

# A Shifting Paradigm of HIV and AIDS Therapy

The important role of the pharmacist

by Nicholas Olson, PharmD; Nicole Lentz, PharmD; Anne Daniels, PharmD, BCPS; and Richard Fons, RPh



CE FOR PHARMACISTS ONLY.

It has been over 30 years since the first identified cases of Human Immunodeficiency Virus (HIV) were reported. Patients that were admitted to hospitals succumbed to rare opportunistic infections and cancers. The patients had inexplicably compromised immune systems that, until that point, had only occurred in people who underwent immunosuppressive therapy for organ transplantation or who had a diagnosed immune system disorder. Although undiagnosed at the time, patients were suffering from the end stages of a disease later named Acquired Immune Deficiency Syndrome (AIDS).

HIV/AIDS is an epidemic that since its discovery was uniquely marred with social and political turmoil. No disease prior to HIV/AIDS had such an incendiary effect in pop-culture and political arenas. This emotional baggage played an important role in the history and development of this epidemic. Because the early cases of the disease were predominately localized in Caucasian men who had sex with other men, federal and local governments as well as public health organizations were reluctant to fund research into the causes of the disease and its subsequent prevention and treatment efforts. It was not until 1983-84 when the disease was found to be transmitted through the blood supply, did organizations step up their research efforts and the first real strides in understanding the scope of the disease were made.

HIV/AIDS is a global epidemic that has a large impact on the global health care system. In the mid-1980s, during the height of the epidemic in the United States, AIDS was the number one killer of young adults. Though treatment exists to control the progression of the disease, HIV/AIDS still has massive effects in countries with inadequate health care

resources. These same countries are experiencing devastating social and economic repercussions from the disease. Their health care systems are overwhelmed with patients; there are drug supply shortages, and in some countries, up to 30% of the work force is afflicted.

Although HIV/AIDS has existed as a diagnosis for only 25 years, extraordinary progress has been made in epidemiological research and treatment development. In a very short time, an arsenal of pharmacological treatments has been developed and transmission risk-reduction programs have been deployed. Conventional thoughts and paradigms of the disease have shifted from that of an acute, end-of-life management style to one more similar to a chronic disease management style.

Currently, the developments in HIV infection and AIDS therapy provide many opportunities for pharmacist involvement and management. Pharmacists are experts in managing chronic disease therapy, and HIV/AIDS treatment developments qualify it as a chronic disease state. HIV/AIDS is managed with drug therapies that have extreme effects on decreasing mortality, but carry risks of toxicity, interactions and adherence issues that endear it uniquely to pharmacists' therapy management skills. The purpose of this article is to overview the paradigm shift of HIV/AIDS in the

United States and review conventional and emerging treatments. Though there is much development and discussion of HIV/AIDS on a global perspective, these global issues are beyond the scope of this paper.

## HISTORY

The first cases of what was to be later named AIDS were seen in 1981 in eight gay men from New York hospitalized for Kaposi's sarcoma.<sup>1</sup> Kaposi's sarcoma is a relatively rare cancer generally seen in Mediterranean-European middle-age males.<sup>2</sup> The men succumbing to Kaposi's sarcoma were considered to be otherwise young and healthy, but suffering from extreme cases of immunosuppression. At that point, the disease could only be described as a syndrome, and researchers searched to identify a cause. In 1984, the Pasteur Institute in France and the National Cancer Institute in the United States both identified the cause of AIDS as an infection of a retrovirus that specifically targeted t-helper lymphocytes.<sup>3</sup> This discovery started a cascade of transmission risk reduction and prevention



**Objectives.** 1) Explain the current trends of incidence and prevalence of the human immune deficiency virus (HIV) and the acquired immune deficiency syndrome (AIDS) nationally and locally; 2) Discuss the changes in and differences between the Department of Health and Human Services HIV/AIDS treatment guidelines and the International AIDS Society Treatment guidelines; 3) Discuss the pharmacotherapeutic rationale for current highly active antiretroviral therapy (HAART) as well as the etiologies of toxicities and common pharmacologic interactions; 4) Explain the pharmacology and role of the new classes of HIV/AIDS medications including the CCR5 inhibitors, integrase inhibitor and second generation non-nucleoside reverse transcriptase inhibitor; 5) Discuss the shift of HIV/AIDS care from an acute care model to a chronic disease state model and discuss the role pharmacists can play in this model. Demonstrate the importance pharmacists can play in adherence coaching and adverse event management for HIV/AIDS patients.

ACPE Universal Program Number: 175-000-08-069-H01-P

Target Audience: **Pharmacists**

work as well as research in direct viral suppression and eradication drug therapies.

The mortality rates for HIV/AIDS between 1984 and 1995 steadily inclined, peaking in 1995 with a mortality rate of 17 per 100,000 individuals. During this

same time period, HIV/AIDS became the number one killer in males between 25-44 years of age and there were over 550,000 cases of infection reported in the United States.<sup>5</sup> In 1995, there was an important pharmacotherapeutic breakthrough, and the concept of using multiple antiretroviral drugs to attack the virus, otherwise known as highly-active antiretroviral therapy (HAART), was born. This shift in the paradigm of HIV treatment caused a dramatic decrease in mortality rates. It is important to note that all therapies tested to completely eradicate the virus and have a “cure” for the disease had failed, and it became the primary goal of therapy to completely suppress the virus in the system and improve health-related outcomes.

### EPIDEMIOLOGY AND NATURAL PROGRESSION

There are two major subtypes of the HIV virus (HIV-1 and HIV-2). HIV-1 is the predominant subtype in the world and accounts for the majority of cases seen in the United States. The HIV-2 subtype tends to be localized to specific regions in Western Africa. This paper will focus on the treatment and progression of HIV-1 infection. Beneath the subtype of HIV-1 there are many different families and clades of virus, each genetically different, but they offer no real clinical difference in disease progression and treatment outcome.

Currently there are an estimated 40.3 million cases of HIV infection in the world with over 25.8 million in sub-Saharan Africa. There is a current global infection rate of 4.9 million new cases per year. The United States accounts for an estimated 850,000 to 950,000 of the total global case pool with 40,000 new cases of HIV steadily reported each year. In Wisconsin, there are currently 6,294 cases with 407 new infections reported in 2007.<sup>4</sup> These statistics are only estimates secondary

to challenges in surveillance reporting systems and state-controlled disclosure laws. The statistics are further complicated because an estimated 25% of cases involve patients unaware of their HIV status due to lack of knowledge of transmission factors and long lag time between infection and symptomatology.<sup>5</sup>

The demographics of the disease have shifted over the course of the epidemic. In the early 1980s, HIV infections were predominately seen in the Caucasian population specifically, in men who had sex with men. Now, the disease demographics have shifted to encompass a disproportionate percentage of minority populations including African and Hispanic Americans [see Table 1]. There has also been an increase in the proportion of women who are infected and are living with AIDS, though infections in men still out number women three to one.<sup>6</sup> The causes of these shifts are multifactorial and include increased heterosexual and bisexual cross infection, lack of knowledge of infection risks and a prevailing sex trade and intravenous drug use in lower socioeconomic populations.

Of note, the average age of the HIV infected individual has increased to between 35 and 40 years of age.<sup>6</sup> The average life expectancy of a patient diagnosed with AIDS has increased from only six to eight years from diagnosis in the pre-HAART era to almost 30 years from diagnosis in the post-HAART era.<sup>7-9</sup> This combination of factors makes the management of HIV/AIDS patients similar to that of a chronic disease. This offers many opportunities for pharmacists to utilize their unique medication disease state management skills.

### PATHOLOGY

The human immunodeficiency virus belongs to a family of ribonucleic acid (RNA) retroviruses. A defining characteristic of a retrovirus’s lifecycle is its require-

ment to incorporate its genetic material into the host’s nuclear deoxyribonucleic acid (DNA). Retroviruses utilize the host’s genetic translation and transcription processes to manufacture the proretroviral proteins to perpetuate its own replication. The primary cell infected by HIV is the cell differentiation factor 4 (CD4)-positive t-helper lymphocyte. The infection and subsequent incorporation into the t-cell genome triggers apoptosis of the cell, thus the primary pathology of the disease – the loss of t-helper lymphocyte activity and immune system dysfunction. HIV’s replication cycle can be broken down into several steps (attachment/cell entry, reverse transcription of RNA to DNA, integration, assembly and budding), each of which offers a unique target for antiretroviral drug activity.

The glycoprotein 120 (gp120) moiety located on the retroviral envelope of HIV targets the CD4 receptor on the surface of the t-helper lymphocyte. The binding of these two proteins starts a cascade of cellular activity which incorporates other extracellular coreceptors such as chemokine receptor 5 (CCR5), chemokine receptor 4 (CXCR4), and CD8. These coreceptors are all involved in transmitting the viral RNA into the cell. Once in the cell, the RNA is reverse transcribed to DNA via the reverse transcriptase enzyme transmitted with the virus. The viral DNA gets integrated into the host CD4-positive cell genome via an integrase enzyme.

Once the DNA is integrated, the host cell’s enzymes will express the proteins responsible for replication and assembly of new HIV particles. The HIV particles are assembled by the enzymatic activity of proteases; the new viruses mature, and then bud off from the CD4 t-helper cell to infect other cells. The t-helper cells that are infected but not activated will not undergo apoptosis and thus serve as a latent

TABLE 1. PERCENTAGES OF U.S. POPULATIONS LIVING WITH AIDS BY RACE

Race	% of U.S. Population*	% of AIDS Population	% of WI Population**	% of AIDS Population
White	~70%	35%	90%	50%
African-American	12%	43%	6%	36%
Hispanic	13%	20%	4.7%	14%

\*<http://www.cdc.gov/hiv/resources/factsheets/At-A-Glance.htm>, accessed March 15, 2008

\*\*<http://www.dhfs.state.wi.us/AIDS-HIV/Stats/StatewideRevisedQtrly0108.pdf>, accessed March 17, 2008

**TABLE 2. ANTIRETROVIRAL AGENTS**

<b>Generic Name</b>	<b>Dose</b>	<b>Class</b>	<b>Renal Dose Adjustment</b>	<b>Notes</b>
Abacavir	300 mg BID or 600 mg daily	NRTI	No	Available in coformulated products with lamivudine and zidovudine/lamivudine
Didanosine	Wt ≥60 kg = 400 mg daily Wt <60 kg = 250 mg daily	NRTI	Yes	Dose adjustments required if used with tenofovir
Emtricitabine	200 mg daily	NRTI	Yes	Available in coformulated products with tenofovir and efavirenz/tenofovir
Lamivudine	150 mg BID or 300 mg daily	NRTI	Yes	Available in coformulated products with zidovudine, abacavir and zidovudine/abacavir
Stavudine	Wt ≥60 kg = 40 mg BID Wt <60 kg = 30 mg BID	NRTI	Yes	Should not be used with zidovudine
Tenofovir disoproxil fumarate	300 mg daily	NRTI	Yes	Available in coformulated products with emtricitabine and efavirenz/emtricitabine
Zidovudine	300 mg BID or 200 mg TID	NRTI	Yes	Available in coformulated products with lamivudine and lamivudine/abacavir
Delavirdine	400 mg TID	NNRTI	No	
Efavirenz	600 mg daily	NNRTI	No	Available in coformulated product with emtricitabine/tenofovir
Etravirine	200 mg BID	NNRTI	No	Take following a meal
Nevirapine	200 mg BID	NNRTI	No	Has initial dose-escalation phase
Atazanavir	400 mg daily without ritonavir 300 mg daily with 100 mg ritonavir	PI	No*	Absorption influenced by gastric pH. Take with food
Darunavir	600 mg BID with 100 mg ritonavir BID	PI	No	Take with food, contains sulfa moiety
Fosamprenavir	1400 mg daily alone, or with 100 mg or 200 mg ritonavir 700 mg BID with 100 mg ritonavir BID	PI	No	Contains sulfa moiety
Indinavir	800 mg TID or 800 mg BID with 100 mg or 200 mg ritonavir BID	PI	No	Unboosted indinavir should be taken on an empty stomach
Lopinavir/ritonavir	400 mg/100 mg BID or 800 mg/200 mg daily	PI	No	Oral solution formulation should be taken with food
Nelfinavir	1250 mg BID or 750 mg TID	PI	No	Take with food No ritonavir boosting
Ritonavir	600 mg BID (when used as the sole PI)	PI	No	Food improves tolerability
Saquinavir	1000 mg BID with 100 mg ritonavir BID	PI	No	
Tipranavir	500 mg BID with 200 mg ritonavir BID	PI	No	Stored in the refrigerator; use within 60 days at room temperature
Enfuvirtide	90 mcg (1mL) SQ BID	Fusion inhibitor	No	Must be reconstituted
Maraviroc	150 mg BID 300 mg BID 600 mg BID**	CCR5 antagonist	No	Caution use if CrCl <50 mL/min and using with CYP3A inhibitor
Raltegravir	400 mg BID	Integrase inhibitor	No	

\*Atazanavir is not recommended in treatment-experienced patients on hemodialysis

\*\*Dosing depends on other agents (see Table 5)

reservoir of virus replication, effectively making HIV incurable though there is no detectable virus in the blood.

### WHEN TO START THERAPY

Just like patients with other chronic diseases, patients with HIV-1 infection do not require medication management at all stages of their disease. There are stages in which lifestyle modifications and disease prevention are the treatment objectives. If this is the case, when do we start antiretroviral therapy for HIV patients? Antiretroviral medications should be started in patients with a CD4 T-cell count less than 200 cells/mm<sup>3</sup> or with a history of an AIDS-defining illness, such as *Pneumocystis jirovecii* pneumonia.<sup>10</sup> Strong data also exist that HAART should be started in patients with a CD4 T-cell count less than 350 cells/mm<sup>3</sup>, as the short term (six month) and long term (three to five year) risk of AIDS progression and death is less than if therapy is delayed until the 200 cells/mm<sup>3</sup> threshold is reached.<sup>11-13</sup> In addition, the SMART study, a prospective cohort study, showed that patients who were randomized to receive antiretroviral therapy after their CD4 T-cell count dropped to less than 250 cells/mm<sup>3</sup> (compared to receiving treatment immediately, when CD4 T-cell counts were greater than 350 cells/mm<sup>3</sup>) had an increased risk of opportunistic diseases and death at an av-

erage of 18 months follow-up with a rate of 4.8% vs. 1.1% (p=0.01).<sup>14</sup>

Specific populations of HIV-1 infected patients should receive antiretroviral therapy regardless of CD4 T-cell count or AIDS defining illness. Patients with HIV requiring treatment of hepatitis B (HBV) should receive a fully active antiretroviral regimen, even if CD4 T-cell counts are high. Tenofovir plus lamivudine or emtricitabine, nucleoside/nucleotide reverse transcriptase inhibitors, a common combination used as part of an initial antiretroviral HIV regimen, have activity against HBV. If a full antiretroviral HIV regimen is not initiated, HBV should be treated with one agent with the least potential to select for HIV resistance mutations.<sup>10</sup> Patients with HIV-associated nephropathy should also receive antiretroviral therapy regardless of T-cell count, as treatment has been shown to both preserve renal function and prolong survival. Although this condition does not seem to be correlated with CD-4 T-cell decline, renal damage is likely associated with ongoing viral replication, and antiretroviral therapy should be initiated to halt further injury.<sup>15</sup> Lastly, HIV-infected pregnant women should have antiretroviral therapy initiated even if CD4 T-cell counts are greater than 350 cells/mm<sup>3</sup>. Treatment in this population will reduce the risk of perinatal HIV transmission by reducing viral load.<sup>10</sup>

### INITIAL THERAPY GUIDELINES

Currently, more than 20 antiretroviral medications categorized into six pharmacologic classes exist on the market [see Table 2]. These six classes are nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 antagonists, and integrase inhibitors. With all these treatment options available, we have opportunities to use more effective and convenient regimens than ever before. Regimens should be individualized, and factors to consider when choosing a new antiretroviral regimen include comorbidities, adherence issues, drug interactions, drug resistance, pregnancy potential, gender and CD4 T-cell count if considering the use of nevirapine, and HLA B\*5701 test results if considering abacavir.<sup>10</sup> Initial antiretroviral regimens generally contain two NRTIs with one NNRTI or one PI (with or without ritonavir-boosting). See Table 3 for initial antiretroviral combinations recommended by the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents.<sup>10</sup>

Side effect profiles, drug resistance and convenience are the factors usually considered when choosing whether to use an NNRTI or PI-based regimen. NNRTI regimens tend to have a side effect pro-

**TABLE 3. DHHS RECOMMENDATIONS FOR INITIAL ANTIRETROVIRAL COMBINATIONS<sup>10</sup>**

To make an antiretroviral regimen, select one component each from column A and column B			
	<b>COLUMN A (NNRTI OR PI OPTION)</b>		<b>COLUMN B (DUAL-NRTI OPTION)</b>
<b>Preferred Components</b>	<u>NNRTI</u> or <u>PI</u> efavirenz    atazanavir + ritonavir fosamprenavir + ritonavir (BID dosing) lopinavir/ritonavir (coformulated) (BID dosing)	<b>Preferred Components</b>	abacavir/lamivudine (coformulated) (if test negative for HLAB*5701) or tenofovir/emtricitabine (coformulated)
<b>Alternative Components</b>	<u>NNRTI</u> or <u>PI</u> nevirapine    atazanavir fosamprenavir fosamprenavir + ritonavir (QD dosing) lopinavir/ritonavir (coformulated) (QD dosing) saquinavir + ritonavir	<b>Alternative Components</b>	zidovudine/lamivudine (coformulated) or didanosine + (emtricitabine or lamivudine)

file of central nervous system/psychiatric changes (with efavirenz) and rash development. PI regimens tend to include dyslipidemia, insulin resistance, stomach upset and diarrhea in their side effect profile. Drug resistance to efavirenz or nevirapine (NNRTIs) is present after a single mutation in the reverse transcriptase genetic code, while several mutations in HIV protease enzyme is required to confer resistance to most PIs. In fact, it is estimated that 10% of treatment-naïve HIV patients are infected with a virus that has mutations for antiretroviral drug resistance and therefore, genotypic testing should be performed before the selection of their antiretroviral regimen.<sup>16</sup> Convenience is also a key issue when choosing a regimen, as the more convenient a regimen is, the probability of patient adherence increases. NNRTI-based regimens are usually a bit simpler, especially with the co-formulated once-daily tablet of Atripla<sup>®</sup> (efavirenz/emtricitabine/tenofovir). Although there have been improvements over the years with PI-based regimens, they still tend to require more pills and more frequent dosing than NNRTI-based regimens.<sup>1</sup>

#### *Non-nucleoside reverse transcriptase inhibitors (NNRTIs)*

Of the four NNRTIs on the market, efavirenz is the preferred NNRTI, nevirapine is the alternative NNRTI, and delavirdine and etravirine are not recommended as components of an initial antiretroviral regimen. Although efavirenz and nevirapine produce similar virologic responses, nevirapine is associated with more serious side effects, namely hepatic events and rash. Nevirapine should be avoided in

women with baseline CD4 T-cell counts greater than 250 cells/mm<sup>3</sup> and in men with counts greater than 400 cells/mm<sup>3</sup>, as these groups of patients have a higher incidence of symptomatic and serious hepatic events. Nevirapine therapy may continue, without increased risk of hepatic events, when patients who were started below these CD4 T-cell count thresholds have T-cell count increases above the stated levels. Nevirapine should be initiated at a dose of 200 mg daily for two weeks and then dose-escalated to 200 mg twice daily. Hepatic liver enzymes should be monitored at baseline, at two weeks and four weeks post-initiation of therapy, and then monthly for the first 18 weeks. Efavirenz is not without risk of adverse events, one of the most common being central nervous system (CNS) side effects. These CNS changes usually resolve a few weeks to two months after initiating therapy. Efavirenz, shown to cause CNS congenital defects in primate studies and neural tube defects in human newborns, should be avoided in pregnant women, especially in their first trimester. In addition, efavirenz is a pregnancy category D and should not be used in women planning to conceive or who are sexually active and not using effective contraception.<sup>10</sup>

#### *Protease inhibitors (PIs)*

Choosing a PI-based antiretroviral regimen should be based on convenience, drug interactions and toxicity profile. Low-dose ritonavir, used as a pharmacokinetic “booster” of protease inhibitors has its advantages and disadvantages. Ritonavir boosting increases drug exposure by

inhibiting the cytochrome P450 enzyme metabolism of co-administered PIs, allowing for reductions in dose frequency and pill burden. However, there is an increased risk of hyperlipidemia and drug interactions when ritonavir is used. Atazanavir, with or without ritonavir boosting, is convenient with low pill burden and once-daily dosing. In addition, it tends to have less effect on lipids than other PIs. A boosted atazanavir regimen is preferred over an unboosted regimen due to an improved pharmacokinetic profile and possibly improved virologic activity. Atazanavir does have its disadvantages, namely a risk of indirect hyperbilirubinemia and its absorption depends on food and low gastric pH. If a patient fails on atazanavir, it is unlikely that cross-resistance exists to other PIs in the class. Unlike atazanavir, the absorption of fosamprenavir does not rely on food. Fosamprenavir side effects include rash and gastrointestinal disturbance, especially if dosed once-daily versus twice-daily. If a patient fails on unboosted fosamprenavir, there is potential for cross-resistance to other PIs, especially darunavir. Lopinavir/ritonavir, a coformulated product, can be dosed once-daily in treatment naïve patients, however gastrointestinal disturbance may be higher than if dosed twice-daily. This coformulated product has no food restrictions. Lopinavir/ritonavir has a low risk for cross-resistance to other PIs if a patient fails on a lopinavir/ritonavir-based regimen. Saquinavir boosted with ritonavir has equal efficacy as other boosted PIs, but leads to a higher pill burden and gastrointestinal intolerance. Darunavir boosted

**TABLE 4. MOTIVATE 1 AND 2<sup>24</sup>**

Motivate 1 and 2 were randomized, double-blind, placebo-controlled, parallel phase IIb/III studies. Forty-four percent of patients failed initial screening secondary to the lack of CCR5-tropic HIV-1 virus. The primary endpoint, mean change in HIV-1 RNA at week 24, is the data the FDA used to approve maraviroc in August 2007.

	<b>Placebo + OBR (n=209)</b>	<b>Maraviroc QD + OBR (n=414)</b>	<b>Maraviroc BID + OBR (n=426)</b>
Median HIV-1 RNA change from baseline, log <sub>10</sub> copies/mL	-0.99	-1.88	-1.96
HIV-1 RNA <400 copies/mL, n (%)	28	55	61
HIV-1 RNA <50 copies/mL, n (%)	23	44	45
Mean CD4+ cell count change from baseline, cells/mm <sup>3</sup>	57	109	106

OBR = optimized background regimen  
‡p=0.0001 vs. placebo group

with ritonavir does not have enough data yet available to recommend wide-spread use in treatment-naïve patients. Indinavir is not recommended for treatment-naïve patients due to more frequent dosing and risk of nephrolithiasis. Nelfinavir is not recommended in these patients due to increased pill burden and recent news of a contaminant, ethyl methane sulfonate, a known carcinogen. Lastly, tipranavir is not a first-line agent for treatment-naïve patients due to risks of hepatotoxicity, rash and intracranial hemorrhage.<sup>10</sup>

#### *Nucleoside/nucleotide reverse transcriptase Inhibitors (NRTIs)*

Dual-NRTI combinations are usually the backbone of an antiretroviral regimen. An NRTI such as abacavir, tenofovir, didanosine, zidovudine or stavudine is often paired with lamivudine or emtricitabine. Both lamivudine and emtricitabine select for the M184V reverse transcriptase mutation, which confers resistance to these agents, but decreases the robustness of the virus and improves the susceptibility to other NRTIs, (namely zidovudine, tenofovir and stavudine). Didanosine is the only NRTI that has any food restrictions – it should be taken on an empty stomach. Once-daily dosing is possible with all NRTIs except stavudine and zidovudine. Abacavir/lamivudine, a once-daily coformulated product, is a preferred component of an initial antiretroviral regimen due to convenience and virologic potency. Abacavir does have a potential for hypersensitivity reactions, but a negative pretreatment HLAB\*5701 test greatly decreases the risk for a reaction. Tenofovir/emtricitabine, another once-daily coformulated preferred product, has great virologic potency and less loss of limb fat and anemia than zidovudine/lamivudine.<sup>17,18</sup> Tenofovir has been associated with renal impairment, and renal function should be monitored while using this agent. Tenofovir plus emtricitabine or lamivudine is preferred if the HIV patient is co-infected with HBV. Zidovudine/lamivudine is considered an alternative combination tablet due to twice-daily dosing, an increased risk of bone marrow suppression and lipoatrophy. Didanosine used in combination with emtricitabine or lamivudine is another alternative combination due to limited clinical trial data

and an increased risk of pancreatitis and peripheral neuropathy.<sup>10</sup>

#### *Upcoming options for treatment-naïve patients*

There are several treatment options that are approved for treatment-experienced HIV patients that are currently in Phase II and III trials. These innovative therapies may be upcoming treatment options to add to our choices for treatment regimens for treatment-naïve patients. The ARTEMIS study, a non-inferiority trial compares darunavir/ritonavir 800/100 mg daily with lopinavir/ritonavir either 400/100 mg twice daily or 800/200 mg daily in treatment-naïve patients. Preliminary data show similar efficacy between the two groups, with less serious side effects (mainly diarrhea) in the darunavir/ritonavir group. Currently darunavir/ritonavir is not available in a formulation to obtain a dose of 800/100 mg.<sup>19</sup> Raltegravir, a novel integrase inhibitor, is currently being studied in Phase III trials of treatment-naïve patients. A small phase II trial compared several doses of raltegravir-based regimens with an efavirenz-based regimen in treatment-naïve patients. Efficacy was similar, as well as adverse effects, except for an increased incidence of psychiatric side effects in the efavirenz group.<sup>20</sup> Maraviroc, a new CCR5 antagonist, was compared with an efavirenz-based regimen in the MERIT study of treatment-naïve patients. At 48 weeks, 65.3% of the maraviroc group had an HIV RNA viral load of <50 copies/mL, while 69.3% of the efavirenz group met this viral suppression measurement. For this end-point, maraviroc did not meet the non-inferiority standards set by the investigators.<sup>21</sup> The approval trials and indications of raltegravir and maraviroc will be discussed later.

#### **DRUG COMBINATIONS TO AVOID**

Choosing an antiretroviral regimen for the treatment-naïve patient is not as simple as matching up one NNRTI or PI with two NRTIs. There are some antiretroviral combinations to avoid. Atazanavir and indinavir should not be used together due to the additive potential of hyperbilirubinemia. Didanosine and stavudine should not be used in the same antiretroviral regimen due to the high potential of side effects, particularly peripheral

neuropathy, pancreatitis and lactic acidosis. Two NNRTIs should not be used in combination. Efavirenz and nevirapine used together have shown increased toxicities. Efavirenz or nevirapine with etravirine may result in decreased etravirine exposure due to the induction of its metabolism. Emtricitabine and lamivudine should not be used together due to similar resistance profiles and no additive benefit. Emtricitabine is essentially the same chemical structure as lamivudine, just with a fluorine moiety substitution at one position. Stavudine and zidovudine have an antagonistic effect on HIV-1 and thus should not be used in combination. Finally, darunavir, saquinavir, or tipranavir should never be used unboosted due to insufficient bioavailability.<sup>1</sup>

#### **TREATMENT-EXPERIENCED PATIENTS**

When a patient fails an antiretroviral regimen, either by virologic or immunologic means, a new regimen must be constructed. The patient's treatment history and drug resistance test results should guide the design of the new antiretroviral regimen. Drug resistance testing should be performed while the patient is failing his/her current regimen or is at least within four weeks of discontinuation. General strategies to choose a new regimen include using multiple fully-active agents, using agents that do not have cross resistance with previously used agents, and using a mechanistically different class of antiretroviral agents. The new regimen should contain at least three active agents; some may be the same agents contained in the failing regimen, if determined active by resistance testing. It is not recommended to add only one fully active agent to a failing regimen due to the risk of new resistance. Overall, expert advice from HIV and infectious disease specialists should be consulted for treatment-experienced patients.<sup>10</sup>

#### **NUANCES OF ANTIRETROVIRAL THERAPY**

Treating the HIV-infected patient has several nuances to therapy when choosing treatment regimens. Atazanavir is a PI with many factors to consider when dosing. Atazanavir should be boosted with ritonavir (300 mg atazanavir with

100 mg ritonavir) if given with tenofovir or efavirenz due to metabolic induction. Atazanavir absorption and bioavailability is influenced by gastric pH. Thus, if atazanavir is used in the treatment-naïve patient with famotidine 20 mg twice daily (or similar H<sub>2</sub>-receptor antagonist), the dose should be 300 mg with 100 mg of ritonavir. If the patient is also using tenofovir as part of his/her regimen, the dose should be 400 mg atazanavir with 100 mg ritonavir. If the patient using atazanavir is treatment-experienced, famotidine 20 mg, or similar equivalent, should only be used daily and the dose of atazanavir should be 300 mg with 100 mg ritonavir. Another nuance of therapy is that lopinavir/ritonavir is the protease inhibitor of choice for the pregnant patient, but once-daily dosing should not be used in this population. It is important to note that nelfinavir is the only protease inhibitor that should not be boosted using ritonavir, as it is metabolized through different cytochrome P450 enzymes.<sup>1</sup>

A few particular antiretroviral issues should be factored when a patient is planning to interrupt therapy. Efavirenz, etravirine and nevirapine all tend to have longer half-lives than the other components of the antiretroviral regimen (NRTIs). If all medications in the regimen are stopped at one time, it may leave levels of the NNRTI in the body for one to three weeks, essentially causing monotherapy for the patient and putting the patient at risk for selection of mutations. This is less of a concern when tenofovir and emtricitabine are used as the NRTIs, due to their longer intracellular half-lives. The optimal time to discontinue the NNRTI before the rest of the NRTI regimen is unknown. Another possible strategy is substituting the NNRTI with a PI for a few weeks before therapy interruption. In addition, therapy disruption and consequential reintroduction of nevirapine needs special

attention. Nevirapine induces its own hepatic metabolism and if reintroduced at full dose without the low-dose escalation phase, the patient is at an increased risk of toxicity. Therefore, if a patient has been off nevirapine therapy for more than two weeks, the medication should be reintroduced as 200 mg daily for two weeks and then 200 mg twice daily thereafter. An additional nuance of therapy interruption is the discontinuation of emtricitabine, lamivudine or tenofovir in patients with hepatitis B co-infection. These agents have activity against the hepatitis B virus and, in the event of their discontinuation, the patient may experience an exacerbation in hepatitis.<sup>10</sup>

**Recently approved antiretroviral agents**

During the end of 2007 through the beginning of 2008, the FDA reviewed and accelerated approval for three new treatments for HIV-1 infection. Two of these medications, maraviroc and raltegravir, provide us with new mechanisms of action to add to our armamentarium of antiretroviral agents. The third medication, etravirine, is part of the NNRTI class. Etravirine does not follow the same resistance patterns as our previous NNRTIs (efavirenz, nevirapine, and delavirdine), therefore allowing NNRTI treatment-experienced adults infected with HIV-1 to have another regimen option.<sup>22</sup>

The binding of gp120 to the CD4 t-cell represents the first step of HIV-1 entry into the host cell. The second necessary step in viral entry requires binding of gp120 to human chemokine co-receptors. In vivo studies have identified human chemokine receptor 5 (CCR5) and chemokine receptor 4 (CXCR4) as the most commonly utilized chemokine co-receptors of HIV-1. Gp120 has the ability to bind to one or both of these receptors, which defines the tropism of the virus. Viruses that only use CCR5 as the co-receptor are referred to as CCR5-tropic

while viruses that only utilize CXCR4 as the co-receptor are referred to as CXCR4-tropic. Patients may also have viruses that utilize both CCR5 and CXCR4 co-receptors (dual tropic) or have mixtures of virus that utilize CCR5 or CXCR4 (mixed-tropic virus).

Maraviroc (Selzentry®, Pfizer) is a selective, slowly reversible, small molecule antagonist of CCR5. It inhibits the interaction of the gp120 from CCR5-tropic HIV-1 virus with CCR5, preventing the virus from entering the host cell.<sup>23</sup> Maraviroc, in combination with other antiretroviral agents, has been FDA approved for treatment-experienced adults infected with only the CCR5-tropic HIV-1 detectable virus which is resistant to multiple antiretrovirals. This approval was based on two, randomized, double-blind, placebo-controlled superiority studies, MOTIVATE-1 and 2 trials [Table 4]. To determine if the HIV will be susceptible to the medication, a tropism test must be initiated prior to treatment to determine if the patient has only CCR5-tropic HIV-1 virus.<sup>25</sup>

Maraviroc was well tolerated in clinical trials. The most common treatment-related adverse events occurring in >5% of patients treated with maraviroc were diarrhea, nausea, headache, pyrexia, and fatigue (similar to the placebo group). Other events which occurred in the maraviroc-treated patients included elevated lipids, liver-related events, infection-related adverse events, and an increase in the incidence of cardiac events related to coronary artery disease. HIV tropism switching from CCR5 to CXCR4 or dual/mixed utilizing virus has been identified during Phase III trials, thus leaving the medication less effective, potentially requiring a regimen change.<sup>25</sup>

The recommended dose of maraviroc depends on the concomitant therapy because of drug interactions. Maraviroc is a

**TABLE 5. DOSAGE AND ADMINISTRATION OF MARAVIROC®<sup>25</sup>**

When given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except tipranavir/ritonavir), and delavirdine	150 mg by mouth twice daily (with or without food)
With NRTIs, tipranavir/ritonavir, nevirapine, and other drugs that are not strong CYP3A inhibitors or CYP3A inducers	300 mg by mouth twice daily (with or without food)
With CYP3A inducers including efavirenz (without a strong CYP3A inhibitor)	600 mg by mouth twice daily (with or with out food)

substrate of CYP 3A and P-glycoprotein (Pgp), therefore its pharmacokinetics are likely to be modified by inhibitors and inducers of these enzymes and transporters (Table 5). Caution should be used in patients with renal impairment, as the safety and efficacy were not specifically studied and renal excretion accounts for 25% of total maraviroc clearance. Patients at an increased risk for cardiovascular events or with preexisting liver dysfunction should also use caution with maraviroc.<sup>25</sup>

Raltegravir (Isentress®, Merck) is an HIV-1 integrase strand transfer inhibitor. It inhibits the catalytic activity of HIV-1 integrase, an enzyme that is required for viral DNA to be integrated into host DNA. This inhibition prevents HIV-1 replication.<sup>26</sup> Raltegravir, in combination with other antiretroviral agents, has been FDA approved for treatment-experienced adults who have evidence of viral replication and HIV-1 resistant strains to multiple antiretroviral agents. Raltegravir was approved based on the results of the BENCHMRK 1 and 2 trials [Table 6].

The usual dose of raltegravir is 400 mg administered orally, twice daily, with or without food. It is primarily eliminated by glucuronidation in the liver. No dosage adjustment is needed in renal impairment or mild-to-moderate hepatic impairment. The effect of severe hepatic impairment has not been studied. Raltegravir does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, uridine diphosphate glucosyltransferase (UGT) or Pgp-mediated transport. However, caution should be used when coadministering raltegravir with strong inducers of UGT 1A1 (i.e. rifampin) because of reduced raltegravir plasma concentrations.<sup>26</sup>

Raltegravir was well tolerated in the

BENCHMRK 1 and 2 clinical trials. The most common treatment-related adverse events occurring in >10% of patients were diarrhea, nausea, and headache. These events were similar to placebo. Other events which occurred with more frequency in the raltegravir-treated patients included rash, elevated ALT/AST and elevated CPK. Because of the risk of myopathy or rhabdomyolysis, caution should be used when prescribing raltegravir with other medications that can increase CPK.<sup>26</sup>

Etravirine (Intelence®, Tibotec) is a member of the NNRTI class. It binds directly onto reverse transcriptase and prevents the enzymatic conversion of HIV RNA to DNA.<sup>28</sup> Etravirine, in combination with other antiretroviral agents, has FDA approval for use in treatment-experienced adults who have HIV strains that are resistant to other NNRTIs. Its approval was based upon two, randomized, double-blind, placebo-controlled trials, DUET 1 and 2. [Table 7] In the DUET trials, etravirine was well tolerated with the most common adverse events being rash (16.9%) and nausea (13.9%). The rash was generally mild to moderate in severity, mostly occurred in the second week of treatment and resolved within one to two weeks while continuing therapy. Rare cases of Stevens-Johnson syndrome have been reported. Other events which occurred with more frequency in etravirine-treated patients included elevated total cholesterol and low-density lipoproteins.<sup>28</sup>

The recommended dose of etravirine is 200 mg administered orally, twice daily following a meal. Etravirine is an inducer and substrate of CYP3A4 and an inhibitor and substrate of CYP2C9 and 2C19. Drugs that are substrates, inhibitors or inducers of these enzymes may change

the therapeutic effect of etravirine or the coadministered drug. Careful use with protease inhibitors is especially warranted. Data for safe administration with darunavir/ritonavir, lopinavir/ritonavir, and saquinavir/ritonavir is available. Caution is needed in adults with severe hepatic impairment, risk factors for cardiovascular events and pancreatitis.<sup>28</sup>

### PHARMACIST INTERVENTIONS

The numerous options for HIV/AIDS therapy coupled with increasing life expectancies and increasing co-morbidities make pharmacist involvement with care more important than ever before. While pharmacists have always been noted for their abilities to screen for drug-drug interactions and counsel on appropriate medication use, there are other important interventions that pharmacists can provide to increase the health outcomes of patients. Pharmacists in an outpatient setting are in the best position to monitor for adherence to prescribed therapy and make recommendations for over-the-counter and complementary therapies, while pharmacists in clinic and inpatient settings are in good position to monitor and triage adverse events and make appropriate dose formulation selections.

#### *Maximizing medication therapy adherence*

Until recently, the gold standard for adherence to HAART was taking the regimen as prescribed greater than or equal to 95% of the time.<sup>31</sup> Now, with more potent therapies with longer half-lives being available, there is some debate as to whether 90% adherence may be more appropriate.<sup>34</sup> Regardless of the benchmark, a high level of adherence is essential to positive health outcomes. Using these percent-

TABLE 6. BENCHMRK 1 AND 2<sup>27</sup>

BENCHMRK 1 and 2 are randomized, double-blind, placebo-controlled trials in antiretroviral treatment-experienced HIV-1 infected adult subjects. The primary endpoint included mean change of HIV-1 RNA and CD4 cell counts at week 24.

BENCHMRK 1 and 2 Pooled	Raltegravir 400 mg twice daily + OBR (n=462)	Placebo + OBR (n=237)	
Outcome at week 24	n (%)	n (%)	p-value
Subjects with Week 24 data	286 (61.9)	150 (63.3)	<0.001
Subjects with HIV-1 RNA <400 copies/mL	216 (75.5)	59 (39.3)	<0.001
Subjects with HIV-1 RNA <50 copies/mL	179 (62.6)	50 (33.3)	<0.001
CD4 cell count gain	84	37	<0.001

ages, patients cannot miss their HAART more than one time in a week. Estimates suggest that 10% of patients with HIV in the United States report missing one or more medication doses in any single day.<sup>32</sup> Non-adherence is not unique to HAART, but unlike medication therapies for other chronic conditions, even brief interruptions of adherence to HAART can render anti-retroviral regimens permanently ineffective due to resistance development.<sup>33</sup>

There are many factors that can contribute to lower adherence, some of which include active substance abuse, side effects, regimen complexity, psychiatric disorders and belief.<sup>32</sup> The challenge in ad-

ressing these issues is the lack of clinical literature supporting specific interventions to increase adherence levels.<sup>34</sup> Adherence interventions that show promising outcomes include proactive telephone calls to assess patient therapy, triage for adverse events and reminders for upcoming re-fills.<sup>35</sup> Utilization of pill boxes and other pneumonic reminder systems have had mixed reviews in the literature, but all can be specifically tailored to match with an individual patient's needs.<sup>34</sup>

Pharmacists can have the greatest impact on the outcome of a patient's HAART during the initial regimen consultation. Care should be taken to assess

potential barriers to adherence, and set realistic expectations for the patient. Interventions such as setting tangible goals, creating an adverse event management plan and creating a simple plan for follow up will all empower a patient to take control of his or her regimen. Pharmacists should have consistent follow up with the prescriber as well as with all members of the health care team including nurses, clinic staff, social workers and third parties. Pharmacists also need to help prevent lapses in treatment for patients who are hospitalized or incarcerated.

Creativity and customization are important attributes to an effective adher-

**TABLE 7. DUET 1 AND 2** <sup>29,30</sup>

DUET 1 and 2 are randomized, double-blind, placebo-controlled, parallel, multinational trials in antiretroviral treatment-experienced HIV-1 infected adult subjects undergoing etravirine treatment. The primary endpoint included a confirmed viral load <50 copies/mL at weeks 24 and 48.

Endpoint	Duet-1		Duet-2		Pooled results from both studies
	week 24	week 48	week 24	week 48	week 48
Viral load <50 copies/mL	56% treatment vs. 39% placebo (p=0.005)	60% treatment vs. 39% placebo (p<0.0001)	62% treatment vs. 44% placebo (p=0.0003)	61% treatment vs. 41% placebo (p<0.0001)	61% treatment vs. 40% placebo (p<0.0001)
Mean change in HIV-RNA vs. baseline (log10 copies/mL)	-2.41 treatment vs. -1.7 placebo (p<0.0001)	-2.29 treatment vs. -1.52 placebo (p<0.0001)	-2.34 treatment vs. -1.68 placebo (p<0.0001)	2.22 treatment vs. -1.46 placebo (p<0.0001)	-2.25 treatment vs. -1.49 placebo (p<0.0001)
Mean change in CD4 cell count vs. baseline (cells/mm <sup>3</sup> )	89 treatment vs. 64 placebo (p=0.0002)	103 treatment vs. 74 placebo (p=0.0025)	78 treatment vs. 66 placebo (p=0.3692)	94 treatment vs. 72 placebo (p=0.160)	98 treatment vs. 73 placebo (p=0.0006)

**TABLE 8. POCKET GUIDE FOR THE NEWEST ANTIRETROVIRAL AGENTS**

	Maraviroc (Selzentry®) 300 mg PO BID (adjust according to drug interactions) with or without food	Raltegravir (Isentress®) 400 mg PO BID  with or without food	Etravirine (Intelence®) 200 mg PO BID Diet restrictions following a meal
Metabolism	CYP3A4	UGT-mediated glucuronidation	CYP3A4, 2C9, and 2C19
Excretion	76% fecal 20% renal	51% fecal 32% renal	93.7% fecal 1.2% renal
Side Effects	URTIs, cough, pyrexia, rash, musculoskeletal pain, dizziness	diarrhea, nausea, dizziness, fatigue	rash, nausea, abdominal pain, vomiting

ence plan. When assessing a patient for potential non-adherence, pharmacists need to take great care to avoid making false assumptions and predicting adherence based upon the initial presentation of the patient. With all else being equal, race, gender, socioeconomic status, age and education level by themselves do not predict non-adherence.<sup>32-34</sup>

## CONCLUSION

The treatment and understanding of HIV/AIDS has been constantly changing since it was first seen over 30 years ago. New treatments and large increases in life expectancy have drastically changed the management of the disease. Pharmacists will be seeing more HIV positive patients with diabetes, coronary artery disease and other chronic metabolic and inflammatory disorders. New antiretroviral medications are approved almost every year and there is a robust pipeline of therapies, all of which bring new challenges in adherence, toxicities and interactions. Pharmacists, now more than ever, are a crucial part of the HIV/AIDS management team. Pharmacists can apply a chronic disease management approach to HIV/AIDS therapy and adapt the skills they use in other chronic disease states to maximize therapy adherence and outcomes. ●

Nicholas Olson and Nicole Lentz are staff pharmacists at Bioscrip Pharmacy in Milwaukee. Anne Daniels is a clinical pharmacist at the Infectious Disease Clinic at Froedtert Hospital in Milwaukee. Richard Fons is the pharmacy manager at Bioscrip Pharmacy.

## REFERENCES

- Hymes KB, Greene JB, Marcus A, et al. Kaposi's sarcoma in homosexual men: A report of eight cases. *Lancet* 1981; 2:598-600.
- National Cancer Institute. <http://www.cancer.gov/cancertopics/pdq/treatment/kaposi/patient>. Accessed May 10, 2008.
- Marx JL. Strong new candidate for AIDS agent. *Science* 1984; 224:475-477.
- Centers for Disease Control and Prevention HIV Surveillance. <http://www.cdc.gov/nchs/deaths.htm>. Accessed May 10, 2008.
- MMWR. 2006; 55:589-592.
- Center for Disease Control and Prevention Cases of HIV infection and AIDS in the United States and Dependent Areas, 2005. <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2005report/default.htm>. Accessed May 10, 2008.
- Hellinger FJ. The lifetime costs of treating a person with HIV. *JAMA* 1993; 270:474-478.
- Schackman B, Gebo K, Walensky R, et al. The lifetime costs of current human immunodeficiency virus in the United States. *Med Care* 2006; 44:990-997.
- Martinez E, Milinkovic A, Buira E, et al. Incidence and causes of death in HIV-infected persons receiving highly active antiretroviral therapy compared with estimates for the general population of similar age and from the same geographical area. *HIV Med* 2007; 8:251-258.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. January 29, 2008;1-128. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed May 4, 2008.
- Egger M, May M, Chêne G, et al. Prognosis of HIV-1 infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002; 360:119-129.
- Phillips A. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naïve individuals and those treated in the monotherapy era. *AIDS* 2004; 18:51-58.
- Hogg RS, Yip B, Chan KJ, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA* 2001; 286:2568-2577.
- Emery S, the SMART Study Group and INSIGHT. Major clinical outcomes in patients not treated with antiretroviral therapy (ART) at baseline in SMART; a rationale for a trial to examine early treatment of HIV disease. Poster exhibition: 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 2007; Sydney, Australia. Abstract WEPEB018.
- Atta MG, Gallant JE, Rahman MH, et al. Antiretroviral therapy in the treatment of HIV-associated nephropathy. *Nephrol Dial Transplant* 2006; 21:2809-2813.
- Wheeler W, Mahle K, Bodnar U, et al. Antiretroviral drug-resistance mutations and subtypes in drug-naïve persons newly diagnosed with HIV-1 infection, US, March 2003 to October 2006. Presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 648.
- Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006; 354:251-260.
- Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naïve patients: 144-week analysis. *J Acquir Immune Defic Syndr* 2008; 47:74-78.
- DeJesus E, Ortiz R, Khanlou H, et al. Efficacy and safety of darunavir/ritonavir vs lopinavir/ritonavir in ARV treatment-naïve HIV-1-infected patients at week 48: ARTEMIS. Presented at: 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17-20, 2007; Chicago, IL. Abstract H-718b.
- Markowitz M, Nguyen BY, Gotuzzo E, et al. Rapid and durable antiretroviral effect of the HIV-1 integrase inhibitor raltegravir as part of combination therapy in treatment-naïve patients with HIV-1 infection: results of a 48-week controlled study. *J Acquir Immune Defic Syndr* 2007; 46:125-133.
- Saag M, Iye P, Heere J, et al. A multicenter, randomized, double blind, comparative trial of a novel CCR5 antagonist, maraviroc versus efavirenz, both in combination with Combivir (zidovudine [ZDV]/lamivudine [3TC]), for the treatment of antiretroviral-naïve subjects infected with R5 HIV 1: week 48

- results of the MERIT study. Presented at: 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 2007; Sydney, Australia. Abstract WESS104.
- U.S. Food and Drug Administration Center for Drug Evaluation and Research. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>. Accessed April 10, 2008.
  - Palani A, Tagat JR. Discovery and development of small molecule chemokine coreceptor CCR5 antagonists. *J Med Chem* 2006; 49:2851-2857.
  - Gulick RM, Van der Ryst E, Lampiris H, et al. Efficacy and safety of once-daily (QD) compared with twice-daily (BID) maraviroc plus optimized background therapy (OBT) in treatment-experienced patients infected with CCR5-tropic-HIV-1: 24-week combined analysis of the MOTIVATE 1 and 2 studies. In: Program and abstracts of the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 2007; Sydney, Australia. Abstract WEPEB116LB.
  - Selzentrup [package insert]. NY, NY: Pfizer Inc.; August 2007.
  - Isentress [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; October 2007.
  - Kumar PN, Cooper DA, Steigbigel RT, et al. Efficacy of raltegravir, an HIV integrase inhibitor, in combination with regimens containing efavirenz, darunavir, or tipranavir in patients with triple-class resistant virus: Combined results from BENCHMRK 1 and BENCHMRK 2. Presented at the 11th European AIDS Conference, Madrid, Spain, Oct. 23-27, 2007.
  - Intencele [package insert]. Raritan, NJ: Tibotec Therapeutics, Inc.; January 2008.
  - Madruca J, Cahn P, Grinsztajn B, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomized, double-blind, placebo-controlled trial. *Lancet* 2007; 370:29-38.
  - Lazzarin A, Campbell T, Bonaventura C, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomized, double-blind, placebo-controlled trial. *Lancet* 2007; 370:39-48.
  - Paterson DL. Abstract-172, 38th ICAAC, San Diego, September 1998.
  - Reynolds NR. Adherence to antiretroviral therapies: state of science. *Curr HIV Res* 2004; 2:207-214.
  - Lucas GM. Antiretroviral therapy adherence, drug resistance, viral fitness, and HIV disease progression: a tangled web is woven. *J Antimicrob Chemother* 2005; 55:413-416.
  - Simoni JM, Frick PA, Pantalone DW, et al. Antiretroviral adherence interventions: a review of current literature and ongoing studies. *Top HIV Med* 2003; 11:185-198.
  - Reynolds NR, Testa M, Su M, et al. Telephone support to improve antiretroviral medication adherence: a multisite, randomized controlled trial. *J AIDS* 2008; 47:62-68.

## UWSOP Faculty News

Michelle Chui is an assistant professor with the Social and Administrative Sciences Division with the University of Wisconsin School of Pharmacy. Chui received her BA in Biological Sciences, her PharmD from Creighton University in Omaha, NE, and her MS and PhD in Pharmacy Administration from Purdue University in West Lafayette, Ind. For her MS degree, she conducted an empirical evaluation of the benefits and burden that computer-generated drug utilization review alerts contributed to community pharmacy practice. Her focus of study for her PhD degree was patient adherence, quality of life and outcomes research. Chui practiced pharmacy in community settings during her graduate studies.

Before joining the UW School of Pharmacy faculty in 2008, Dr. Chui was on the faculty at Midwestern University College of Pharmacy - Glendale in Arizona, where she taught behavioral medicine and ethics, and health economics and outcomes assessment courses.

Chui's research centers on contributing to community pharmacy practice and its practitioners. Specifically she has three primary goals: to provide necessary evidence to policy makers and the lay population for advanced care in the community pharmacy setting, facilitate communication and networking among community pharmacists, and improving workflow so that community pharmacists can provide effective and efficient pharmaceutical care to their patients.

In her free time, she enjoys hiking, reading good fiction, and spending time with her husband (also a pharmacist) and four children. ●



## SELF ASSESSMENT QUESTIONS

# A Shifting Paradigm of HIV and AIDS Therapy

- The overall rate of new HIV infections in the United States is currently
  - Increasing
  - Decreasing
  - Staying about the same
- Young African-Americans, Hispanic-Americans and women are demographic groups that are at an increased risk of contracting the HIV virus.
  - True
  - False
- Since its inception in 1995, highly-active antiretroviral therapy has had little impact on the mortality and morbidity of HIV/AIDS.
  - True
  - False
- Which of these following attributes of HIV/AIDS offer unique opportunities for pharmacist involvement in therapy:
  - Antiretroviral medications have unique toxicities and drug-drug interaction issues
  - There is an increasing amount of HIV positive patients suffering from co-morbid conditions such as hyperlipidemia, diabetes, and cardiac disease.
  - There is an increase of patients suffering from more acute effects of HIV infection and are going into hospice and end-of-life care, and less are being managed as a chronic disease state.
  - A and B
  - All of the above
- There are relatively few steps in the HIV replication cycle that offer targets for antiretroviral drug therapy
  - True
  - False
- A 35-year-old male with HIV and HBV co-infection presents to your clinic. He has never received antiretroviral therapy before. His CD4 T-cell count is 420 cells/mm<sup>3</sup> and you wish to start him on therapy. His resistance testing shows all antiretroviral agents are active. What is your best option:
  - No treatment because his CD4 T-cell count is too high to receive antiretroviral therapy
  - Treat with combination tenofovir and lamivudine
  - Treat with combination tenofovir, lamivudine and another antiretroviral, such as a efavirenz
  - Treat with combination abacavir and stavudine
- A follow-up appointment of a treatment-naïve 30-year-old female with HIV shows her CD4 T-cell count has dropped to 124 cells/mm<sup>3</sup>. You wish to begin antiretroviral therapy. Her liver and renal function tests are within normal limits. She is hepatitis B negative. Her HLAB\*5701 test comes back positive. Her initial resistance test shows that all antiretroviral agents are fully active. She informs you that she is heterosexually active without consistent use of contraception. What is your best option:
  - Atripla® (efavirenz/emtricitabine/tenofovir)
  - Atazanavir boosted with ritonavir and Epzicom® (lamivudine/abacavir)
  - Atazanavir boosted with ritonavir and Truvada® (emtricitabine/tenofovir)
  - Darunavir boosted with ritonavir and Truvada® (emtricitabine/tenofovir)
- A treatment-naïve 45-year-old female with HIV comes to your clinic for an initial visit. Her CD4 T-cell count is 300 cells/mm<sup>3</sup>. She is not sexually active at this time. Her HLAB\*5701 test is negative. You decide to start therapy, but she is very concerned with convenience, hyperlipidemia, and gastrointestinal side effects. What is your best option:
  - Atripla® (efavirenz/emtricitabine/tenofovir)
  - Nevirapine with Truvada® (emtricitabine/tenofovir)
  - Lopinavir/ritonavir daily dosing and Truvada® (emtricitabine/tenofovir)
  - Either A or B
- A 26-year-old male patient that you have been following for two years presents to your clinic with acid reflux. His only antiretroviral therapy, which he is doing well on, has been atazanavir 300 mg boosted with 100 mg ritonavir daily and Truvada® (emtricitabine/tenofovir). He wants to continue on this regimen, but is wondering if he can buy Pepcid® (famotidine) over-the-counter. How do you respond?
  - He cannot use any medications like famotidine because it reduces the absorption of atazanavir
  - He can use 20 mg famotidine twice daily
  - He can use as much of any medication that he wants – antacids or famotidine-like products
  - He can use 20 mg famotidine twice daily, but change his dose of atazanavir to 400 mg daily, still boosting with 100 mg ritonavir and continue with the Truvada®
- AB is a 67 year-old male with multi-drug resistant HIV. Dr. X wants to change the regimen, and is thinking about using maraviroc. What should Dr. X do first?
  - Perform a blood draw to get BMP, CBC, LFTs, viral load and CD4 count.
  - Perform a blood draw to get a tropism test.
  - Perform a blood draw to get a Phenosense® GT.

11. In the MOTIVATE 1 and 2 trials, the most difficult challenge for qualifying a study patient was:
- There are not enough HIV treatment-experienced patients to conduct trials.
  - Lack of interest from health care providers.
  - Lack of CCR5-tropic HIV-1 virus in treatment-experienced patients.
12. MH is a 44 year-old male with multi drug-resistant HIV and tuberculosis. He is currently on ethambutol 2 gm MWF, isoniazid 900 mg MWF, pyrazinamide 2500 mg MWF, and rifabutin 150 mg MWF. Which of the following medications do we need to use caution in prescribing?
- Maraviroc
  - Raltegravir
  - Etravirine
  - A and C
13. Etravirine is part of a new class of antiretrovirals that was recently approved by the FDA.
- True
  - False

14. BENCHMRK 1 and 2 were random, double-blind, placebo-controlled trials that demonstrated:
- Raltegravir significantly decreases CD4 count
  - Raltegravir significantly decreases HIV-1 RNA
  - Raltegravir is no different when compared to placebo
15. The following can all be components of a HAART adherence management plan
- Pill boxes
  - Proactive phone calls
  - Prescriber involvement
  - Adverse event management plan
  - All of the above
16. How do you rate this lesson?
- Very Good
  - Good
  - Poor
17. Did it meet the learning objectives?
- Yes
  - No
18. How long did it take you to complete this lesson?



Submit CE Online  
www.pswi.org



CE FOR PHARMACISTS ONLY.

### CONTINUING EDUCATION CREDIT INFORMATION



The Pharmacy Society of Wisconsin is accredited by the Accreditation Council for Pharmacy Education as a provider

of continuing pharmacy education. ACPE approved continuing education credit can be earned by circling the appropriate letters and sending the completed answer form to PSW, 701 Heartland Trail, Madison, WI 53717.

Participants receiving a score of 70% or better will receive by mail a statement acknowledging 1.0 hour (0.10 CEU) of continuing education credit within 4 to 6 weeks.

This CE offering is offered free-of-charge to all PSW member pharmacists. Nonmembers are charged \$10 for each exam submitted to cover administrative costs.

### QUIZ ANSWER FORM *circle one answer per question*

- |              |             |                            |
|--------------|-------------|----------------------------|
| 1) a b c     | 8) a b c d  | 15) a b c d e              |
| 2) a b       | 9) a b c d  | 16) a b c                  |
| 3) a b       | 10) a b c   | 17) a b                    |
| 4) a b c d e | 11) a b c   | If b, please explain _____ |
| 5) a b       | 12) a b c d | _____                      |
| 6) a b c d   | 13) a b     | _____                      |
| 7) a b c d   | 14) a b c   | 18) _____                  |

Name \_\_\_\_\_ Designation (RPh, PharmD, etc.) \_\_\_\_\_

Preferred Mailing Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

Is this your home  or work  address?

July/August 2008

#### A Shifting Paradigm of HIV and AIDS Therapy

ACPE Universal Program Number: 175-000-08-069-H01-P Target Audience: Pharmacists

(No longer valid for CE credit after July 1, 2011)

Release Date: July 1, 2008