along with standard zidovudine therapy has been shown to decrease the transmission rate to 1.9% as compared to 6.3% in the zidovudine alone group (Lallemant, 2004). Nevertheless, concerns about rapid development of NNRTI resistance in the mother (Jourdain, 2004) and severe hepatotoxicity (Knudtson, 2003; Thorne, 2005) limit its use.

Selection of a highly active antiretroviral regimen in a pregnant woman should follow the guidelines as listed for non-pregnant adolescents and adults (Dybul, 2002) with the caveats listed below.

Many NRTIs appear to carry a high risk of hyperlactatemia and hepatic steatosis (Brinkman, 1998; Gerard, 2000). The combination of stavudine and didanosine should be avoided in pregnancy due to the high incidence of these toxicities–including three deaths (Bristol-Myers Squibb, 2001).

Pregnant women using a protease inhibitor based regimen appear to be at a higher risk of hyperglycemia, and may require close monitoring (Dube, 1998). Atazanavir can cause an elevated unconjugated hyperbilirubinemia and should be avoided in pregnancy due to the theoretical concern for neonatal kernicterus (Havlir, 2004). Likewise, indinavir may also cause hyperbilirubinemia and should also be used with caution (Minkoff, 1997).

Earlier in the epidemic, it was shown that elective cesarean section prior to rupture of membranes decreased perinatal transmission by 50%, and further decreased it by 87% when coupled with zidovudine prophylaxis (International Perinatal HIV Group, 1999). Given the currently

known low risk of transmission attainable with HAART alone, recent recommendations are to do an elective cesarean section as an adjunct of HIV prophylaxis only if the viral load is greater than 1,000 copies/mL (American College of Obstetricians and Gynecologists, 2000).

Women should be counseled against breastfeeding their newborns, as this may carry an approximate 15% risk of viral transmission (Nduati, 2000; Piwoz, 2004).

Occupational exposure

Recommendations addressing occupational exposure were published in the Morbidity and Mortality Weekly Report (MMWR) in September 2005. Briefly, chemoprophylaxis is recommended based on the type of bodily fluids involved and the route and severity of exposure. For hollow bore or solid needle exposures with HIV infected blood, or for mucous membrane exposure, chemoprophylaxis with 3 medications is recommended. For low risk exposures such as scratches with a solid needle, chemoprophylaxis with a 2-drug regimen 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, 2005; 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 are recommended. Choice of medications includes 2 nucleosides such as lamivudine/zidovudine or tenofovir/emtricitabine with the addition of a third agent such as lopinavir/ritonavir, atazanavir +/- ritonavir or nelfinavir in high-risk exposure. Individualization is recommended based on the source patient's history of antiretrovirals and possible resistant patterns (CDC, 2005; Gerberding, 1996). Up to this point there are 6 published cases of transmission in the setting of HIV postexposure prophylaxis. (CDC, 2005)

Nonoccupational exposure

There is a lack of efficacy data for the use of antiretroviral agents to reduce HIV transmission after a nonoccupational exposure. There are published recommendations for nonoccupational exposure prophylaxis. It is recommended to use prophylaxis for those who had unprotected receptive anal or vaginal intercourse with a known HIV positive person. The medicines should be the ones described in the previous section (CDC, 2005); Lurie, 1998).

HIV and Hepatitis B and C co-infection

With successful treatments lowering the mortality of AIDS, liver disease morbidity and death has risen. Hepatitis B (HBV) and Hepatitis C (HCV) viruses have similar modes of transmission as HIV and patients are often co-infected with HIV and one or both of these hepatitis viruses.

Hepatitis B virus (HBV)

HBV infects some 350-400 million people worldwide (Lee, 1997; McMahon, 2005). Surveys have shown serologic evidence of past or current HBV infection in up to 80% of HIV infected individuals in certain subgroups such as men who have sex with men (MSM) in the Multicenter AIDS Cohort Study (MACS) (Solomon, 1990). A different study of the MACS group showed a prevalence of HIV-1 infected individuals who were also carriers of the hepatitis B surface antigen (HBsAg) of about 6%, whereas the worldwide estimate is believed to be 8-11% (Thio, 2002; Lee, 1997).

The interaction between HIV-1 and HBV is complex, but it is believed that HIV more heavily influences HBV disease (Núñez, 2003). Early in the AIDS epidemic, HBV was thought to increase HIV replication, increase drug-related hepatotoxicity, decrease CD4 cell counts *via* hypersplenism in cirrhosis, and possibly decrease CD4 cell concentrations directly (Eskild, 1992; den Brinker, 2000; Colin, 1999; Goldin, 1990).

HIV negatively impacts HBV by increasing chronicity, increasing HBV viral load, decreasing anti-HBe and anti-HBs seroconversion, increasing hepatitis flares, increasing progression to cirrhosis, decreasing HBV response to interferon-α and nucleoside therapies, and by possibly increasing hepatocellular carcinoma (Di Martino, 2002; Perrillo, 1986; Bodsworth, 1991; Shire, 2005).

With the advent of HAART, HIV can be brought under control. This has led to a rise in mortality due to hepatitis among co-infected patients. Among a cohort of men who have sex with men (MSM), liver mortality was 1.1/1000 person years in HIV negative and HBsAg negative men, compared with 14.2/1000 in HIV positive and HBsAg positive persons and only 1.7/1000 in men positive for HIV alone (Thio, 2002).

Treatment goals for HBV should aim for a minimum of suppressing HBV DNA from the blood. The next higher goal is conversion from HBeAg to anti-HBeAg status. Finally, seroconversion to anti-HBsAg and thus ending the chronic carrier status is the ultimate, but often unachievable goal (Pramoolsinsup, 2002; Núñez, 2003). The main classes of HBV therapies include the interferons (interferon-α and pegylated interferon-α) and nucleoside analogs (lamivudine, emtricitabine, adefovir, tenofovir, and entecavir).

Interferon-α therapy for HBV appears to be less effective in patients co-infected with HIV. Therapy most

often consists of 10 million units of interferon-α thrice weekly for six months (Brook, 1989; di Martino, 1996). HIV infected persons tend to have poorer prognostic indicators than HIV negative ones: lower transaminase levels, lower CD4 counts, and more frequent co-infection with HCV (Hoofnagle, 1997). Side effects of interferon include myalgias, fever, arthralgias, alopecia, bone marrow suppression, depression, and suicide (Hoffmann-LaRoche, 2001; Soriano, 2005). Most interferon-α studies on patients co-infected with HBV and HIV occurred before the introduction of both HAART and pegylated interferon-α. The impact of these two variables is only now being fully investigated (Konoponicki, 2005).

With the poor outcomes with interferon-α interest has turned to DNA replication inhibition with nucleoside analogs. The best studied is lamivudine, which has anti-HBV activity at 100 mg/day but must be given at 300 mg/day in combination with two or more active agents in the setting of HIV co-infection. Over 86% of co-infected patients have their HBV DNA inhibited by lamivudine (Dore, 1999; Hoff, 2001; Benhamou, 1999). These studies also demonstrated the rapid emergence of lamivudine resistance. Approximately 30% of patients treated develop the YMDD mutation in their viral genome after one year, conferring resistance to this drug (Marrone, 2005). After 2 and 4 years, the mutation prevalence is 50% and 90%, respectively (Núñez, 2003). Emtricitabine, an anti-HIV nucleoside analog similar to lamivudine, also has similar anti-HBV effects, including the rapid development of resistance (Marcellin, 2005).

Adefovir suppresses HBV replication and can normalize alanine aminotransferase levels in about 70% of HIV and HBeAg negative patients. HBeAg seroconversion occurs in some 23% of patients with this drug. This drug retains activity against YMDD mutant virus, and has been found to be safe at 10mg/day (Benhamou, 2001; de Franchis, 2003). Adefovir was originally studied as an anti-HIV drug at a much higher dose until it was found to have renal toxicity. Although HBV is slow to develop resistance, it has been documented (Brunelle, 2005). HIV/HBV co-infection studies await.

Tenofovir has activity both against HIV and HBV, and can be used in the presence of the YMDD mutation (Ying, 2000; Ristig,, 2002). It appears to be more resistant to viral escape than lamivudine.

The promising drug entecavir has recently been approved by the FDA for the treatment of HBV. At 1mg/day and 0.5mg/day, it appears to be potent with few side effects. This drug has activity against the YMDD virus (Levine, 2002). Resistance requires multiple mutations, some of which overlap with lamivudine patterns (Tenney, 2004).

HBV disease may flare with an elevation in transaminases once antiretrovirals are started as the immune system is reconstituted, if resistance develops to an anti-HBV drug, or if a drug is withdrawn (Marcellin, 2005; Shire, 2005; Marrone, 2005). Care must be taken if lamivudine, emtricitabine, or tenofovir must be withdrawn due to changes in the patient's HIV disease, and another anti-HBV agent may need to be added to prevent a flare of HBV disease.

The nucleosides have a low incidence of seroconversion to anti-HBsAg and anti-HBeAg. Interferon-α, and probably pegylated interferon-α, have the greatest chance of converting a patient, but they are poorly tolerated (Pramoolsinsup, 2002). Dual therapy with interferon and lamivudine have been tried to increase the chance of seroconversion but has been shown to be no better than interferon-α alone. Further studies are warranted exploring different combinations to achieve greater success with fewer side effects (Marcellin, 2005).

Hepatitis C virus

Hepatitis C virus (HCV) is thought to infect 3% of the world's population, making it perhaps four times more prevalent than HIV. Like HIV, HCV is transmitted through exposure to blood, e.g., *via* sharing intravenous needles or receiving contaminated blood products. Accordingly, an estimated 13-43% of the 1 million HIV positive persons in the United States are thought to be co-infected with HCV (Winnock, 2004; Soriano, 2005). Unlike HIV, however, HCV has limited sexual transmission (Lauer 2001). As expected, intravenous drug users and hemophiliacs have a higher incidence of HCV than do MSM (van Ameijden, 1993; Troisi, 1993; Quaranta, 1994; Monga, 2001). All HIV positive patients should be screened for HCV (Soriano, 2004).

HCV impacts HIV in multiple ways. HCV may accelerate HIV disease (Piroth, 1998; Greub, 2000), although this is uncertain (Sulkowski, 2002; Tedaldi, 2003; Soriano, 2005). HCV can negatively influence liver tolerance of HAART (Spengler, 2002), and may (Greub, 2000) or may not (Sulkowski, 2002) hinder immune reconstitution.

HIV most certainly impacts the natural course of HCV. HIV limits the clearance of HCV acute infection--some 85% of HIV patients who are antibody positive have detectable HCV RNA, as compared with 75% of HIV negative persons (Soriano, 2005). Severe immunosuppression can cause HCV antibody loss (Chamont, 1990; Bonacini, 2001), so HCV RNA detection by PCR should be done on HIV positive/HCV antibody negative patients in whom HCV is strongly suspected. Multiple studies have shown enhanced liver toxicity and complications in co-infected persons on HAART. Progression of hepatic fibrosis is accelerated in HCV/HIV infected individuals as compared with HCV monoinfected persons (Di Martino,

2001). For instance, a cross-sectional study showed a 15% development of cirrhosis in co-infected patients after 10 years of HCV infection as compared with 3% in HIV negative patients (Soto, 1997). Development of hepatocellular carcinoma (HCC) among cirrhotic HCV patients is higher with HIV co-infection (Garcia-Samaniego, 2001), with one study showing a median of 10 years since exposure to HCV among hemophiliacs (Darby, 1997).

Unlike HBV, the treatment goal for HCV is complete eradication of the virus, and secondarily to slow liver fibrosis in those whose virus cannot be eliminated (Winnock, 2004). In monoinfected patients, treatment is indicated in those with risk factors of progressive liver disease, such as those with persistently high ALT and portal fibrosis with moderate inflammation on liver biopsy (Fargion, 2004). One study showed that treatment of these patients with pegylated interferon-α plus ribavirin for 48 weeks gives a sustained viral response (SVR) six months after treatment cessation of 56% for patients with genotype 1. For others with genotypes more responsive to therapy, the SVR was 88% (Fried, 2002).

The dually infected patient presents added complexities. Due to the increased risk of liver disease, all HIV/HCV patients should be considered for therapy. SVR is increased in patients with a CD4 count greater than 500/μL and an HIV load less than 10,000 (Soriano, 2002), so many patients may require HAART therapy in order to improve the chance of HCV cure. Additionally, interferon is associated with a decline in CD4 count (Vento, 1993), which may put patients at risk for opportunistic infections (Pesce, 1993). Ribavirin, zidovudine, and stavudine use the same phosphorylation pathway and are antagonistic *in vitro*, but no changes in HIV have been noted *in vivo* (Landau, 2000; Morsica, 2000). Ribavirin increases phosphorylated didanosine levels (Japour, 1996), which has been correlated with increased mitochondrial toxicity and pancreatitis (Salmon-Céron, 2001; Kakuda, 2001; Lafeuillade, 2001). Patients on any of these NRTIs may require a rearrangement of their HAART regimen prior to initiation of HCV therapy (Soriano, 2004). Patients with a history of neuropsychiatric disorders should be followed closely as interferon may cause severe relapses (Soriano, 2004).

Pegylated interferon-α coupled with ribavirin is now the mainstay of HCV therapy both in mono- and co-infected patients (Soriano, 2004). Nevertheless, SVR in co-infected patients remains significantly lower than in monoinfected persons. Most recently, the APRICOT study showed an SVR of 29% in patients with HCV genotype 1, the most common type in the US. Genotypes 2 and 3 faired better, with an SVR of 62% (Torriani, 2004). The Spanish PRESCO trial, currently underway, is examining if 18 month therapy will yield better results in treatment of genotype 1 (Núñez, 2004).

Side effects of therapy can be considerable, and treatment discontinuation occurred in 12-40% of patients in recent clinical trials of co-infected persons. (Winnock, 2004). Patients often experience fatigue, myalgias, arthralgias, weight loss, anxiety and irritability (Soriano, 2002). Ribavirin can cause hemolytic anemia, requiring a dose adjustment, treatment with erythropoietin, or both. Interferon is associated with neutropenia that may require granulocyte colony stimulating factors. Interferon-induced depression may require antidepressants (Musselman, 2001), and the authors have one patient who attempted suicide while on therapy.

The low rate of success and high incidence of side effects of interferon and ribavirin therapy have prompted research into alternative approaches to hepatitis C. Polymerase inhibitors *in vitro* (Sarisky, 2004) and protease inhibitors *in vivo* (Hinrichsen, 2005) appear to have promise, but are still years away from becoming effective therapies.

Hepatitis A virus (HAV) superinfection can cause fulminant hepatitis, and all HCV positive patients should be vaccinated against HAV (Lauer, 2001).

HIV and TB

Since co-infection with both *Mycobacterium tuberculosis* and HIV is common, concurrent treatment of both infections may be needed. In general, treatment of HIV related tuberculosis should follow the general principles for those without HIV. Treatment should include a 6-month regimen consisting of isoniazid, rifampin or rifabutin, ethambutol and pyrazinamide for 2 months followed by isoniazid and rifampin or rifabutin for 4 months when the infection is due to susceptible organisms. A prolonged treatment of 9 months in patients with a delayed response to treatment is accepted (CDC, 2004).

The rifamycins are important drugs for the treatment of TB; however they have significant interactions with antiretrovirals. Rifampin is a very potent inducer of the CYP-3A4. The NRTI have no interactions with the rifamycins, however the NNRTI and PIs do interact. In general, rifampin should not be administered in patients on nelfinavir, saquinavir, indinavir, amprenavir, atazanavir, lopinavir or tipranavir. Rifabutin at 150 mg three times weekly can be given as an alternative. Efavirenz given at the higher dose of 800 mg daily along with rifampin has been shown to give adequate levels of both drugs. Nevirapine and rifampin may be safe, but studies are lacking (CDC, 2004).

The optimal timing of HAART and TB treatment is unknown. Treatment for tuberculosis should never be delayed because of the risk of transmission. Early administration of HAART may lead to a high incidence of side

effects and paradoxical reactions. Delaying the initiation of HAART for 4-8 weeks may decrease adverse events and improve adherence. This decision should however be individualized (CDC, 2004).

CONCLUSION

HIV medicine is an area that is continually changing and growing. The advances made in the last two and a half decades have changed this disease from a certain death sentence to a chronic infection. There will certainly be newer medications with better pharmacokinetics and safety profiles, as well as new classes. This could improve our treatment options and also our diagnostic options as we enter the new millennium. However, we do not have a cure, a vaccine or all the answers for the treatment of this disease. What we do know at present is that the best approach is prevention of this infection.

These resources and technologies are available to us 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, and India. In order to contain this epidemic over the next 25 years, we must get these resources to these countries.

REFERENCES

Aarnoutse, R. E., Grintjes, K. J., Telgt, D. S., Stek, M., Hugen, P. W., Reiss, P., Koopmans, P. P., Hekster, Y.A., and Burger, D. M., The influence of efavirenz on the pharmacokinetics of a twice-daily combination of indinavir and low-dose ritonavir in healthy volunteers. *Clin. Pharmacol. Ther.*, 71, 57-67 (2002).

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

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

Alberti, A., Clumeck, N., Collins, S., Gerlich, W., Lundgren, J., Palu, G., Reiss, P., Thiebaut, R., Weiland, O., Yazdanpanah, Y., and Zeuzem, S., Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J. Hepatol.,* 42, 615-624 (2005).

American College of Obstetricians and Gynecologists Committee Opinion. Scheduled cesarean delivery and the prevention of vertical transmission of HIV infection. Number 234. Washington DC: The American College of Obstetricians and Gynecologists, May (2000).

Antoniou, T. and Tseng, A. L., Interactions between recreational drugs and antiretroviral agents. *Ann. Pharmacother.*, 36, 1598-1613 (2002).

Arvieux, C. and Tribut, O., Amprenavir or fosamprenavir plus ritonavir in HIV infection: pharmacology, efficacy and tolerability profile. *Drugs*, 65, 633-659 (2005).

Bartlett, J. A., 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., Hoover, M. L., Winters, M. A., Mannheimer, S. B., Thompson, M. A., Abrams, D. I., Brizz, B. J., Ioannidis, J. P., and Merigan, T. C., A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS.*, 14, F83-93 (2000).

Benhamou, Y., Bochet, M., Thibault, V., Di Martino, V., Caumes, E., Bricaire, F., Opolon, P., Katlama, C., and Poynard T., Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology,* 30, 1302-1306 (1999).

Benhamou, Y., Bochet, M., Thibault, V., Calvez, V., Fievet, M. H., Vig, P., Gibbs, C. S., Brosgart, C., Fry, J., Namini, H., Katlama, C., and Poynard T., Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet.*, 358, 718-723 (2001).

Benhamou, Y., Tubiana, R., and Thibault, V., Tenofovir disoproxil fumarate in patients with HIV and lamivudine-resistant hepatitis B virus. *N. Engl. J. Med.*, 348, 177-178 (2003).

Bergshoeff, A., Burger, D., Verweij, C., Farrelly, L., Flynn, J., Le Prevost, M., Walker, S., Novelli, V., Lyall, H., Khoo, S., and Gibb, D., for the PENTA-13 Study Group. Plasma pharmacokinetics of once-versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). *Antivir. Ther.*, 10, 239-246 (2005)

Bodsworth, N. J., Cooper, D. A., and Donovan B., The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state. *J. Infect. Dis.*, 163, 1138-1140 (1991).

Bonacini, M., Lin, H. J., and Hollinger, F. B., Effect of coexisting HIV-1 infection on the diagnosis and evaluation of hepatitis C virus. *J. AIDS.*, 26, 340-344 (2001).

Bonnet, F., Bonarek, M., Morlat, P., Mercie, P., Dupon, M., Gemain, M. C., Malvy, D., Bernard, N., Pellegrin, J. L., and Beylot, J., Risk factors for lactic acidosis in HIV-infected patients treated with nucleoside reverse-transcriptase inhibitors: a case-control study. *Clin. Infect. Dis.*, 36, 1324-1328 (2003).

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

Bozzette, S. A., Ake, C. F., Tam, H. K., Chang, S. W., and Louis, T. A., Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N. Engl. J. Med.,* 348, 702-710 (2003).

Brinkman, K., ter Hofstede, H. J. M., Burger, D. M., Smeitink, J. A., and Koopmans, P. P., Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. *AIDS.,* 12, 1735-1744 (1998).

Bristol-Myers Squibb. Important drug warning: January 5, 2001. Rockville, Md.: Food and Drug Administration, 2001. (Accessed February 15 2006, at http://www.fda.gov/medwatch/safety/2001/zerit&videx_letter.htm.

Brook, M. G., McDonald, J. A., Karayiannis, P., Caruso, L., Forster, G., Harris, J. R., and Thomas, H. C., Randomised controlled trial of interferon alfa 2A (rbe) (Roferon-A) for the treatment of chronic hepatitis B virus (HBV) infection: factors that influence response. *Gut.*, 30, 1116-1122 (1989).

Brunelle, M. N., Jacquard, A. C., Pichoud, C., Durantel, D., Carrouee-Durantel, S., Villeneuve, J. P., Trepo, C., and Zoulim, F., Susceptibility to antivirals of a human HBV strain with mutations conferring resistance to both lamivudine and adefovir. *Hepatology*, 41, 1391-1398 (2005).

Buti, M. and Esteban, R. Drugs in Development for Hepatitis B. *Drugs.*, 65, 1451-1460 (2005).

CDC. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States. Recommendations from the US Department of Health and Human Services. *MMWR*, 54, RR-2 (2005).

CDC. Treating Opportunistic Infections among HIV-infected adults and adolescents. Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR*, 53, RR-15 (2004).

CDC. Updated US Public health service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *MMWR*, 54, RR-9 (2005).

Cameron, D. W., Japour, A. J., Xu, Y., Hsu, A., Mellors, J., Farthing, C., Cohen, C., Poretz, D., Markowitz, M., Follansbee, S., Angel, J. B., McMahon, D., Ho, D., Devanarayan, V., Rode, R., Salgo, M., Kempf, D. J., Granneman, R., Leonard, J. M., and Sun, E., Ritonavir and saquinavir combination therapy for the treatment of HIV infection. *AIDS.*, 13, 213-224 (1999).

Campo, R. E., Lalanne, R., Tanner, T. J., Jayaweera, D. T., Rodriguez, A. E., Fontaine, L., and Kolber, M. A., Lopinavir/ritonavir maintenance monotherapy after successful viral suppression with standard highly active antiretroviral therapy in HIV-1-infected patients. *AIDS.*, 19, 447-449 (2005).

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

Cervia, J. S. and Smith, M. A., Enfuvirtide (T-20): A novel human immunodeficiency virus type 1 fusion inhibitor. *Clin. Infect. Dis.*, 37, 1102-1106 (2003).

Chamot, E., Hirschel, B., Wintsch, J., Robert, C. F., Gabriel, V., Deglon, J. J., Yerly, S., and Perrin, L., Loss of antibodies against hepatitis C virus in HIV-seropositive intravenous drug users. *AIDS.*, 4, 1275-1277 (1990).

Chapman, T. M., Plosker, G. L., and Perry, C. M., Fosamprenavir: a review of its use in the management of antiretroviral therapy-naive patients with HIV infection. *Drugs.*, 64, 2101-2124 (2004).

Clavel, F. and Hance, A. J., HIV Drug Resistance. *N. Engl. J. Med.*, 350, 1023-1035 (2004).

Clevenbergh, P., Corcostegui, M., Gerard, D., Hieronimus, S., Mondain, V., Chichmanian, R. M., Sadoul, J. L., and Dellamonica, P., Iatrogenic Cushing's syndrome in an HIV-infected patient treated with inhaled corticosteroids (fluticasone propionate) and low dose ritonavir enhanced PI containing regimen. *J. Infection.*, 44, 194-195 (2002).

Cohen, C. J., Hunt, S., Sension, M., Farthing, C., Conant, M., Jacobson, S., Nadler, J., Verbiest, W., Hertogs, K., Ames, M., Rinehart, A. R., Graham, N. M., and the VIRA3001 Study Team. A randomized trial assessing the impact of phenotypic resistance testing on antiretroviral therapy. *AIDS.*, 16, 579-588 (2002).

Colfax, G. N., Buchbinder, S. P., Corneliss, P. G., Vittinghoff, E., Mayer, K., and Celum, C., Sexual risk behaviors and implications for secondary HIV transmission during and after HIV seroconversion. *AIDS.*, 16, 1529-1535 (2002).

Colin, J. F., Cazals-Hatem, D., Loriot, M. A., Martinot-Peignoux, M., Pham, B. N., Auperin, A., Degott, C., Benhamou, J. P., Erlinger, S., Valla, D., and Marcellin P. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology*, 29, 1306-1310 (1999)

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).

Connor, E. M., Sperling, R. S., Gelber, R., and Kiselev, P., Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N. Engl. J. Med.,* 331, 1173-1180 (1994).

Cooper, C. L., van Heeswijk, R. P. G., Gallicano, K., and Cameron, D. W., A Review of Low-Dose Ritonavir in Protease Inhibitor Combination Therapy. *Clin. Infect. Dis.*, 36, 1585-1592 (2003).

Cooper, E. R., Charurat, M., Mofenson, L., Hanson, I. C., Pitt, J., Diaz, C., Hayani, K., Handelsman, E., Smeriglio, V., Hoff, R., Blattner, W., and the Women and Infants' Transmission Study Group. Combination antiretroviral strategies for the

treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J. Acquir. Immune Defic. Syndr.*, 29, 484-494 (2002).

Croom, K. F. and Keam, S. J., Tipranavir, A ritonavir boosted protease inhibitor. *Drug*, 65, 1669-1677 (2005).

D'Aquila, 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).

Darby, S. C., Ewart, D. W., Giangrande, P. L., Spooner, R. J., Rizza, C. R., Dusheiko, G. M., Lee, C. A., Ludlam, C. A., and Preston, F. E., Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation. *Lancet.*, 350, 1425-1431 (1997).

Deeks, S. G., Wrin, T., Liegler, T., Hoh, R., Hayden, M., Barbour, J. D., Hellmann, N. S., Petropoulos, C. J., McCune, J. M., Hellerstein, M. K., and Grant, R. M., Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *N. Engl. J. Med.*, 344, 472-480 (2001).

de Franchis, R., Hadengue, A., Lau, G., Lavanchy, D., Lok, A., McIntyre, N., Mele, A., Paumgartner, G., Pietrangelo, A., Rodes, J., Rosenberg, W., Valla, D., and the EASL Jury. EASL International Consensus Conference on Hepatitis B. 13-14 September, 2002 Geneva, Switzerland. Consensus statement (long version). *J. Hepatol.*, 39 (Suppl 1), S3-25 (2003).

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

den Brinker, M., Wit, F. W., Wertheim-van Dillen, P. M., Jurriaans, S., Weel, J., van Leeuwen, R., Pakker, N. G., Reiss, P., Danner, S. A., Weverling, G. J., and Lange, J. M., Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS.*, 14, 2895-2902 (2000).

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).

Dickover, R. E., Garratty, E. M., Herman, S. A., Sim, M. S., Plaeger, S., Boyer, P. J., Keller, M., Deveikis, A., Stiehm, E. R., and Bryson, Y. J., Identification of levels of maternal HIV-1 RNA associated with risk of perinatal transmission: effect of maternal zidovudine treatment on viral load. *JAMA.*, 275, 599-605 (1996).

di Martino, V., Lunel, F., Cadranel, J. F., Hoang, C., Parlier, Y., Le Charpentier, Y., and Opolon, P., Long-term effects of interferon-alpha in five HIV-positive patients with chronic hepatitis *B. J. Vir. Hepat.*, 3, 253-260 (1996).

Di Martino, V., Thevenot, T., Boyer, N., Degos, F., and Marcellin, P., Serum alanine transaminase level is a good predictor of response to interferon alfa therapy for chronic hepatitis B in human immunodeficiency virus-infected patients. *Hepatology*, 31, 1030-1031 (2000).

Di Martino, V., Rufat, P., Boyer, N., Renard, P., Degos, F., Martinot-Peignoux, M., Matheron, S., Le Moing,V., Vachon, F., Degott, C., Valla, D., and Marcellin, P. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. *Hepatology*, 34, 1193-1199 (2001).

Di Martino, V., Thevenot, T., Colin, J. F., Boyer, N., Martinot, M., Degos, F., Coulaud, J. P., Vilde, J. L., Vachon, F., Degott, C., Valla, D., and Marcellin, P., Influence of HIV infection on the response to interferon therapy and the long-term outcome of chronic hepatitis B. *Gastroenterology*, 123, 1812-1822 (2002).

Dore, G. J., Cooper, D. A., Barrett, C., Goh, L. E., Thakrar, B., and Atkins, M., Dual efficacy of lamivudine treatment in human immunodeficiency virus/hepatitis B virus-coinfected persons in a randomized, controlled study (CAESAR). The CAESAR Coordinating Committee. *J. Infect. Dis.*, 180, 607-613 (1999).

Dorenbaum, A., Cunningham, C. K., Gelber, R. D., Culnane, M., Mofenson, L., Britto, P., Rekacewicz, C., Newell, M. L., Delfraissy, J. F., Cunningham-Schrader, B., Mirochnick, M., Sullivan, J. L., and the International PACTG 316 Team. Two-dose--intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV-1 transmission: a randomized trial. *JAMA.*, 288, 189-198 (2002).

Doyon, L., Croteau, G., Thibeault, D., Poulin, F., Pilote, L., and Lamarre, D., Second locus involved in human immunodeficiency virus type 1 resistance to protease inhibitors. *J. Virol.*, 70, 3763-3769 (1996).

Dragsted, U. B., Gerstoft, J., Pedersen, C., Peters, B., Duran, A., Obel, N., Castagna, A., Cahn, P., Clumeck, N., Bruun, J. N., Benetucci, J., Hill, A., Cassetti, I., Vernazza, P., Youle, M., Fox, Z., Lundgren, J. D., and the MaxCmin1 Trial Group. Randomized trial to evaluate indinavir/ritonavir versus saquinavir/ritonavir in human immunodeficiency virus type 1-infected patients: the MaxCmin1 Trial. *J. Infect. Dis.*, 188, 635-642 (2003).

Dube, M. P., Disorders of glucose metabolism in patients infected with human immunodeficiency virus. *Clin. Infect. Dis.*, 31, 1467-1475 (2000).

Dube, M. P. and Sattler, F. R., Metabolic complications of antiretroviral therapies. *AIDS Clin. Care.*, 10, 41-44 (1998).

Dube, M. P., Stein, J. H., Aberg, J. A., Fichtenbaum, C. J., Gerber, J. G., Tashima, K. T., Henry, W. K., Currier, J. S., Sprecher, D., and Glesby, M. J., Adult AIDS Clinical Trials Group Cardiovascular Subcommittee. HIV Medical Association of the Infectious Disease Society of America. Guidelines for the evaluation and management of dyslipidemia in human

immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin. Infect. Dis.*, 37, 613-627 (2003).

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

Dybul, M., Fauci, A. S., Bartlett, J. G., Kaplan, J. E., and Pau, A. K., Guidelines for Using Antiretroviral Agents Among HIV-Infected Adults and Adolescents. *MMWR.*, 51(RR7), 1-64 (2002).

El-Sadr, W. and Neaton, J., Episodic CD4-guided use of antiretroviral therapy is inferior to continuous therapy: results of the SMART study. Abstract 106LB Conference on Retroviruses and Opportunistic Infections. Denver, CO. U.S.A., (2006).

Eskild, A., Magnus, P., Petersen, G., Sohlberg, C., Jensen, F., Kittelsen, P., and Skaug, K., Hepatitis B antibodies in HIV-infected homosexual men are associated with more rapid progression to AIDS. *AIDS.*, 6, 571-574 (1992).

Esnouf, R. M., Ren, J., Hopkins, A. L., Ross, C. K., Jones, E. Y., Stammers, D. K., and Stuart, D. I., Unique features in the structure of the complex between HIV-1 reverse transcriptase and the bis(heteroaryl)piperazine (BHAP) U-90152 explain resistance mutations for this nonnucleoside inhibitor. *P. Natl. Acad. Sci. U.S.A.*, 94, 3984-3989 (1997).

The European Collaborative Study. Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. *AIDS.*, 13, 1377-1385 (1999).

Fargioin, S., Fracanzani, A. L., and Valenti, L., Treatment Choices for people infected with HCV. *J. Antimicrob. Chemother.*, 53, 708-712 (2004).

Feng, J. Y., Myrick, F. T., Margot, N. A., Mulamba, G. B., Rimsky, L., Borroto-Esoda, K., Selmi, B., and Canard, B., Virologic and enzymatic studies revealing the mechanism of K65R- and Q151m-associated HIV-1 drug resistance towards emtricitabine and lamivudine. *Nucleos. Nucleot. Nucl.*, 25, 89-107 (2006).

Finzi, D., Hermankova, M., Pierson, T., Carruth, L. M., Buck, C., Chaisson, R. E., Quinn, T. C., Chadwick, K., Margolick, J., Brookmeyer, R., Gallant, J., Markowitz, M., Ho, D. D., Richman, D. D., and Siliciano, R. F., Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science*, 278, 1295-300 (1997).

Fischl, M. A., Zidovudine, p. 17-31. In Dolin R, Masur H, and Saag MS (ed),AIDS Therapy. Churchill Livingstone, Philadelphia. (1999).

Fish, D. E., Hay, A., Waters, J. A., McGarvey, M. J., Main, J., and Thomas, H. C., Histological and immunohistochemical study of hepatitis B virus in human immunodeficiency virus infection. *J. Clin. Pathol.*, 43, 203-205 (1990).

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).

Fried, M. W., Shiffman, M. L., Reddy, K. R., Smith, C., Marinos, G., Goncales, F. L. Jr., Haussinger, D., Diago, M., Carosi, G., Dhumeaux, D., Craxi, A., Lin, A., Hoffman, J., and Yu, J., Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N. Engl. J. Med.*, 347, 975-982 (2002).

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).

Friis-Moller, N., Sabin, C. A., Weber, R., d'Arminio Monforte, A., El-Sadr, W. M., Reiss, P., Thiebaut, R., Morfeldt, L., De Wit, S., Pradier, C., Calvo, G., Law, M. G., Kirk, O., Phillips, A. N., and Lundgren, J. D., Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N. Engl. J. Med.*, 349, 1993-2003 (2003).

Gallant, J. E., DeJesus, E., Arribas, J. R., Pozniak, A. L., Gazzard, B., Campo, R. E., Lu, B., McColl, D., Chuck, S., Enejosa, J., Toole, J. J., and Cheng, A. K., Study 934 Group. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N. Engl. J. Med.*, 354, 251-260 (2006).

Gallant, J. E. and Deresinski, S., Tenofovir disoproxil fumarate. *Clin. Infect. Dis.*, 37, 944-950 (2003).

Gallant, J. E., Rodriguez, A. E., Weinberg, W. G., Young, B., Berger, D. S., Lim, M. L., Liao, Q., Ross, L,. Johnson, J., and Shaefer, M. S., ESS30009 Study. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J. Infect. Dis.*, 192, 1921-1930 (2005).

Gallant, J. E., Staszewski, S., Pozniak, A. L., DeJesus, E., Suleiman, J. M., Miller, M. D., Coakley, D. F., Lu, B., Toole, J. J., and Cheng, A. K., 903 Study Group. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA.*, 292, 191-201 (2004).

Gao, H. Q., Boyer, P. L., Sarafianos, S. G., Arnold, E., and Hughes, S. H., The role of steric hindrance in 3TC resistance of human immunodeficiency virus type-1 reverse transcriptase. *J. Molec. Biol.*, 300, 403-418 (2000).

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).

Garcia-Samaniego, J., Rodriguez, M., Berenguer, J., Rodriguez-Rosado, R., Carbo, J., Asensi, V., and Soriano, V., Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am. J. Gastroenterol.*, 96, 179-183 (2001).

Gathe, J. C. Jr., Ive, P., Wood, R., Schurmann, D., Bellos, N. C., DeJesus, E., Gladysz, A., Garris, C., and Yeo, J., SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS.*, 18, 1529-1537 (2004).

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

Gerard, Y., Maulin, L., Yazdanpanah, Y., De La Tribonniere, X., Amiel, C., Maurage, C. A., Robin, S., Sablonniere, B., Dhennain, C., and Mouton, Y., Symptomatic hyperlactataemia: an emerging complication of antiretroviral therapy. *AIDS.*, 14, 2723-2730 (2000).

Gerstoft, J., Dragsted, U. B., and Cahn, P., Final analysis of a randomized trial to evaluate safety and efficacy of indinavir/ritonavir versus saquinavir/ritonavir in adult HIV-1 infection: the MAXCmin1 trial [abstract P29]. 6th International Congress on Drug Therapy in HIV Infection (Glasgow). London: Lippincott Williams & Wilkins, (2002).

Gerstoft, J., Mallolas, J., and Lundgren, J., A randomized trial comparing continued indinavir vs. switching to indinavir plus ritonavir in HIV patients having suppressed viral load with indinavir plus two nucleoside analogue reverse transcriptase inhibitors: the best study [abstract O-8]. In: 8th European Conference on Clinical aspects and Treatment of HIV Infection. Athens (2001).

Greub, G., Ledergerber, B., Battegay, M., Grob, P., Perrin, L., Furrer, H., Burgisser, P., Erb, P., Boggian, K., Piffaretti, J. C., Hirschel, B., Janin, P., Francioli, P., Flepp, M., and Telenti A., Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet.*, 356, 1800-1805 (2000).

Grinspoon, S. and Carr, A., Cardiovascular risk and body-fat abnormalities in HIV infected adults. *N. Engl. J. Med.*, 352, 48-62 (2005).

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. M., Ribaudo, H. J., Shikuma, C. M., Lustgarten, S., Squires, K. E., Meyer, W. A. 3rd., Acosta, E. P., Schackman. B. R., Pilcher. C. D., Murphy, R. L., Maher, W. E., Witt, M. D., Reichman, R. C., Snyder, S., Klingman, K. L., and Kuritzkes, D. R., AIDS Clinical Trials Group Study A5095 Team. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N. Engl. J. Med.*, 350, 1850-1861 (2004).

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 Hirsch, M. S., New Drugs in Development p. 263-272 In Dolin R, Masur H, and Saag MS (ed), AIDS Therapy. Churchill Livingstone, Philadelphia. (2003).

Haubrich, R. H., Kemper, C. A., Hellmann, N. S., Keiser, P. H., Witt, M. D., Tilles, J. G., Forthal, D. N., Leedom, J., Leibowitz, M., McCutchan, J. A., Richman, D. D., and the California Collaborative Treatment Group. A randomized, prospective study of phenotype susceptibility testing versus standard of care to manage antiretroviral therapy: CCTG 575. *AIDS.*, 19, 295-302 (2005).

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).

Havlir, D. V. and O'Marro, S. D., Atazanavir: New Option for Treatment of HIV Infection. *Clin. Infect. Dis.*, 38, 1599-1604 (2004).

Hecht, F. M., Grant, R. M., Petropoulos, C. J., Dillon, B., Chesney, M. A., Tian, H., Hellmann, N. S., Bandrapalli, N. I., Digilio, L., Branson, B., and Kahn, J. O., Brief Report: Sexual Transmission of an HIV-1 Variant Resistant to Multiple Reverse-Transcriptase and Protease Inhibitors *N. Engl. J. Med.*, 339, 307-311 (1998).

Hewitt, R. G., Abacavir hypersensitivity reaction. *Clin. Infect. Dis.*, 34, 1137-1142 (2002).

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).

Hinrichsen, H., Benhamou, Y., Wedemeyer, H., Reiser, M., Sentjens, R. E., Calleja, J. L., Forns, X., Erhardt, A., Cronlein, J., Chaves, R. L., Yong, C. L., Nehmiz, G., and Steinmann, G. G., Short-term antiviral efficacy of BILN 2061, a hepatitis C virus serine protease inhibitor, in hepatitis C genotype 1 patients. *Gastroenterol.*, 127, 1347-1355 (2004).

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

Hirsch, M. S., Brun-Vezinet, F., Clotet, B., Conway, B., Kuritzkes, D. R., D'Aquila, R. T., Demeter, L. M., Hammer, S. M., Johnson, V. A., Loveday, C., Mellors, J. W., Jacobsen, D. M., and Richman, D. D., Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an International AIDS Society-USA Panel. *Clin. Infect. Dis.,* 37, 113-128 (2003).

Hoff, J., Bani-Sadr, F., Gassin, M., and Raffi, F., Evaluation of chronic hepatitis B virus (HBV) infection in coinfected patients receiving lamivudine as a component of anti-human immunodeficiency virus regimens. *Clin. Infect. Dis.,* 32, 963-969 (2001).

Hoffman-LaRoche, Inc. Roferon-A Package Insert. (2001).

Hoofnagle, J. H., and Di Bisceglie, A. M., Drug Therapy: The Treatment of Chronic Viral Hepatitis. *N. Engl. J. Med.*, 336, 347-356 (1997).

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).

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

Imhof, A., Ledergerber, B., Gunthard, H. F., Haupts, S., and Weber, R., Swiss HIV Cohort Study. Risk factors for and outcome of hyperlactatemia in HIV-infected persons: is there a need for routine lactate monitoring? *Clin. Infect. Dis.,* 41, 721-728 (2005).

The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1. A meta-analysis of 15 prospective cohort studies. *N. Engl. J. Med.*, 340, 977-987 (1999).

Ioannidis, J. P. A., Abrams, E. J., Ammann, A., Bulterys, M., Goedert, J. J., Gray, L., Korber, B. T., Mayaux, M. J., Mofenson, L. M., Newell, M. L., Shapiro, D. E., Teglas, J. P., and Wilfert, C. M., Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/mL. *J. Infect. Dis.*, 183, 539-545 (2001).

Iversen, A. K., Shafer, R. W., Wehrly, K., Winters, M. A., Mullins, J. I., Chesebro, B., and Merigan, T. C., Multidrug-resistant human immunodeficiency virus type 1 strains resulting from combination antiretroviral therapy. *J. Virol.*, 70, 1086-1090 (1996).

Japour, A., Lertora, J., Meehan, P. M., Erice, A., Connor, J. D., Griggith, B. P., Clax, P. A., Holden-Wiltse, J., Hussey, S., Walesky, M., Cooney, E., Pollard, R., Timpone, J., McLaren, C., Johanneson, N., Wood, K., Booth, D., Bassiakos, Y., and Crumpacker, C. S., A phase I study on the safety, pharmacokinetics and antiviral activity of combination didanosine and ribavirin in patients with HIV-1 disease (ACTG 231 protocol). *JAIDS.*, 13, 235-246 (1996).

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

Joint United Nations Programme on HIV/AIDS (UNAIDS), and World Health Organization (WHO). Global Summary of the AIDS Epidemic. AIDS epidemic update: December 2005, 1-2 (2005).

Jourdain, G., Ngo-Giang-Huong, N., LeCour, S., Bowonwatanuwong, C., Kantipong, P., Leechanachai, P., Ariyadej, S., Leenasirimakul, P., Hammer, S., Lallemant, M., and the Perinatal HIV Prevention Trial Group. Intrapartum Exposure to Nevirapine and Subsequent Maternal Responses to Nevirapine-Based Antiretroviral Therapy. *N. Engl. J. Med.,* 351, 229-240 (2004).

Kakuda, T. and Brinkman, K., Mitochondrial toxic effects of ribavirin. *Lancet.*, 357, 1802-1803 (2001).

Katlama, C., Berger, D., Bellos, N., Grinsztejn, B., Haubrich, R., Wilkin, T., Monlina, J. M., Steinhart, C., Pedro, R., de Bethune, M. P., De Meyer, S., Hoetelmans, R., Parys, W., Vangeneuden, T., and Lefebvre, E., Efficacy of TMC114/r in 3 class experienced patients with limited treatment options: 24 week planned interim analysis of 2 96 week multinational dose-finding trials. Abstract 164LB Conference on Retroviruses and Opportunistic Infections, Boston, MA. U.S.A. (2005).

Katner, H. P., Paar, D. P., Nadler, J. P., Jensen, E. H., Wilson, H. M., Finn, T. S., Petruschke, R. A., and Zeldin, R. K., Open-label study of a twice-daily indinavir 800-mg/ritonavir 200 mg regimen in HIV-infected adults failing a protease inhibitor regimen. *J. AIDS.*, 483-487 (2002).

Karrer, U., Ledergerber, B., Furrer, H., Elzi, L,. Battegay, M., Cavassini, M., Gayet-Ageron, A., Hirschel, B., Schmid, P., Russotti, M., Weber, R., and Speck, R. F., Swiss HIV Cohort Study. Dose-dependent influence of didanosine on immune recovery in HIV-infected patients treated with tenofovir. *AIDS.*, 19, 1987-1994 (2005).

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

Kearney, B. P., Mittan, A., Sayre, J., Flaherty, J. F., Zhong, L., Toole, J. J., and Cheng, A. K., Pharmacokinetic drug interaction and long term safety profile of tenofovir DF and lopinavir/ritonavir. Abstract A-1617. ICAAC September 2003 Chicago Ill.

Kearney, B. P., Flaherty, J. F., and Shah, J., Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. *Clin. Pharm.*, 43, 595-612 (2004).

Kempf, D. J., Marsh, K. C., Kumar, G., Rodrigues, A. D., Denissen, J. F., McDonald, E., Kukulka, M. J., Hsu, A., Granneman, G. R., Baroldi, P. A., Sun, E., Pizzuti, D., Plattner, J. J., Norbeck, D. W., and Leonard, J. M., Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir. *Antimicrob. Agents. Chemother.*, 41, 654-660 (1997).

Keswani, S. C., Pardo, C. A., Cherry, C. L., Hoke, A. and McArthur, J. C., HIV-associated sensory neuropathies. *AIDS.*,

16, 2105-2117 (2002).

Kilby, J. M., Inhibitors of HIV attachment and fusion. P. 252-262. In Dolin R, Masur H, and Saag MS (ed),AIDS Therapy. Churchill Livingstone, Philadelphia. (1999).

Kilby, J. M. and Eron, J. J., Novel therapies based on mechanisms of HIV-1 cell entry. N. *Engl. J. Med.*, 348, 2228-2238 (2003).

Kilby, J. M., Sfakianos, G., Gizzi, N., Siemon-Hryczyk, P., Ehrensing, E., Oo, C., Buss, N., and Saag, M. S. Safety and pharmacokinetics of once-daily regimens of soft-gel capsule saquinavir plus minidose ritonavir in human immunodeficiency virus-negative adults. *Antimicrob Agents Chemother.*, 44, 2672-2678 (2000).

Kohlbrenner, V. M., Development of a tipranavir mutation score: analysis of protease mutations associated with phenotypic drug susceptibility and antiviral response in Phase II clinical trials. XIII International HIV Drug Resistance Workshop. Tenerife, Spain. (2004).

Kosalaraksa, P., Kavlick, M. F., Maroun, V., Le R., and Mitsuya, H., Comparative fitness of multi-dideoxynucleoside-resistant human immunodeficiency virus type 1 (HIV-1) in an *in vitro* competitive HIV-1 replication assay. *J. Virol.*, 73, 5356-5363 (1999).

Knudtson, E., Para, M., Boswell, H., and Fan-Havard, P., Drug Rash with Eosinophilia and Systemic Symptoms Syndrome and Renal Toxicity with a Nevirapine-Containing Regimen in a Pregnant Patient with Human Immunodeficiency Virus. *Obstet. Gynecol.*, 101, 1094-1097 (2003).

Konopnicki, D., Mocroft, A., de Wit, S., Antunes, F., Ledergerber, B., Katlama, C., Zilmer, K., Vella, S., Kirk, O., Lundgren, J. D., and the EuroSIDA Group. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS.*, 19, 593-601 (2005).

Kuhn, L., Abrams, E. J., Matheson, P. B., Thomas, P. A., Lambert, G., Bamji, M., Greenberg, B., Steketee, R. W., Thea, D. M., for the New York City Perinatal HIV Transmission Collaborative Study Group. Timing of maternal-infant HIV transmission: associations between intrapartum factors and early polymerase chain reaction results. *AIDS.*, 11, 429-435 (1997).

Kurowski, M., Kaeser, B., Sawyer, A., Popescu, M., and Mrozikiewicz, A., Low-dose ritonavir moderately enhances nelfinavir exposure. *Clin. Pharmacol. Ther.*, 72, 123-132 (2002).

Lafeuillade, A., Hittinger, G., and Chapadaud, S., Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. *Lancet.*, 357, 280-281 (2001).

Lalezari, J. P., Henry, K., O'Hearn, M., Montaner, J. S., Piliero, P. J.. Trottier, B., Walmsley, S., Cohen, C., Kuritzkes, D. R., Eron, J. J. Jr., Chung, J., DeMasi, R., Donatacci, L., Drobnes, C., Delehanty, J., and Salgo, M., TORO 1 Study Group. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N. Engl. J. Med.*, 348, 2175-2185 (2003).

Lallemant, M., Jourdain, G., LeCoeur, S., Mary, J. Y., Ngo-Giang-Huong, N., Koetsawang, S., Kanshana, S., McIntosh, K., Thaineua, V., and the Perinatal HIV Prevention Trial (Thailand) Investigators. Single-Dose Perinatal Nevirapine plus Standard Zidovudine to Prevent Mother-to-Child Transmission of HIV-1 in Thailand. *N. Engl. J. Med.*, 351, 217-228 (2004).

Landau, A., Batisse, D., Piketty, C., Jian, R., and Kazatchkin, M., Lack of interference between ribavirin and nucleoside analogues in HIV/HCV coinfected individuals undergoing concomitant antiretroviral and anti-HCV combination therapy. *AIDS.*, 14, 1857-1858 (2000).

Larder, B. A., and Kemp, S. D., Multiple mutations in HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT). *Science*, 246, 1155-1158 (1989).

Larder, B. A., Kemp, S. D., and Harrigan, P. R., Potential mechanism for sustained antiretroviral efficacy of AZT-3TC combination therapy. *Science.*, 269, 696-699 (1995).

Lauer, G. M. and Walker, B. D., Hepatitis C Virus Infection. *N. Engl. J. Med.*, 345, 41-52 (2001).

Lawrence, J., Mayers, D. L., Hullsiek, K. H., Collins, G., Abrams, D. I., Reisler, R. B., Crane, L. R., Schmetter, B. S., Dionne, T. J., Saldanha, J. M., Jones, M. C., and Baxter, J. D., 064 Study Team of the Terry Beirn Community Programs for Clinical Research on AIDS. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N. Engl. J. Med.*, 349, 837-846 (2003).

Lazzarin, A., Clotet, B., Cooper, D., Reynes, J., Arasteh, K., Nelson, M., Katlama, C., Stellbrink, H. J., Delfraissy, J. F., Lange, J., Huson, L., DeMasi, R., Wat, C., Delehanty, J., Drobnes, C., and Salgo, M., TORO 2 Study Group. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N. Engl. J. Med.*, 348, 2186-2195 (2003).

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).

Lee, W. M., Medical Progress: Hepatitis B Virus Infection. *N. Engl. J. Med.*, 337, 1733-1745 (1997).

Le Tiec, C., Barrail, A., Goujard, C., and Taburet, A. M., Clinical pharmacokinetics and summary of efficacy and tolerability of atazanavir. *Clin. Pharmacokinet.*, 44, 1035-50 (2005).

Levine, S., Hernandez, D., Yamanaka, G., Zhang, S., Rose, R., Weinheimer, S., and Colonno, R. J., Efficacies of Entecavir against lamivudine-resistant hepatitis B virus replication and recombinant polymerases *in vitro*. *Antimicrob. Agents. Chemother.*, 46, 2525-2532 (2002).

Lisziewicz, J., Rosenberg, E., Lieberman, J., Jessen, H., Lopalco, L., Siliciano, R., Walker, B., and Lori, F., Control of HIV

despite the discontinuation of antiretroviral therapy. *N. Engl. J. Med.,* 340,1683-1684 (1999).

Little, S. J., Holte, S., Routy, J.-P., Daar, E. S., Markowitz, M., Collier, A. C., Koup, R. A., Mellors, J. W., Connick, E., Conway, B., Kilby, M., Wang, L., Whitcomb, J. M., Hellmann, N. S., and Richman, D. D., Antiretroviral-Drug Resistance among Patients Recently Infected with HIV. *N. Engl. J. Med.,* 347, 385-394 (2002a).

Little, S. J., Daar, E. S., Holte, S., Frost, S., Routy, J. P., Markowitz, M., Collier, A. C., Margolick, J. B., Koup, R. A., Conway, B., Connick, E., Kilby, M., Wrin, T., Petropoulos, C. J., Hellmann, N. S., and Richman, D. D., Persistence of transmitted drug resistance among subjects with primary HIV infection not receiving antiretroviral therapy. In: 9th Conference on Retroviruses and Opportunistic Infections. Abstract 95. (2002b).

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

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).

McMahon, B. J., Epidemiology and natural history of hepatitis B. *Sem. Liver. Disease.,* 1 (25 Suppl), 3-8 (2005).

Maitland, D., Moyle, G., Hand, J., Mandalia, S., Boffito, M., Nelson, M., and Gazzard, B., Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. *AIDS.* 19,1183-1188 (2005)

Malik, A., Abraham, P., and Malik, N. Acute renal failure and Fanconi syndrome in an AIDS patient on tenofovir treatment--case report and review of literature. *J. Infect.* 51, E61-65 (2005)

Marcelin, A. G., Delaugerre, C., Wirden, M., Viegas, P., Simon, A., Katlama, C., and Calvez, V., Thymidine analogue reverse transcriptase inhibitors resistance mutations profiles and association to other nucleoside reverse transcriptase inhibitors resistance mutations observed in the context of virological failure. *J. Med. Virol.*, 72, 162-165 (2004).

Marcellin, P., Asselah, T., and Boyer, N., Treatment of chronic hepatitis B. *J. Viral. Hepatit.*, 12, 333-345 (2005).

Marrone, A., Zampino, R., Karayannis, P., Cirillo, G., Cesaro, G., Guerrera, B., Ricciotti, R., del Giudice, E. M., Utili, R., Adinolfi, L. E., and Ruggiero, G., Clinical reactivation during lamivudine treatment correlates with mutations in the precore/core promoter and polymerase regions of hepatitis B virus in patients with anti-hepatitis B e-positive chronic hepatitis. *Aliment. Pharm. Therap.*, 22, 707-714 (2005).

Martin, A., Smith, D. E., Carr, A., Ringland, C., Amin, J., Emery, S., Hoy, J., Workman, C., Doong, N., Freund, J., and Cooper, D. A., Mitochondrial Toxicity Study Group. Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *AIDS.*, 18, 1029-1036 (2004).

Martinez, E., Arnaiz, J. A., Podzamczer, D., Dalmau, D., Ribera, E., Domingo, P., Knobel, H., Riera, M., Pedrol, E., Force, L., Llibre, J. M., Segura, F., Richart, C., Cortes, C., Javaloyas, M., Aranda, M., Cruceta, A., de Lazzari, E., and Gatell, J. M., Nevirapine, Efavirenz, and Abacavir (NEFA) Study Team. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N. Engl. J. Med.*, 349, 1036-1046 (2003).

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., and 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).

Menzo, S., Castagna, A., Monachetti, A., Hasson, H., Danise, A., Carini, E., Bagnarelli, P., Lazzarin, A., and Clementi, M., Genotype and phenotype patterns of human immunodeficiency virus type 1 resistance to enfuvirtide during long-term treatment. *Antimicrob. Agents. Chemother.,* 48, 3253-3259 (2004).

Meynard, J. L., Vray, M., Morand-Joubert, L., Race, E., Descamps, D., Peytavin, G., Matheron, S., Lamotte, C., Guiramand, S., Costagliola, D., Brun-Vezinet, F., Clavel, F., Girard, P. M., and the Narval Trial Group. Phenotypic or genotypic resistance testing for choosing antiretroviral therapy after treatment failure: a randomized trial. *AIDS.*, 16, 727-736 (2002).

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).

Minkoff, H. and Augenbraun, M., Antiretroviral therapy for pregnant women. *Am. J. Obstet. Gynecol.,* 176, 478-489 (1997).

Mock, P. A., Shaffer, N., Bhadrakom, C., Siriwasin, W., Chotpitayasunondh, T., Chearskul, S., Young, N. L., Roongpisuthipong, A., Chinayon, P., Kalish, M. L., Parekh, B., and Mastro, T. D., Maternal viral load and timing of mother-to-child HIV transmission, Bangkok, Thailand. *AIDS.*, 13, 407-414 (1999).

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 immunode-

ficiency virus infection. *Arch. Intern. Med.*, 158, 491-497 (1998).

Mofenson, L. M., Lambert, J.S., Stiehm, E.R., Bethel, J., Meyer, W. A., Whitehouse, J., Moye 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).

Mofenson, L. M. and the U.S. Public Health Service Task Force Recommendations for Use--of Antiretroviral Drugs in Pregnant HIV-1--Infected Women for Maternal Health and Interventions To Reduce Perinatal HIV-1 Transmission in the United States. *MMWR.*, 51 (RR18), 1-38 (2002).

Molto, J., Ruiz, L., Romeu, J., Martinez-Picado, J., Negredo, E., Tural, C., Sirera, G., and Clotet, B., Influence of prior structured treatment interruptions on the length of time without antiretroviral treatment in chronically HIV-infected subjects. *AIDS Res. & Hum. Retrovir.*, 20, 1283-1288 (2004).

Monga, H. K., Rodriguez-Barradas, M. C., Breaux, K., Khattak, K., Troisi, C. L., Velez, M., and Yoffe, B., Hepatitis C virus infection-related morbidity and mortality among patients with human immunodeficiency virus infection. *Clin. Infect. Dis.*, 33, 240-247 (2001).

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).

MMWR. Incidence of Acute Hepatitis B—United States, 1990-2002. *MMWR.*, 51, 1252-1254 (2004).

Morsica, G., De Bona, A., Uberti, C., Sitia, G., Finazzi, R., and Lazzarin, A., Ribavirin therapy for chronic hepatitis C does not modify HIV viral load in HIV-1 positive patients under antiretroviral treatment. *AIDS.*, 14, 1656-1658 (2000).

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., Brun, S., and King, M., Lopinavir/ritonavir (Kaletra) in antiretroviral naïve HIV+ patients: 4 year follow-up [abstract H-165]. 42nd Interscience on Conference on Antimicrobial Agents and Chemotherapy (San Diego). (2002).

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., and 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).

Musselman, D. L., Lawson, D. H., Gumnick, J. F., Manatunga, A. K., Penna, S., Goodkin, R. S., Greiner, K., Nemeroff, C. B., and Miller, A. H., Paroxetine for the Prevention of Depression Induced by High-Dose Interferon Alfa. *N. Engl. J. Med.,* 344, 961-966 (2001).

Nduati, R., Grace, J., Mbori-Ngacha, D., Richardson, B., Overbaugh, J., Mwatha, A., Ndinya-Achola, J., Bwayo, J., Onyango, F. E., Hughes, J., and Kreiss, J., Effect of breast-feeding and formula feeding on transmission of HIV-1: a randomised clinical trial. *JAMA.*, 283, 1167-1174 (2000).

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).

Núñez, M., Puoti, M., Camino, N., and Soriano, V., Treatment of chronic hepatitis B in the human immunodeficiency virus-infected patient: present and future. *Clin. Infect. Dis.,* 37, 1678-1685 (2003).

Núñez, M., Maida, I., Berdún, M., and Soriano, V., Efficacy and safety of pegylated interferon a-2a plus ribavirin for the treatment of hepatitis C in HIV-coinfected patients: the PRESCO trial. In: 44th ICAAC, Abstract V-1148 (2004).

O'Brien, 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 anti-retroviral 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 immunodeficiency virus infection. *N. Engl. J. Med.*, 338, 853-60 (1998).

Department of Health and Human Services. 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. (2005).

Panlilio, A. L., Cardo, D. M. Grohskopf, L. A., Heneine, W., and Ross, C. S., Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis. *MMWR.*, 54 (RR09), 1-17 (2005).

Perrillo, R. P., Regenstein, F. G., and Roodman, S. T., Chronic hepatitis B in asymptomatic homosexual men with antibody to the human immunodeficiency virus. *Ann. Intern. Med.*, 105, 382-3 (1986).

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*, 53, 657-680 (1997).

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

Pesce, A., Taillan, B., and Rosenthal, E., Opportunistic infections and CD4 lymphocytopenia with interferon treatment in HIV-1 infected patients. *Lancet.*, 341, 1597 (1993).

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).

Picard, V., Angelini, E., Maillard, A., Race, E., Clavel, F., Chene, G., Ferchal, F., and Molina, J. M., Comparison of genotypic and phenotypic resistance patterns of human immunodeficiency virus type 1 isolates from patients treated with stavudine and didanosine or zidovudine and lamivudine. *J. Infect. Dis.*, 184, 781-784 (2001).

Piroth, L., Duong, M., Quantin, C., Abrahamowicz, M., Michardiere, R., Aho, L. S., Grappin, M., Buisson, M., Waldner, A., Portier, H., and Chavanet, P., Does hepatitis C virus co-infection accelerate clinical and immunological evolution of HIV-infected patients? *AIDS.*, 12, 381-388 (1998).

Piscitelli, S. C. and Gallicano, K. D., Interactions among drugs for HIV and opportunistic infections. *N. Engl. J. Med.,* 344, 984-996 (2001).

Piwoz, E. G., Ross, J., and Humphrey, J., Human immunodeficiency virus transmission during breastfeeding: knowledge, gaps, and challenges for the future. *Adv. Exp. Med. Biol.*, 554, 195-210 (2004).

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).

Pramoolsinsup, C., Management of viral hepatitis B. *J. Gastroen. Hepatol.*, 17, S125-S145 (2002).

Preston, D. B., Poiesz, B. J., and Loeb, L. A., Fidelity of HIV-1 reverse transcriptase. *Science*, 242, 1168-1171 (1998).

Public Health Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States. *MMWR.*, 47(RR-2) 1-30 (1998).

Public Health Service Task Force. Recommendations for Use of Antiretroviral drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States. *MMWR.*, 47 (RR-2) 1-55 (2005).

Quaranta, J. F., Delaney, S. R., Alleman, S., Cassuto, J. P., Dellamonica, P., and Allain, J. P., Prevalence of antibody to hepatitis C virus (HCV) in HIV-1-infected patients (nice SEROCO cohort). *J. Med. Virol.,* 42, 29-32 (1994).

Quinn, T. C., Wawer, M. J., Sewankambo, N., Serwadda, D., Li C., Wabwire-Mangen, F., Meehan, M. O., Lutalo, T., and Gray R. H., Viral load and heterosexual transmission of immunodeficiency virus type 1. *N. Engl. J. Med.*, 342, 921-929 (2000).

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

Resch, W., Parkin, N., Stuelke, E. L., Watkins, T., and Swanstrom, R., A multiple-site-specific heteroduplex tracking assay as a tool for the study of viral population dynamics. *P. Natl. Acad. Sci. U.S.A.*, 98, 176-181 (2001).

Rodriguez-French, A., Boghossian, J., Gray, G. E,. Nadler, J. P., Quinones, A. R., Sepulveda, G. E., Millard, J. M., and Wannamaker, P. G., The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naive HIV-1-infected patients. *J. AIDS.*, 35, 22-32 (2004).

Ristig, M. B., Crippin, J., Aberg, J. A., Powderly, W. G., Lisker-Melman, M., Kessels, L., and Tebas, P., Tenofovir disoproxil fumarate therapy for chronic hepatitis B in human immunodeficiency virus/hepatitis B virus-coinfected individuals for whom interferon-alpha and lamivudine therapy have failed. *J. Infect. Dis.*, 186, 1844-1847 (2002).

Roberts, J. D., Bebenek, K., and Kunkel, T. A., The accuracy of reverse transcriptase from HIV-1. *Science*, 242, 1171-1173 (1998).

Rockstroh, J. K., Mocroft, A., Soriano, V., Tural, C., Losso, M. H., Horban, A., Kirk, O., Phillips, A., Ledergerber, B., Lundgren, J., and the EuroSIDA Study Group. Influence of Hepatitis C Virus Infection on HIV-1 Disease Progression and Response to Highly Active Antiretroviral Therapy. *J. Infect. Dis.*, 192, 992-1002 (2005).

Rodriguez, M., Berenguer, J., Rodriguez-Rosado, R., Carbo, J., Asensi, V., and Soriano, V., Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am. J. Gastroenterol.*, 96, 179-183 (2001).

Saag, M. S., Emtricitabine, a new antiretroviral agent with activity against HIV and Hepatitis B Virus. *Clin. Infect. Dis.,* 42, 126-131 (2006).

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 immunological and virological responses to HAART. Abstract 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, U.S.A. (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).

Salmon-Céron, D., Chauvelot-Moachon, L., Abad, S., Silbermann, B., and Sogni, P., Mitochondrial toxic effects and ribavirin. *Lancet.*, 357, 1803-1804 (2001).

Samuel, R. and Suh, B., Antiretroviral therapy 2000. *Arch. Pharm. Res.*, 23, 425-437 (2000).

Sarisky, R. T., Non-nucleoside inhibitors of the HCV polymerase. *J. Anitmicrob. Chemother.*, 54, 14-16 (2004).

Schuurman, R., Nijhuis, M., van Leeuwen, R., Schipper, P., de Jong, D., Collis, P., Danner, S. A., Mulder, J., Loveday, C., and Christopherson, C., Rapid changes in human immunodeficiency virus type 1 RNA load and appearance of drug-resistant virus populations in persons treated with lamivudine (3TC). *J. Infect Dis.*, 171, 1411-1419 (1995).

Scully, C. and Porter, S., HIV topic update: oro-genital transmission of HIV. *Oral Dis.*, 6, 92-98 (2000).

Shire, N. J. and Sherman, K. E., Management of HBV/HIV coinfected patients. *Seminars in Liver Disease*, 25 (Suppl 1), 48-57 (2005).

Solomon, R. E., VanRaden, M., Kaslow, R. A., Lyter, D., Visscher, B., Farzadegan, H., and Phair, J., Association of hepatitis B surface antigen and core antibody with acquisition and manifestations of human immunodeficiency virus type 1 (HIV-1) infection. *Am. J. Public Health.*, 80, 1475-1478 (1990).

Soriano, V., Sulkowski, M., Bergin, C., Hatzakis, A., Cacoub, P., Katlama, C., Cargnel, A., Mauss, S., Dieterich, D., Moreno, S., Ferrari, C., Poynard, T., and Rockstroh, J., Care of patients with chronic hepatitis C and HIV co-infection: recommendations from the HIV-HCV International Panel. *AIDS.*, 16, 813-828 (2002).

Soriano, V., Puoti, M., Sulkowski, M., Mauss, S., Cacoub, P., Cargnel, A., Dieterich, D., Hatzakis, A., and Rockstroh, J., Care of patients with hepatitis C and HIV co-infection. Updated recommendations from the HIV-HCV International Panel. *AIDS.*, 18, 1-12 (2004).

Soriano, V., Martin-Carbonero, L., Maida, I., Garcia-Samaniego, J., and Núñez, M., New paradigms in the management of HIV and hepatitis C virus coinfection. *Curr. Opin. Infect. Dis.*, 18, 550-560 (2005).

Soto, B., Sanchez-Quijano, A., Rodrigo, L., del Olmo, J. A., Garcia-Bengoechea, M., Hernandez-Quero, J., Rey, C., Abad, M. A., Rodriguez, M., Sales Gilabert, M., Gonzalez F., Miron, P., Caruz, A., Relimpio, F., Torronteras, R., Leal, M., and Lissen, E. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J. Hepatol.*, 26, 1-5 (1997).

Spengler, U., Lichterfeld, M., and Rockstroh, J. K., Antiretroviral drug toxicity -- a challenge for the hepatologist? *J. Hepatol.* 36, 283-294 (2002).

Squires, K., Lazzarin, A., Gatell, J. M., Powderly, W. G., Pokrovskiy, V., Delfraissy, J. F., Jemsek, J., Rivero, A., Rozenbaum, W., Schrader, S., Sension, M., Vibhagool, A., Thiry, A., and Giordano, M., Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J. AIDS.*, 36, 1011-1019 (2004).

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).

Steel, H. M., Special presentation on aplaviroc-related hepatotoxicity. Program and abstracts of the European AIDS Clinical Society 10th European AIDS Conference; November 17-20, Dublin, Ireland (2005).

Sterling, T. R., Chaisson, R. E., and Moore, R. D., Initiation of highly active antiretroviral therapy at CD4+ T lymphocyte counts of >350 cells/mm3: disease progression, treatment durability, and drug toxicity. *Clin. Infect. Dis.*, 36, 812-815 (2003).

Sulkowski, M. S., Moore, R. D., Mehta, S. H., Chaisson, R. E., and Thomas, D. L., Hepatitis C and progression of HIV disease. *JAMA.*, 288, 199-206 (2002).

Tedaldi, E. M., Baker, R. K., Moorman, A. C., Alzola, C. F., Furhrer, J., McCabe, R. E., Wood, K. C., and Holmberg, S. D., HIV Outpatient Study (HOPS) Investigators. Influence of coinfection with hepatitis C virus on morbidity and mortality due to human immunodeficiency virus infection in the era of highly active antiretroviral therapy. *Clin. Infect. Dis.*, 36, 363-367 (2003).

Tenney, D. J., Levine, S. M., Rose, R. E., Walsh, A. W., Weinheimer, S. P., Discoto, L., Plym, M., Pokornowski, K., Yu, C. F., Angus, P., Ayres, A., Bartholomeusz, A., Sievert, W., Thompson, G., Warner, N., Locarnini, S., and Colonno, R., J. Clinical emergence of entecavir-resistant hepatitis B virus requires additional substitutions in virus already resistant to lamivudine. *Antimicrob. Agents. Chemother.*, 48, 3498-5307 (2004).

Thea, D. M, Steketee, R. W., Pliner, V., Bornschlegel, K., Brown, T., Orloff, S., Matheson, P. B., Abrams, E. J., Bamji, M., Lambert, G., Schoenbaum, E. A., Thomas, P. A., Heagarty, M., and Kalish, M. L., The effect of maternal viral load on the risk of perinatal transmission of HIV-1. *AIDS.*, 11, 437-44 (1997).

Thio, C. L., Seaberg, E. C., Skolasky, R., Phair, J., Visscher, B., Munoz, A., and Thomas, D. L., for the Multicenter AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet.*, 360, 1921-1926 (2002).

Thorne, C. and Newell, M. L., Treatment options for the prevention of mother-to-child transmission of HIV. *Cur. Opin. Invest. Drugs.*, 6, 804-811 (2005).

Torriani, F. J., Rodriguez-Torres, M., Rockstroh, J. K., Lissen, E., Gonzalez-Garcia, J., Lazzarin, A., Carosi, G., Sasadeusz, J., Katlama, C., Montaner, J., Sette, H. Jr., Passe, S., De Pamphilis, J., Duff, F., Schrenk, U. M., and Dieterich, D. T., for the APRICOT Study Group. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N. Engl. J. Med.*, 351, 438-450 (2004).

Troisi, C. L., Hollinger, F. B., Hoots, W. K., Contant, C., Gill, J., Ragni, M., Parmley, R., Sexauer, C., Gomperts, E., and Buchanan, G., A multicenter study of viral hepatitis in a United States hemophilic population. *Blood*, 81, 412-418 (1993).

Tuomala, R. E., Shapiro, D. E., Mofenson, L. M., Bryson, Y., Culnane, M., Hughes, M. D., O'Sullivan, M. J., Scott, G., Stek, A. M., Wara, D., and Bulterys, M., Antiretroviral Therapy During Pregnancy and the Risk of an Adverse Outcome. *N. Engl. J. Med.*, 346, 1863-1870 (2002).

Tural, C., Ruiz, L., Holtzer, C., Schapiro, J., Viciana, P., Gonzalez, J., Domingo, P., Boucher, C., Rey-Joly, C., and Clotet, B., for the Havana Study Group. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. *AIDS.*, 16, 209-218 (2002).

UNAIDS/WHO. Report on the Global HIV/AIDS Epidemic. January (2006).

US Department of Health and Human Services, HIV/AIDS Treatment and Information Service. Safety and toxicity of individual antiretroviral agents in pregnancy, May 17, 2002. In: Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. *MMWR.*, 51(RR7), 1-64 (2002).

Van Ameijden, E. J., van den Hoek, J. A., Mientjes, G. H., and Coutinho, R. A., A longitudinal study on the incidence and transmission patters on HIV, HBV and HCV infection among drug users in Amsterdam. *Eur. J. Epidemiol.*, 9, 255-262 (1993).

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. Method.*, 49, 157-168 (1994).

van Leth, F., Phanuphak, P., Ruxrungtham, K., Baraldi, E., Miller, S., Gazzard, B., Cahn, P., Lalloo, U. G., van der Westhuizen, I. P., Malan, D. R., Johnson, M. A., Santos, B. R., Mulcahy, F., Wood, R., Levi, G. C., Reboredo, G., Squires, K., Cassetti, I., Petit, D., Raffi, F., Katlama, C., Murphy, R. L., Horban, A., Dam, J. P., Hassink, E., van Leeuwen, R., Robinson, P., Wit, F. W., and Lange, J. M. 2NN Study team. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet.*, 363, 1253-1263 (2004).

van Heeswijk, R. P., Veldkamp, A. I., Hoetelmans, R. M., Mulder, J. W., Schreij, G., Hsu, A., Lange, J. M., Beijnen, J. H., and Meenhorst, P. L., The steady-state plasma pharmacokinetics of indinavir alone and in combination with a low dose of ritonavir in twice daily dosing regimens in HIV-1-infected individuals. *AIDS.*, 13, F95-99 (1999).

Veldkamp, A. I., van Heeswijk, R. P., Mulder, J. W., Meenhorst, P. L., Schreij, G., van der Geest, S., Lange, J. M., Beijnen, J. H., and Hoetelmans, R. M., Steady-state pharmacokinetics of twice-daily dosing of saquinavir plus ritonavir in HIV-1-infected individuals. *J. AIDS.*, 27, 344-349 (2001).

Vento, S., Di Perri, G., Cruciani, M., Garofano, T., Concia, E., and Bassetti, D., Rapid decline of CD4+ cells after interferon treatment in HIV-1 infection. *Lancet.*, 341, 958–959 (1993).

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).

Walmsley, S., Bernstein, B., King, M., Arribas, J., Beall, G., Ruane, P., Johnson, M., Johnson, D., Lalonde, R., Japour, A., Brun, S., and Sun, E., M98-863 Study Team. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N. Engl. J. Med.*, 346, 2039-2046 (2002).

Watts, D. H., Management of Human Immunodeficiency Virus Infection in Pregnancy. *N. Engl. J. Med.*, 346, 1879-1891 (2002).

Weinheimer, S., Discotto, L., Friborg, J., Yang, H., and Colonno, R., Atazanavir signature I50L resistance substitution accounts for unique phenotype of increased susceptibility to other protease inhibitors in a variety of human immunodeficiency virus type 1 genetic backbones. *Antimicrob. Agent. Chemother.*, 49, 3816-3824 (2005).

White, K. L., Margot, N. A., Ly, J. K., Chen, J. M., Ray, A. S., Pavelko, M., Wang, R., McDermott, M., Swaminathan, S., and Miller, M. D., A combination of decreased NRTI incorporation and decreased excision determines the resistance profile of HIV-1 K65R RT. *AIDS.*, 19, 1751-1760 (2005).

Winnock, M., Salmon-Céron, D., Dabis, F., and Chêne, G., Interaction between HIV-1 and HCV infections: towards a new entity? *J. Antimicrob. Chemother.*, 53, 936-946 (2004).

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).

Ying, C., De Clercq, E., Nicholson, W., Furman, P., and Neyts, J. Inhibition of the replication of the DNA polymerase M550V mutation variant of human hepatitis B virus by adefovir, tenofovir, L-FMAU, DAPD, penciclovir and lobucavir. *J. Viral. Hepat.*, 7, 161-165 (2000).

Young, B., Fischl, M. A., Wilson, H. M., Finn, T. S., Jensen, E.

H., DiNubile, M. J., and Zeldin, R. K., Open-label study of a twice-daily indinavir 800-mg/ritonavir 100 mg regimen in protease inhibitor-naive HIV-infected adults. *JAIDS.*, 31, 478-482 (2002).

Youle, M., Mocroft, A., and Johnson, M., Lipid profiles in patients on ritonavir/indinavir containing salvage regimens [abstract 24]. *Antivir. Ther.*, 4 (Suppl 2), 22 (1999).

Zhang, Y. M., Imamichi, H., Imamichi, T., Lane, H. C., Falloon, J., Vasudevachari, M. B., and Salzman, N. P., Drug resistance during indinavir therapy is caused by mutations in the protease gene and in its Gag substrate cleavage sites. *J. Virol.*, 71, 6662-6670 (1997).