brought to pharmacists by Pfizer Inc., USPG and Midwestern University

InetCE

Volume 9	2005	Number 5
Karen J. MacKinnon, R.Ph. Editor		Linda S. Swanson Copy Editor

Internet Continuing Education (***InetCE***) provides free, continuing education to pharmacists and other health care providers for 24 hours a day over the Internet at www.InetCE.com. Since 1997, these home study programs have assisted in keeping practitioners apprised of treatment-related topics, general pharmacy, and law in the changing health care environment.

InetCE grew out of a need for relevant, continuing education in health care, and to make it accessible to pharmacy practitioners in various practice settings. This format provides convenient instruction, on-line testing, evaluation, and certification. Continuing education examinations are graded automatically and, if successfully passed, the user can print the statement of credit.

Accreditation

ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ACPE Universal Program Number 221-999-05-010-H02 has been assigned to this home study program (initial release date August 8, 2005). This program is acceptable for 2.0 contact hours (0.20 CEUs) in states that recognize ACPE providers. The program is provided at no cost to participants. Statements of credit will be issued online upon successful completion (>70% score) of the posttest.

Faculty Disclosure

It is the policy of ProCE, Inc. to ensure balance, independence, objectivity and scientific rigor in all of its continuing education programs. Faculty must disclose to program participants any significant relationships with companies that manufacture or market products discussed during their presentation. Drs. Crank, Patel, and Philibrick report having no relationships to disclose.

Please note: The opinions expressed in this program should not be construed as those of the CE provider. The information and views are those of the faculty through clinical practice and professional literature. Portions of this program may include the use of drugs for unlabeled indications. Use of drugs outside of labeling should be considered experimental and participants are advised to consult prescribing information and professional literature.

ProCE, Inc.
848 W. Bartlett Road
Suite 9E
Bartlett, IL 60103
www.ProCE.com

Antiretrovirals: Pharmacotherapy and Adverse Drug Reactions

***InetCE* 221-999-05-010-H02**

Alexander H. Philbrick, Pharm.D.
Assistant Professor of Pharmacy Practice
Midwestern University–Chicago College of Pharmacy
Downer's Grove, Illinois

Christopher W. Crank, Pharm.D., BCPS
Clinical Specialist, Infectious Diseases
Rush University Medical Center
Department of Pharmacy
Chicago, Illinois

Gourang P. Patel, Pharm.D., BCPS
Clinical Specialist, Critical Care
Medical Intensive Care Unit
Rush University Medical Center
Department of Pharmacy
Section of Pulmonary and Critical Care Medicine
Chicago, Illinois

PLEASE NOTE: The content of this article was current at the time it was written. The exam for this article is not valid for CE credit after August 8, 2008.

LEARNING OBJECTIVES

1. Review the epidemiology and transmission of human immunodeficiency virus (HIV).
2. Develop appropriate recommendations for initiating antiretroviral (ARV) treatment based on a patient's symptoms, $CD4^+$ T-cell count, and viral load.
3. Design appropriate initial ARV regimens.
4. List adverse drug reactions that are common or life threatening with ARV agents.
5. Identify important drug interactions requiring intervention by the pharmacist.
6. Describe appropriate therapy for post-exposure prophylaxis.
7. Describe appropriate therapy for the prevention of perinatal transmission.
8. Identify new therapies for HIV.

ABSTRACT: Human Immunodeficiency Virus (HIV) currently affects approximately 850,000 to 950,000 patients in the United States. Since the disease was first discovered, about 524,060 people have died secondary to HIV. There were approximately 18,000 deaths caused by HIV in 2003. With the advent of antiretroviral (ARV) therapy, survival and quality of life have improved significantly. ARV therapy has also dramatically decreased mother-to-child transmission rates, as well as occupational transmission. However, ARV therapy, specifically highly active antiretroviral therapy (HAART), has introduced a number of complications previously unseen in pre-HAART patients. Complex interplay among adverse reactions (ranging from minor to life threatening), factors that affect adherence, and temperamental drug interactions make ARV therapy an art strongly rooted in science; thus, the door is open to many health care professionals, especially pharmacists, for contributions to optimize the care of these patients. This review will explain the pharmacology and appropriate use of ARV agents (ARVs), including an overview of the current guidelines for initiation of ARV therapy, and describe

notable adverse reactions. New and future therapies will also be discussed.

ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. An on-screen statement of credit verifying participation in 0.20 CEUs (2.0 contact hours) will be displayed for printing to participants who successfully complete the examination. This article has been assigned ACPE ID number 221-999-05-010-H02. For more information, visit http://www.InetCE.com.

Epidemiology

Since the first identified case in 1981 through 2000, more than 1.4 million people in the United States have become infected with HIV. This number increases by an estimated 40,000 cases each year. Through the end of 2003, 524,060 deaths secondary to HIV were reported; there were 18,000 deaths alone in 2003.[1] Acquired Immunodeficiency Syndrome (AIDS) is a pandemic. Currently, it is the leading infectious cause of adult death in the world.[2] In sub-Saharan Africa, approximately 25.4 million adults and children were living with HIV.[3] In the poorest and most affected areas of the world, life expectancy gains made over the last 3 decades of the 20th century were reversed by the impact of HIV.[2] In Botswana, the impact of AIDS decreased life expectancy from birth by 20 years.[4]

Definition

Currently, the Centers for Disease Control and Prevention (CDC) defines AIDS as having serologic laboratory evidence of HIV infection (positive enzyme immunoassays and confirmatory Western Blot test), plus at least the presence of one of the following:

- $CD4^+$ T-cell count <200 cells/mm^3
- $CD4^+$ T-cell count <14%
- Presence or history of an AIDS indicator condition (Table 1)

Transmission of Human Immunodeficiency Virus

The primary mode of HIV transmission is through sexual intercourse. Transmission may be enhanced by factors such as presence of high-grade viremia, advanced HIV in the infecting partner, receptive anal intercourse, sex during menses, and the presence of other sexually transmitted diseases. Use of latex or polyurethane condoms has been shown to successfully decrease the risk of HIV transmission. Avoidance of high-risk sexual behavior consists of the following:

- Unprotected intercourse without condom use or unprotected mouth-to-genital contact, except in a long-term monogamous relationship
- Sexual activity before age 18
- Multiple sex partners
- Sex with a high-risk partner
- Anal sex
- Sex with an intravenous (IV) drug abuser also increases the risk of transmission of HIV.

All patients who participate in high-risk sexual intercourse should be instructed on the risks associated with the behavior

and on the use of condoms to reduce the risk of transmission.

The second most common mode of HIV transmission is mother-to-child transmission during pregnancy, delivery, or breast-feeding. ARV therapy has dramatically reduced the incidence of mother-to-child transmission. Maternal vitamin A deficiency, high viral load, low $CD4^+$ T-cell count, chorioamnionitis, prolonged rupture of membranes, and vaginal versus cesarean delivery have been associated with higher rates of mother-to-child transmission.

IV drug abuse also represents a mode of HIV transmission. IV drug abusers who share drug paraphernalia are at increased risk. Transfusion of HIV contaminated blood products remains a method of HIV transmission in undeveloped countries where blood products are not routinely screened for the virus. Health care worker exposure via contaminated body fluid exposure is an infrequent mode of HIV transmission.[5]

Table 2 lists the risk per 10,000 exposures for the modes of transmission listed in the bullet list above. ARV post-exposure prophylaxis will be discussed later in this article.

Therapy of Human Immunodeficiency Virus

Several goals of therapy exist in regard to ARV therapy and the management of HIV infection. Patients should be educated to one important point—HIV is not curable with the current ARV therapy. The goals of therapy proposed by the NIH guidelines are (1) reducing HIV-related morbidity and mortality, (2) improving quality of life, (3) restoring and preserving immunologic function, and (4) suppressing viral load maximally and durably.[6]

Initiating Therapy

Initiating therapy for HIV is an important decision and should involve both the patient and health care provider. ARV therapy reduces HIV-related morbidity and mortality, as well as improves quality of life. ARV therapy, however, has its drawbacks, and several factors must be taken into consideration when determining whether to initiate it. The clinician should consider the prognosis of disease-free survival, $CD4^+$ T-cell count, viral load, patient willingness to begin and remain compliant with therapy, and the benefit of therapy versus risk for adverse drug reactions and future resistance.

A $CD4^+$ T-cell count is a major indicator of immunocompetence. Most clinicians recommend getting at least 2 separate $CD4^+$ T-cell counts when making the decision whether or not to initiate ARV therapy; this is primarily because there may be considerable variance in $CD4^+$ T-cell counts. Table 3 describes the current recommendations of starting ARV therapy in regard to $CD4^+$ T-cell count, viral load, and patient symptoms. Currently, ARV therapy should be offered to any patient with a $CD4^+$ T-cell count <200 cells/mm^3, any patient with an AIDS-defining illness (Table 1), or any patient with severe symptoms. Patients whose $CD4^+$ T-cell count is between 201 to 350 cells/mm^3 should be offered treatment following discussion of the benefits and risks of therapy with the health care provider.

Potential benefits of delayed therapy include the following:

1. Avoidance of adverse drug reactions
2. Preservation of treatment options
3. Delay in the development of resistance
4. More time for the patient to understand treatment demands
5. Less time on medication
6. Less chance for treatment fatigue
7. Potential for the development of more potent and less toxic therapies for HIV

Deferred therapy also poses risks that include the possibility of irreversible damage to the immune system, increased possibility of progression to AIDS, and increased risk of HIV transmission to others during longer, untreated periods.[1] When a patient has a $CD4^+$ T-cell count >350 cells/mm^3 and a viral load ≥100,000 copies/mL, the decision to treat or not to treat is a difficult one, since high viral loads have been associated with a more rapid progression to AIDS. Therapy should be deferred in patients with a $CD4^+$ T-cell count >350 cells/mm^3 and a viral load <100,000 copies/mL.

The National Institutes of Health (NIH) guidelines for initiation of ARV therapy are not an absolute. Clinicians must interpret each case on a patient per patient basis considering the risk-to-benefit ratio of therapy.

Adherence

Adherence to ARV therapy is of utmost importance in the management of HIV. Several strategies have been suggested to improve adherence (Table 4). Virologic success (i.e., maintaining an undetectable viral load indefinitely) correlates with a high rate of adherence. Certain factors affect adherence: patient readiness, regimen complexity, pill burden, and regimen toxicity. It is a complex interplay between host factors and regimen-specific factors that make choosing appropriate ARV therapy challenging.

Preferred Regimens (Naïve)

Currently, therapy for HIV disease is composed of 20 ARVAs in 4 FDA-approved classes of ARVAs. In 1995, results from clinical trials evaluating highly active antiretroviral therapy (HAART) were first published, and HAART has since become the standard of care for these patients. HAART is essentially combination therapy with at least 3 ARVAs and with at least 2 different mechanisms of action. The backbone of HAART is dual nucleoside reverse transcriptase inhibitor (NRTI) therapy combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). In treatment-naïve patients (i.e., those who have never been exposed to ARV therapy, certain combinations are more highly recommended than others.

"Preferred" status of a regimen is achieved when a regimen has demonstrated optimal efficacy (initially attaining virologic suppression and increasing $CD4^+$ T-cell count) and durability in clinical trials (maintaining virologic suppression and preserving elevated $CD4^+$ T-cell count), as well as being tolerable and relatively easy to use. Several regimens have been evaluated in the treatment-naïve patient. (Table 5).

"Alternative" regimens do not have efficacies as firmly established in clinical trials as "preferred" regimens, or those regimens that are very complicated for patients to take and carry a high risk

of nonadherence.

A major development in managing HIV-positive patients is the advent of genotypic and phenotypic testing (a.k.a. "resistance testing"). When a patient experiences virologic failure (e.g., viral load (VL) >400 c/mL at 24 weeks, >50 c/mL at 48 weeks, 0.5 log increase in VL from previous result), it is recommended that genotypic/phenotypic testing be performed to determine which ARVAs are still active. The physician then considers potential for nonadherence, history of medication intolerance, and pharmacokinetic issues (e.g., food/fasting requirements, etc.), when designing a new regimen comprising at least 3 active ARVAs.

Nucleoside Reverse Transcriptase Inhibitor Backbone

NRTIs are nucleoside/tide analogs that incorporate themselves into the new viral deoxyribonucleic acid (DNA) and signal chain termination; this inhibits the transcription of viral ribonucleic acid (RNA) into DNA, which would then be integrated into the host cell's genome. For initial regimens, it is recommended that 2 of the 3 ARVAs be NRTIs. Several of the NRTIs are coformulated into single tablets that are taken either once or twice daily; adding either a PI or a NNRTI to a single combination tablet containing required NRTIs ensures highest regimen simplicity and carries the lowest risk of nonadherence, a well-elucidated cornerstone of virologic success.

Non-nucleoside Transcriptase Inhibitors

NNRTIs bind to the reverse transcriptase enzyme in such a way to cause a conformational change in the active site that inactivates the enzyme. Three NNRTIs are approved for use: efavirenz, nevirapine, and delavirdine. Efavirenz-based regimens are the "preferred" NNRTI-based regimens. Efavirenz demonstrated antiviral potency that was comparable with that of nelfinavir-based, unboosted amprenavir-based regimens and unboosted, indinavir-based regimens in several controlled trials and cohort studies. Most trials suggested superior efficacy of efavirenz versus the comparator—including a trial comparing efavirenz with nevirapine (NVP)—although the differences in virologic failure, disease progression/death, and therapy change were not statistically significant. Efavirenz is the most convenient NNRTI to take, as it is manufactured in 600-mg tablets that can be taken once daily. NVP, on the other hand, is twice-daily therapy (it is recommended to give NVP once daily for the first 14 days of therapy to lessen the frequency of rash). NVP is also efficacious, though it may not be as efficacious as efavirenz; however, more serious complications are associated with its use. NVP is not recommended for use in women with pre-NVP $CD4^+$ T-cell counts >250 cells/mm^3 or for use in men with pre-NVP $CD4^+$ T-cell counts >400 cells/mm^3. These patients are at a significantly increased risk of developing life-threatening hepatic events (e.g., symptomatic hepatitis with grade III and IV elevations in serum transaminases, fulminant hepatitis). Delavirdine is not recommended as initial therapy owing to inferior antiviral potency. One disadvantage to NNRTI therapy is the low genetic threshold for development of resistance.

Protease Inhibitors

PIs limit the cleavage of the newly

translated viral polypeptide chain into functional viral proteins. The PIs are known to be a very potent class of ARVA, and they have been more extensively studied than the NNRTI. As a class, the PIs have the most adverse events associated with long-term use, and they are among the most complex agents to appropriately dose, given their propensity for drug-drug interactions and their temperamental pharmacokinetic profiles. Eight agents are approved for use: amprenavir, fosamprenavir, indinavir (IDV), nelfinavir, lopinavir/ritonavir (RTV), ritonavir, atazanavir, and saquinavir.

RTV has potent CYP 3A4 inhibitory properties, the primary route of elimination for the PI, and this knowledge has been exploited in the name of adherence. Because RTV so effectively inhibits the metabolism of substrates of CYP 3A4 (it has been evaluated in low doses as a "pharmacokinetic booster"), it increases drug exposure of the other PI, thereby allowing for decreased dosing frequency, pill burden and, in some cases, food restrictions.

Lopinavir/ritonavir is the "preferred" PI in the PI-based regimen. It has demonstrated high virologic potency in clinical trials; additionally, it has a high genetic threshold for resistance and is relatively well tolerated. Lopinavir/ritonavir is coformulated into soft-gelatin capsules that must be taken twice daily, whereas atazanavir, the newest approved PI, may be taken once daily.[6]

Although not "preferred," atazanavir is gaining favor among clinicians, and it currently represents a viable alternative for a patient in whom certain complications of PI-based therapy are undesirable. The reasons for this are manyfold:

- Atazanavir-containing regimens have demonstrated efficacy in treatment-naïve patients.
- It is similar to that of efavirenz, a "preferred" regimen.
- In one clinical trial (controversy exists regarding the results of this trial), it has a unique resistance profile (in treatment-naïve patients, I50L mutation has been associated with hypersusceptibility to other protease inhibitors).
- It has the lowest incidence of long-term hyperlipidemia among the protease inhibitors.[7]

Triple Nucleoside Reverse Transcriptase Inhibitor Regimens

In theory, there are several advantages to administering a regimen containing only 3 NRTIs:

1. These regimens spare the patient from adverse events associated with PI- and NNRTI-based regimens.
2. There are fewer drug-drug interactions.
3. There is low pill burden (abacavir + lamivudine + zidovudine are coformulated into one tablet, Trizivir®).

Several clinical trials were terminated attributable to the poor performance of triple-NRTI therapy. Patients that were enrolled in the triple-NRTI arm experienced virologic failure or early virologic nonresponse. At this point, Trizivir® is recommended only for patients in whom a "preferred" or "alternative" regimen cannot be used.

Fusion Inhibitors

The fusion inhibitors are the newest class of ARVAs to be approved, with only one agent currently approved, enfuvirtide (T-20). These agents are large, synthetic peptides that bind to surface proteins on the viral envelope, which are vital in the initial steps of HIV pathogenesis. In binding to the proteins, they inhibit fusion of the virus to $CD4^+$ T-cell count, thereby preventing release of its RNA gene products into the cell, and the subsequent chain of events is halted. The efficacy of enfuvirtide was established in 2 randomized, controlled, multinational trials (TORO-1 and TORO-2), in which highly treatment-experienced patients received either enfuvirtide or placebo in addition to an optimized background regimen (i.e., a regimen that is based on results of resistance testing). When the clinical trials evaluating enfuvirtide were published, they presented data from patient evaluation through 48 weeks of treatment.[6]

Recently data through 96 weeks of treatment were presented at the XV International AIDS Conference. The majority of patients on enfuvirtide therapy who had maintained viral loads <400 c/mL or <50 c/mL at 48 weeks had also maintained this virologic suppression through 96 weeks. This is a testament to enfuvirtide's ability to durably suppress viral load, and it underscores the importance of adding it to regimens in highly treatment-experienced patients.[8] However, it is worth mentioning that enfuvirtide is a twice-daily subcutaneous injection, with near 100% incidence of injections site reactions. It follows that regimens containing enfuvirtide carry a high risk of nonadherence, and its role in the management of HIV infection will likely remain in treatment of these highly treatment-experienced patients.

Adverse Reactions

Protease Inhibitors

Adverse events are a very common complication of ARV therapy (Table 6). Long-term HAART therapy has been associated with increased risk of cardiovascular morbidities. Prolonged abnormalities in lipid metabolism secondary to HAART are thought to be the most likely explanation for this observation. PI therapy carries the highest risk of dyslipidemia, its prevalence ranging from 28% to 80%.[9] The mechanism for this is not fully understood, and it is probably related to multiple and different factors.

Certain adverse events are associated with each class of drugs. In addition to dyslipidemia, PI therapy can cause insulin resistance, bleeding episodes in patients with hemophilia, and osteonecrosis (up to 4% experience asymptomatic osteonecrosis findings on MRI). IDV caused nephrolithiasis/urolithiasis/crystaluria in up 12.5% of patients in clinical trials. The frequency of this adverse event is minimized when patients drink 1.5 to 2L of non-caffeinated fluid per day, and increase their fluid intake at the first sign of darkened urine. IDV has also been associated with nephrotoxicity, which occurs several months after initiation of therapy; concomitant use of other nephrotoxic drugs and inadequate hydration increases a patient's risk of developing IDV-associated nephrotoxicity. Fat maldistribution (increase in abdominal girth, breast size, and dorsocervical fat pad) and lipo-

atrophy (presenting most commonly as facial thinning or thinning of extremities) are also adverse events associated with the PI as a class.

Nucleoside Reverse Transcriptase Inhibitors

As a class, the NRTIs can cause lactic acidosis and hepatic steatosis; cases of fatalities from both have been reported, though the incidence is very low—they are thought to be dose dependent. Use of certain NRTIs (didanosine (ddI), stavudine (d4T), and zalcitabine) has been associated with onset of pancreatitis and peripheral neuropathy, and this risk is increased when the agents are used concomitantly. For this reason, the guidelines recommend that these agents not be used concomitantly at any time. Concomitant use of ddI and either hydroxyurea or ribavirin also increases the frequency of pancreatitis. Anemia and neutropenia secondary to zidovudine can occur in up to 8% of patients. Those who are at highest risk of this bone marrow suppression are patients with advanced HIV, those receiving a high dose, and those receiving concomitant use of bone marrow suppressants.

Abacavir is known to cause a systemic hypersensitivity reaction (SHR), which can be fatal if the patient is rechallenged. It occurred in about 8% of patients in clinical trials, and the constellation of flu-like symptoms included high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms. About 90% of patients who develop SHR experience symptoms within the first 6 weeks of therapy. It is imperative that patients who are taking abacavir-containing regimens immediately report these symptoms to the physician managing their HIV.

Therapy with tenofovir is associated with nephrotoxicity similar to that caused by IDV. Fat maldistributions have been observed in patients taking d4T-containing regimens.

Non-nucleoside Reverse Transcriptase Inhibitors

The NNRTIs can cause hepatotoxicity; patients who had symptomatic hepatotoxicity most frequently experienced anorexia, weight loss, or fatigue. Skin rash is also an adverse event associated with the NNRTIs as a class. The biggest culprit among the NNRTIs in causing rash is NVP, and the rash infrequently progresses to Stephens-Johnson Syndrome, or toxic epidermal necrosis (up to 1% of patients taking NVP, and 0.1% of patients taking either DLV or EFV develop these syndromes).

Efavirenz causes central nervous system (CNS) effects, including dizziness, disorientation, and vivid dreams/nightmares. The CNS effects occur in >50% of patients. Fortunately, they usually abate within 2 to 3 weeks, and almost always by 6 weeks; very rarely do these CNS side effects persist longer than 6 weeks. Counseling the patient on what to expect is an effective way to ensure adherence during the onset.

Fusion Inhibitors

The fusion inhibitors have an extremely high incidence (~98%) of injection site reactions. Most commonly, the symptoms experienced are painful nodules occurring around the site of injection. Adherence should be assessed

frequently in the patients.

Post-exposure Prophylaxis

Non-occupational, Post-exposure Prophylaxis
It is important to realize that non-occupational, post-exposure prophylaxis (nPEP) ARV therapy is not a substitute for taking steps necessary to reduce the risk of exposure to HIV. Examples of such steps include sexual abstinence, sexual monogamy, condom use, abstinence from IV drug abuse, or use of sterile injection devices if abuse cannot be eliminated.

The CDC has published recommendations for the use of ARV for nPEP.[10] These guidelines are not based on a paucity of well-designed trials. The recommendations are primarily based on animal data and small observational studies. The CDC recommends nPEP should be administered within 48 to 72 hours of exposure to blood, genital secretions, or other infectious fluids from a known HIV-infected individual and should be continued for 28 days. Table 7 lists the preferred regimens for nPEP. If presentation occurs greater than 72 hours after exposure to fluid from an HIV-infected individual, then the patient should be counseled for the possible diminished benefit of nPEP, as well as the potential adverse effects. Patients who have had exposure to body fluids (regardless of time of presentation), and whose HIV status is unknown are not recommended to receive nPEP. Choice of regimen should be driven on the basis of adherence, toxicity, cost, and resistance patterns of HIV from the source patient. Also, nPEP should not be used in individuals who repeatedly participate in high-risk behavior. Prophylaxis in this population should be focused on risk-factor modification.

Occupational Post-exposure ProphylaxisSimilar to nPEP, there is not a paucity of data supporting the efficacy of occupational post-exposure prophylaxis (PEP). Currently, available data come from animal models, studies on the prevention of perinatal transmission, one case-control trial, and case reports. The CDC has published excellent guidelines on the prevention of transmission of HIV in health care workers.[11] PEP should be given to all health care workers exposed to fluids from a known HIV-infected patient when the health care worker presents ≤36 hours after exposure. If the health care worker exposed to fluids from an HIV-infected patient presents ≥36 hours after exposure, determination whether to start PEP should be made on a case-by-case basis, taking into account risk for HIV transmission and risk of adverse effects from prophylactic therapy. If PEP is warranted, then clinicians should assess the number of ARVs that should be used for prophylaxis (Tables 8 and 9). Therapy should be continued for 4 weeks if it can be tolerated.

Preventing Perinatal Transmission
Perinatal transmission of HIV contributes significantly to the incidence of new HIV infections. In HIV-infected pregnant women on combination ARV therapy, the current guidelines[12] recommend continuation of that same therapy; however, there are conflicting data regarding benefit versus harm of perinatal combination ARV therapy. Some studies have associated combination ARV use with preterm delivery, especially when ARV therapy

is initiated before becoming pregnant.[13] Other studies have not found an association with premature delivery, low birth weight, low Apgar scores, or stillbirth.[14]

Based on the currently available clinical data on antenatal combination ARV therapy, the NIH guidelines currently recommend continuing therapy with increased monitoring for pregnancy complications or toxicities. The PACTG 076 trial[15] was a randomized trial examining the safety and efficacy of the use of zidovudine (ZVD) to prevent perinatal transmission. Therapy with ZVD was associated with a significant reduction in transmission rates (22.6% placebo vs. 7.6% ZVD). This represented a 66% relative risk reduction in the transmission of HIV. Teratogenic effects were similar between the placebo group and ZVD group. Other studies have also been unable to demonstrate a significant risk of fetal toxicity with perinatal prophylaxis. High viral load at time of childbirth has been associated with increased rates of HIV transmission,[16] and ARV therapy that reduces viral load has been shown to decrease mother-to-child transmission. ARV therapy has also been shown to decrease mother-to-child transmission in patients with HIV RNA levels <1,000 copies/mL.[17] Therefore, prophylactic ARV therapy should be used regardless of HIV RNA levels. Method of child delivery has also been shown to affect transmission rates. Cesarean section has been shown to have lower rates of HIV transmission when compared with vaginal delivery.[18,19]

The NIH guidelines[10] separate recommendations based on 4 clinical situations regarding prophylaxis of mother-to-child transmission that may occur:

1. The first situation involves HIV-infected women who have not received prior ARV therapy. In this situation, all women should at least receive the IV ZVD regimen used in the PACTG 076 trial (Table 9). Combination therapy with appropriate ARV in pregnancy (a regimen with ZDV) should be initiated in women whose clinical, immunologic, or virologic status would require therapy if they were not pregnant. Women in the first trimester may consider delaying therapy until after 10 to 12 weeks' gestation. The decision to use combination therapy should be based on the benefits to the mother and decreasing transmission versus the unknown long-term effects of ARV therapy.

2. The second scenario involves women currently being treated with combination therapy. After the first trimester, attempts should be made to include ZVD in the patient's regimen. Efavirenz should not be used in any pregnant patient's ARV regimen, as the drug has been associated with teratogenicity. Also, a discussion of risk versus benefit of therapy during the first trimester should be discussed with the patient. If the decision is made to withhold therapy, all antivirals should be withheld.

3. The third scenario consists of women currently in labor with no prior therapy. Four different regimens may be used to decrease intrapartum transmission of HIV (Table 10). The

need for combination ARV therapy should be evaluated after delivery.

4. The fourth scenario concerns infants born to mothers who have not received antepartum or intrapartum ARV therapy. ARV therapy with ZVD should be started within 6 to 12 hours of birth. Appropriate steps must be taken to decrease perinatal transmission of HIV, as well as steps to appropriately identify and manage postpartum HIV infection.

New Therapies

Tipranavir (TPV) is a protease inhibitor currently in clinical trials and is probably the next ARVA to be approved by the FDA. Data from trials comparing TPV/RTV + OB vs. LPV/RTV + OB in highly treatment-experienced patients at 24 weeks of treatment patients in the TPV/RTV arm experienced greater virologic response rate ($\geq$1 $\log_{10}$ viral load reduction) than the LPV/RTV arm (P <0.001).[20]

Selective inhibitors of chemokine receptors (CRAs) CCR5 and CXCR4 are the most promising new class of ARVAs in the research pipeline. These agents, currently in Phases 2 and 3 clinical trials, inhibit an essential interaction between the chemokine receptors CCR5 or CXCR4 (located at the surface of $CD4^+$ T cells) and the gp120 molecule on the viral envelope. Inhibiting this step prevents fusion with the cell and subsequent viral replication. The CRAs exhibit favorable pharmacokinetics, as they are small molecules with good oral bioavailability. Early clinical trials show that CCR5 antagonists are efficacious at reducing viral load and exhibit a newly observed "post-viral effect"—the ability to suppress viral load for days to even weeks after discontinuation of the agent. This alludes to the possibility that these agents might be dosed once daily (currently, clinical trials are evaluating twice-daily dosing modalities). The CRAs were well tolerated in early phase-2 studies; however, CCR5 receptors do not appear to be essential for life, whereas CXCR4 might play an important role in normal human inflammatory pathways, suggesting the possibility of more serious adverse events with long-term use. Resistance to these agents has been identified in vitro; however, it is associated with impaired viral fitness.[21,22]

Integrase inhibitors are agents that block integrase, the enzyme responsible for incorporating proviral DNA into the host chromosome. They are attractive options because their target has no host cell function; potentially, there are almost no serious adverse events with long-term use. The agent farthest along in development, however, has recently been pulled out of development owing to toxicities seen in animal models.[22]

Table 1. AIDS –Indicator Conditions[6]		
Candidiasis of bronchi, trachea, or lungs	Encephalopathy, HIV related	*Mycobacterium avium*, complex or kansasii, disseminated or extrapulmonary
Candidiasis esophageal	Herpes simplex chronic ulcers (> 1 month), or bronchitis, pneumonitis, or esophagitis	Wasting syndrome
Invasive cervical cancer	Histoplasmosis, disseminated or extrapulmonary	*Mycobacterium tuberculosis*
Coccidioidomycosis, disseminated or extrapulmonary	Isoporiasis, chronic intestinal (>1 month)	*Pneumocystis jiroveci* pneumonia (previously *Pneumocystis carinii*)
Cryptococcus, extrapulmonary	Kaposi's sarcoma	Pneumonia, recurrent
Cryptosporidiosis, chronic intestinal	Lymphoma, Burkitt's	Progressive multifocal leukoencephalopathy
Cytomegalovirus disease other than liver, spleen, or lymph nodes	Lymphoma, immunoblastic	Salmonella septicemia, recurrent
Cytomegalovirus retinitis	Lymphoma, primary or brain	Toxoplasmosis, brain

Table 2. Estimated Per Act Risk for HIV Acquisition, by Exposure Route[9]	
Exposure Route	Risk per 10,000 Exposures
Blood transfusion	9,000
Needle-sharing injection-drug use	67
Receptive anal intercourse	50
Percutaneous needle stick	30
Receptive penile-vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive penile-vaginal intercourse	5
Receptive oral intercourse	1
Insertive oral intercourse	0.5

Table 3. Initiation of Antiretroviral Therapy[6]			
Clinical Category	$CD4^+$ T-cell Count ($cells/mm^3$)	Plasma HIV RNA (copies/mL)	Recommendation
AIDS-defining illness or severe symptoms	Any value	Any value	Treat
Asymptomatic	<200	Any value	Treat
Asymptomatic	200-350[3]	Any value	Treatment should be considered weighing benefits and risks
Asymptomatic	>350	≥100,000	Most clinicians hold therapy, but some clinicians will treat
Asymptomatic	>350	<100,000	Defer therapy

Table 4. Improving Adherence		
Establish readiness	Anticipate and treat Side effects	Simplify regimens, dosing, and food requirements
Provide education on dosing	Use educational aids	Use team health care approach
Review potential side effects	Engage family and friends	Provide accessible trusting health care team

Table 5a. Preferred Regimens[6]
Efavirenz + (lamivudine or emtricitabine) + (zidovudine or tenofovir DF)
Lopinavir/ritonavir + (lamivudine or emtricitabine) + zidovudine

Table 5b. Alternative Regimens[6†]
Efavirenz + (lamivudine or emtricitabine) + (abacavir or didanosine or stavudine)
Nevirapine + (lamivudine or emtricitabine) + (zidovudine or stavudine or didanosine or abacavir or tenofovir)[†]
Atazanavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir DF/RTV)
Fosamprenavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
Fosamprenavir/ritonavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
Indinavir/ritonavir + (lamivudine or emtricitabine) + (stavudine or abacavir or tenofovir or didanosine)
Lopinavir/ritonavir + (lamivudine or emtricitabine) + (stavudine or abacavir or tenofovir or didanosine)
Nelfinavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
Saquinavir/ritonavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)

[†]Therapy should not be initiated in women with pre-NVP $CD4^+$ T-cell counts >250 cells/mm^3 and men with pre-NVP $CD4^+$ T-cell counts >400 cells/mm.[3]

Table 6. Common Adverse Events Associated With Given ARVA[6]‡	
ARVA	**Adverse Events**
NRTI	
• Abacavir (ABC)	Hypersensitivity → can be fatal, presents not as anaphylaxis, but rather a fairly nonspecific constellation of flu-like symptoms. Sometimes there is a rash, but not necessarily. This reaction can occur anytime within the first 6 weeks. Important to counsel patient that he should see a physician immediately if these symptoms occur, and that he should **never** stop and restart the medication in the presence of these symptoms
Didanosine (ddI)	• Pancreatitis • Peripheral neuropathy
Emtricitibine (FTC)/Lamivudine (3TC)	• Fairly benign • Class effects apply
Stavudine (d4T)	• Peripheral neuropathy • Highest incidence of pancreatitis
Tenofovir disoproxil fumarate (TDF)	Has been associated with nephrotoxicity
Zalcitibine (ddC)	• Peripheral neuropathy • Stomatitis • Pancreatitis • Rarely used agent
Zidovudine (AZT)	• Bone Marrow suppression o Recently published abstracts from an EFV/Combivir vs. EFV/Truvada trial show equivalency, but significantly fewer patients discontinued treatment owing to hematologic side effects in the EFV/Truvada arm • Macrocytic anemia [elevated Mean Corpuscular Volume (MCV)] • Terrible headache and nausea in first 2 weeks of therapy
NNRTI	
Efavirenz (EFV)	• Rash • Teratogenic • Bizarre CNS effects (e.g., vivid dreams, disorientation) o Transient → abate within 6 weeks (usually 2-3 weeks)

	○ Not a reason to choose another regimen ▪ Counseling the patient on what to expect is sufficient
Nevrirapine (NVP)	• Rash → documented cases/fatalities of Stevens-Johnson syndrome • Symptomatic hepatitis, including fatal hepatic necrosis ○ Pregnant women w/pre-NVP CD4 >250 cells/mm^3 are 12X more likely to develop Men with pre-NVP CD4 >400 cells/mm^3
Delavirdine (DLV)	• Rash • Rarely used agent
PI	
Amprenavir (APV)	• Oral solution has propylene glycol → contraindication in certain patients
Fosamprenavir (f-APV)	• Rash
Indinavir (IDV)	• Nephrolithiasis → sludging w/in nephrons, in addition to frank stones → need to hydrate aggressively ○ increased regimen complexity • Indirect hyperbilirubinemia (benign)
Lopinavir/ritonavir (LPV/r)	• GI intolerance very common • Class effects
Nelfinavir (NFV)	• Class effects
Ritonavir (RTV)	• Class effects
Saquinavir (SQV)	• Class effects

‡Please note: Class side effects can occur with any agent in that class and may not necessarily be listed in the adverse event of a particular agent.

Table 7. Antiretroviral Non-occupational PEP-Preferred Regimens[7]	
NRTI based	Efavirenz 600 mg daily **plus** [Lamivudine (300 mg daily or 150 mg BID) or Emtricitabine 200 mg daily] **plus** [Zidovudine (300 mg daily or 150 mg BID) or tenofovir 300 mg daily]
Protease inhibitor based	Lopinavir/ritonavir 1200 mg/300 mg BID **plus** [Lamivudine (300 mg daily or 150 mg BID) or Emtricitabine 200 mg daily] **plus** Zidovudine (300 mg daily or 150 mg BID)

Table 8. Occupational PEP Based on Infection Status of Source[11]					
Exposure type	HIV Positive, Class 1 (Asymptomatic, Less than 1500 HIV RNA copies/mL	HIV Positive, Class 2 (Symptomatic, AIDS, Acute Seroconversion, high viral load)	Source of Unknown HIV Status	Unknown Source	HIV Negative
Less Severe (Solid needle or superficial injury)	2-drug PEP	3-drug PEP	Generally no PEP	Generally no PEP	No PEP
More Severe (Large-bore hollow needle, deep puncture, visible blood on device, needle used in artery or vein)	3-drug PEP	3-drug PEP	Generally no PEP	Generally no PEP	No PEP
Small Volume (Few drops)	2-drug PEP	2-drug PEP	Generally no PEP	Generally no PEP	No PEP
Large Volume (major blood splash)	2-drug PEP	3-drug PEP	Generally no PEP	Generally no PEP	No PEP

Table 9. Recommendations for Prevention of Mother-to-Child Transmission of HIV[12]	
Time of Administration	Regimen
Antepartum	Mother: Zidovudine 100 mg PO 5 times per day, Zidovudine 200 mg PO TID, or Zidovudine 300 mg PO BID starting at 14-34 weeks gestation and continued throughout pregnancy
Intrapartum	Mother: During labor, zidovudine 2 mg/kg loading dose over 1 hour, followed by a continuous infusion of 1 mg/kg until delivery
Postpartum	Newborn: Zidovudine syrup 2 mg/kg Q6H for 6 weeks, beginning 8-12 hours after birth

Table 10. Intrapartum Prophylaxis in Women not Currently on Antiretrovirals[12]		
Drug Regimen	Maternal	Infant
ZDV	2 mg/kg bolus, followed by 1 mg/kg continuous infusion until delivery	2 mg/kg PO Q6H for 6 weeks
ZDV/3TC	ZDV 600 mg PO at onset of labor, followed by 300 mg PO Q3H until delivery and 3TC 150 mg PO at onset of labor, followed by 150 mg PO Q12H until delivery	ZDV 4 mg/kg PO Q12H and 3TC 2 mg/kg PO Q12H for 7 days
Nevirapine	200 mg PO at onset of labor	Single dose 2 mg/kg PO dose at age 48-72H
ZDV/Nevirapine	ZDV 2 mg/kg bolus followed by 1 mg/kg continuous infusion until delivery and Nevirapine 200 mg PO at onset of labor	ZDV 2 mg/kg PO Q6H for 6 weeks and single dose nevirapine 2 mg/kg PO dose at age 48-72H

References

[1] Centers for Disease Control: HIV/AIDS Surveillance Report, Vol. 15, 2003. Available from: http://www.cdc.gov/hiv/stats/2003SurveillanceReport.htm Accessed. Accessed May 2, 2005.

[2] The World Health Report 2003. http://www.who.int/whr/2003/chapter3/en/index.html. Accessed 6/27/2005.

[3] UNAIDS. Report on the global AIDS epidemic. 2004. Geneva, Switzerland.

[4] United Nations Development Programme–Botswana. http://www.unbotswana.org.bw/undp/index.html Accessed 6/27/05.

[5] Piot P, Merson MH. Global Perspectives on Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome. In: Mandell GL, Bennett JE, Dolin R (eds).

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, ed 5. New York: Churchill Livingstone, 2000:1332-1340.
[6] Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infectded adults and adolescents. 2004. Available from: http://aidsinfo.nih.gov/guidelines/adult/AA_040705.pdf Accessed May 2, 2005
[7] Havlir D, OMarro SD. Atazanavir: new option for treatment of HIV infection. *Clin Infect Dis* 2004;38:1599-604.
[8] Gallant JE. XV international AIDS conference in Bangkok: antiretroviral therapy. *The Hopkins HIV Report* September 2004;16(4).
[9] Calza L, Mandredi R, Chiodo F. Dyslipidemia associated with antiretroviral therapy in HIV-infected patients. *J Antimicrob Chemother* 2004;53:10-14.
[10] Centers for Disease Control and Prevention. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. *MMWR*. 2005;54(No. RR-2):1-20.
[11] Centers for Disease Control and Prevention. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. *MMWR*. 2001;50(No. RR-11):1-52.
[12] Centers for Disease Control and Prevention. 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*. 2002;51:1-38.
[13] The European Collaborative Study and the Swiss Mother + Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. *AIDS*. 2000;14(18):2913-20.
[14] Mofenson LM. Perinatal exposure to zidovudine–benefits and risks. *N Engl J Med.* 2000;343(11):803-5.
[15] Sperling RS, Shapiro DE, Coombs RW, Todd JA, Herman SA, McSherry GD et al. Maternal viral load zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. *N Engl J Med*. 1996;335:1621–9.
[16] Garcia PM, Kalish LA, Pitt J, Minkof HF,Quinn TC, Burchett SK et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. *N Engl J Med* 1999;341:394–402.
[17] Melvin AJ, Burchett SK, Watts DH, Hitti J, Hughes JP, McLellan CL, et al.. Effect of pregnancy and zidovudine therapy on viral load in HIV-1-infected women. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;14(3):232-6.
[18] 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.* 1999;340:977-87.
[19] The European Mode of Delivery Collaboration. Elective caesarean section versus vaginal delivery in preventing vertical HIV-1 transmission: a randomized clinical trial. *Lancet.* 1999;353:1035-7.
[20] Lucas GM. Treatment of experience patients and antiretroviral resistance issues from the 12th CROI. *The Hopkins HIV Report* March 2005;17(2).

[21] Shepherd JC, Quinn TC. Entry inhibitors: a primer on the class and on its most promising agents. *The Hopkins HIV Report* July 2004;16(4).
[22] Flexner C. New drugs, new targets: good news on the horizon. *The Hopkins HIV Report* March 2005 17(2):8.