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**"HIV/AIDS UPDATE--THERAPEUTIC OPTIONS" 707-000-10-011-H04-P**

**HIV/AIDS UPDATE**
***Therapeutic Options***

## WE'RE SO SORRY ABOUT OCTOBER QUIZ

- We attempted to provide information on a topic that's becoming mandatory for a portion of CE in many states.
- Additionally, as providers we're being asked to develop assessments (quizzes) that require judgment and expertise of participants. (Answer not necessarily in text).
- We won't try this anymore. Sorry for the confusion.

**MISSING A LESSON? IT'S EASY TO GO TO OUR WEBSITE, & DOWNLOAD WHAT YOU NEED. (www.wfprofessional.com)**

**WHEN YOU SEND IN QUIZZES, ALWAYS KEEP A COPY. YOU MAY EMAIL OR FAX THEM. FAX # IS 847-945-5037. OR SEND A CONVENTIONAL EMAIL WITH YOUR ANSWERS TO INFO@WFPROFESSIONAL.COM**

**CREDIT STATEMENTS FOR 2010 WILL BE MAILED NEAR THE END OF THE YEAR. DEADLINE FOR US TO RECEIVE QUIZZES & HAVE THEM APPEAR ON THAT STATEMENT IS DECEMBER 1, 2010**

**CREDIT FOR QUIZZES RECEIVED IN DECEMBER 2010 WILL APPEAR ON STATEMENTS THAT WILL BE MAILED AFTER JANUARY 1ST.**

This is the annual double-lesson for November & December. It's been a while since we reviewed & updated therapeutic options related to HIV/AIDS. We are responding to your requests. This lesson provides 2.5 hours (0.25 CEUs) of credit, and is intended for pharmacists in all practice settings. **The program ID # for this lesson is 707-000-10-011-H04-P. Pharmacists completing this lesson by November 30, 2013 may receive full credit.**

**To obtain continuing education credit for this lesson,** you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). **Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page** (for continuous participants only).

**The objectives of this lesson are such that upon completion the participant will be able to:**

1. Describe the indications for initiating antiretroviral therapy.
2. Differentiate between the classes of antiretroviral agents that are currently approved for treatment of HIV infection in the U.S.
3. List currently approved antiretroviral agents, describe pharmacology, recognize major adverse effects or toxicities, & identify significant drug-drug interactions associated with each.
4. List preferred first-line & alternative combination therapies for HIV.
5. Discuss antiretroviral therapy in pregnancy to prevent perinatal transmission.

## BACKGROUND

We have discussed the topic of HIV & AIDS a number of times over the past several years. This is a significant subject, and it's time to review again because sometimes it takes a back seat to other therapeutic areas. We're especially interested in re-visiting the treatment and drugs.

**In a couple of places, we refer to two (2) tables that are on our website. These are references and resources for you. Quiz items will NOT be taken from these. To access the tables, go to our website, www.wfprofessional.com, click the button on left side that says LESSONS, click on the Nov/Dec 2010 lesson, scroll through the lesson to the back pages and you'll find these two tables. Again, they are references only.**

## HIV – SUPPORTIVE CARE

The World Health Organization (WHO) estimated in 2008 that approximately 33.4 million people were infected with HIV. This was a 20% increase from the year 2000. The high rates are attributed to both new infections and the beneficial effects of antiretroviral therapy. In 2008, an estimated 2.7 million people were newly infected with HIV. Approximately 2 million people died due to AIDS-related illnesses.(1)

The latest estimates from the CDC indicate that more than 1 million adults and adolescents were living with HIV in the United States at the end of 2006. This represents an 11% increase from previous estimates in 2003. During the past decade, approximately 56,000 people were newly infected each year. HIV in the United States disproportionally affects certain populations, such as the men who have sex with men (MSM), African Americans, and Latino Hispanic populations. HIV and AIDS related illnesses are the third leading cause of death of African Americans aged 35-44. They are the fourth leading cause of death among Hispanic/Latino populations in the same age group.(2) It is estimated that 21% of patients did not know that they are infected with HIV in 2006. This is a reduction from 2003 when 25% of people did not know they were infected. This indicates some progress toward prevention and treatment.(2)

## DIAGNOSIS

In an effort to increase screening for HIV in the United States and foster earlier diagnosis of HIV, the CDC updated recommendations in 2006 for routine HIV testing in all healthcare settings.(3) The major revisions for HIV testing include:

1. Routine testing for all patients aged 13-64 years of age, after they are notified testing will be performed, unless they decline (i.e. opt-out screening)
2. Annual testing for high-risk populations (Injection-drug users and their partners, commercial sex-workers, sex partners of HIV-infected individuals and MSM and their sex partners who have had more than one partner since recent HIV test)
3. Elimination of separate written consent for HIV testing (e.g. general consent for treatment is sufficient)
4. Prenatal testing in all pregnant women.

These updated recommendations are supported by data suggesting early diagnosis may lead to decreased transmission, since most patients modify behaviors that may transmit HIV after the diagnosis is made.(2) In addition, appropriately timed interventions, including the initiation of HAART, can lead to improved outcomes and decreased mortality.(3)

## HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

Antiretroviral therapy has been one of the major advances in the fight against HIV. The field of antiretroviral therapy has seen more dramatic changes than any other antimicrobial development in the past decade. Complete viral eradication is unlikely. Infected patients require lifelong treatment. Clinical evidence shows that viral replication continues in the face of undetectable viral load. In other words, the infection may remain hidden, but virulent. Therefore, two primary goals of antiretroviral therapy remain to be:

1. Virologic control (measured as in reduced HIV RNA level) and,
2. Immune restoration (measured as increased CD4 count). Once these are achieved, clinicians are able to delay the progression of the disease, minimize opportunistic infections & malignancies, prolong survival, and improve quality of life. HAART has significantly decreased the risk of disease progression and prolonged life in HIV-infected patients.(4,5)

Worldwide, as of December 2008, the WHO estimated that 4 million people were receiving antiretroviral therapy, which is a 10-fold increase from 2003. In high income countries, the mortality has declined by 85% following the introduction of HAART. Comparable improvements in the mortality have been seen in people living with HIV in resource-limited countries, but who are receiving antiretrovi-

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ral therapy.(1) Despite these advances, long-term side effects and the need for nearly perfect adherence makes the management of patients difficult.(4,5)

## ADHERENCE

Adherence is an important factor that determines degree and duration of virologic response. The ability of the patient to adhere to the prescribed regimen is critical for success of HAART and prevention of resistance. At least 90%-95% adherence is required to achieve undetectable viral load in 80% of patients. If adherence drops to 70-80%, only 25% of patients will likely achieve undetectable viral load. In short, less than perfect adherence leads to the development of drug resistance, limiting the effectiveness of therapy.(4,5) Poor adherence has been shown to increase the likelihood of virologic failure and has been associated with increased morbidity and mortality. Due to increasing success of HAART, HIV/AIDS has become a chronic disease. Reasons for lack of adherence include:

1. Medication toxicities
2. Complexity of the regimen such as multiple daily doses
3. Increased pill burden
4. Food and hydration requirements.(4,5)

For more predictable success of HAART, the pharmacist can prepare the patient for potential adverse effects, simplify regimens, avoid multiple drug-drug & drug-food interactions, reduce pill burden, explain goals of therapy and the importance of adherence, and most importantly, establish readiness to take medication before initiation of HAART. Once a regimen is initiated, it is vital that adherence is addressed on an ongoing basis.(5)

## ANTIRETROVIRAL AGENTS

Currently, seven different classes of antiretroviral agents are available for the management of HIV:

1. (NRTIs)—Nucleoside reverse transcriptase inhibitors
2. (NNRTIs)—Non-nucleoside reverse transcriptase inhibitors
3. (PIs)—Protease inhibitors
4. (Nucleotide RTIs)—Nucleotide reverse transcriptase inhibitors
5. (FIs)—Fusion inhibitors, and more recently,
6. Integrase inhibitors and,
7. (CCR5) antagonists—C-C chemokine receptor type 5

In this lesson we review the current treatment options for HIV infection. (5)

## (NRTIs)—NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

These were the first antiretroviral agents to be used for the treatment of HIV. They chemically mimic naturally occurring nucleosides used for viral DNA proliferation. Their mechanism of action involves inhibition of the viral enzyme, reverse transcriptase, which is responsible for the transcription of viral RNA to DNA within the host cell.(3) Thus, these agents inhibit viral replication in early stages of the viral life cycle. The currently approved NRTIs for HIV treatment in the U.S. are: zidovudine (AZT, Retrovir®), didanosine (ddI, Videx®), zalcitabine (ddC, Hivid®), stavudine (d4T, Zerit®), lamivudine (3TC, Epivir®), abacavir (ABC, Ziagen®), and most recently emtricitabine (FTC, Emtriva®).(4,5,6) Emtricitabine is a cytidine analogue; therefore, it cannot be used with lamivudine.(4) All of these agents require intracellular metabolism to their triphosphate form before they become active. Once activated, NRTIs competitively inhibit HIV reverse transcriptase, insert themselves into the growing viral DNA as a false nucleotide, block DNA synthesis, lead to chain termination, and subsequently inhibit viral replication.(6)

Three NRTI combination products are available to help improve adherence to HIV therapy by decreasing overall pill burden. Zidovudine and lamivudine are formulated together under the brand name Combivir®, and Trizivir® is a combination product containing zidovudine, lamivudine, and abacavir. Both of these combinations are given twice daily. In addition, Epzicom® is a combination of abacavir and lamivudine, and is dosed once daily.(5) These formulations are based on clinical data demonstrating the efficacy of these NRTIs in combination. Most of these agents are primarily excreted through the kidneys; therefore, dosage adjustments may be necessary for patients with renal impairment. A combination pill of tenofovir 300mg, emtricitabine 200mg, and efavirenz 600mg is available, and is dosed once daily.(7) **See our website (www.wfprofessional.com), click on LESSONS, then click on lesson for Nov/Dec 2010—-Table 1 summarizes dosing & food effects for the antiretroviral agents. None of that information appears on the quiz. It's for resource & reference purposes only.**

## (NUCLEOTIDE RTIs)—NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Tenofovir is an acyclic nucleoside phosphonate (nucleotide) with antiviral activity against HIV. It has recently been approved to treat Hepatitis B. Tenofovir disoproxil fumarate is the first nucleotide analogue reverse transcriptase inhibitor approved in the U.S. Nucleotide analogues are monophosphorylated nucleoside analogues, and they block HIV replication in the same manner as NRTIs. Therefore, tenofovir is classified in several sources under NRTIs. Tenofovir is formulated with emtricitabine under the trade name Truvada®.

**(NNRTIs)—NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS**

Like NRTIs, these drugs inhibit viral enzyme reverse transcriptase. However, they structurally bind to reverse transcriptase through a noncompetitive mechanism, making conformational change, rendering the reverse transcriptase enzyme less available for making proviral DNA.(7) Unlike NRTIs, these drugs do not require intracellular metabolism for activation. Theoretically, drug resistance towards NRTIs would not affect NNRTIs or vice versa due to different site of action on reverse transcriptase. However, significant cross-resistance exists among NNRTIs within their class. There are four NNRTIs available: nevirapine (NVP, Viramune®), delavirdine (DLV, Rescriptor®), efavirenz (EFV, Sustiva®), and etravirine (ETV, Intelence®). All available NNRTIs can cause a rash ranging from mild reactions to serious life threatening Steven's Johnson syndrome.(4,5,9)

**(PIs)—PROTEASE INHIBITORS**

The next class of antiretrovirals, HIV protease inhibitors (PIs), was designed to inhibit viral replication during late stages in the life cycle of HIV. Protease is a viral enzyme responsible for cleaving complex viral polypeptide precursors into functional proteins that are essential for the maturation and assembly of virions. Activity of this enzyme is critical for the completion of HIV viral replication.(10) PIs resemble the amino acid sequence where HIV protease binds or cleaves. Thus, PIs competitively inhibit HIV protease by binding to the active site of the enzyme. In other words, they inhibit production of new virions from chronically infected cells. There are currently nine PIs approved by the FDA for HIV treatment in the U.S.: saquinavir (SQV, Invirase®); ritonavir (RTV, Norvir®); indinavir (IDV, Crixivan®); nelfinavir (NFV, Viracept®); lopinavir/ritonavir (LPV/RTV, Kaletra®), atazanavir (ATZ, Reyataz®), fosamprenavir (Lexiva®), Tipranavir (TPV, Aptivus®), and most recently Darunavir (DRV, Prezista®).(5) See Table #1 on our website for dosing, food effects and storage requirements.

Low dose ritonavir is clinically used in combination with other PIs to help boost the pharmacokinetic levels of these agents to attain better viral suppression. The ritonavir increases the concentrations of the second PI via CYP 450 inhibition, allowing for less frequent administration. The ritonavir dose used to boost the second PI concentration ranges from 100-400 mg daily, which is subtherapeutic when used alone.(5) The combinations of ritonavir with saquinavir, indinavir, fosamprenavir, atazanavir, darunavir, tipranavir and lopinavir have been successfully used in both treatment-naïve and experienced patients. (4,5) Tipranavir is the first non-peptidic protease inhibitor (NPPI) and has been approved for highly treatment experienced patients or HIV strains resistant to multiple protease inhibitors. (11)

**(FIs)—FUSION INHIBITORS**

Enfuvirtide (Fuzeon®) is the first in a new class of drugs called fusion inhibitors. These agents block fusion of HIV with the host cell before the virus enters the cell and begins the replication process.(12) Enfuvirtide is indicated in combination with other antiretroviral agents in treatment of experienced patients who continue to have evidence of HIV-1 replication despite current antiretroviral therapy. Unlike other antiretrovirals, enfuvirtide is administered by subcutaneous injection. The dose is 90mg (1 mL) twice daily subcutaneously injected into the upper arm, anterior thigh or abdomen. Enfuvirtide is supplied as a lyophilized powder to be reconstituted with sterile water. The powder can be stored at room temperature, but once reconstituted the solution should be stored under refrigeration (2°C to 8°C) and used within 24 hours. The most common side effects in clinical trials were local injection site reactions that were described as painful, indurated, erythematous, or nodular cysts.(10) It is important to educate patients on correct injection technique and site rotation to minimize these reactions.

**INTEGRASE INHIBITORS**

Raltegravir (Isentress®) is the only approved antiretroviral that targets the HIV-1 integrase, an enzyme required for viral replication.(13) Inhibiting the integrase enzyme prevents the integration of HIV DNA into the host cell genome, thus preventing the formation of progeny virus. Initially, raltegravir was FDA-approved for clinically advanced HIV patients with multiple-class treatment experience. Raltegravir was evaluated in combination with an optimized backbone regimen compared standard optimized therapy (OT) without raltegravir. Seventy-two percent of patients had a significant reduction in viral load in the raltegravir group compared to 37% in the OT group. More recently, it was compared to the standard regimen of Atripla (efavirenz/tenofovir/emtricitabine) in naïve patients. Twice daily raltegravir with Truvada® had comparable virologic efficacy to efavirenz up to 96 weeks. Raltegravir has not been compared with protease inhibitors nor studied in combination with alternate NRTI (such as abacavir or zidovudine). In clinical trials in treatment naïve patients, a low percentage of patients (3%) discontinued the drug due to adverse events. Adverse events occurring with raltegravir include: nausea, headache, diarrhea and pyrexia and occasional creatinine kinase elevations. In addition, raltegravir may affect lipids less than efavirenz-based regimens. With its potency and lack of serious side effects, it has been incorporated into the armamentarium against HIV, as a first line therapy for newly-infected HIV patients.(5) Raltegavir requires twice daily dosing and has a low barrier for resistance.

**CCR5 INHIBITORS**

Maraviroc (Selzentry®) is the only approved agent in the therapeutic class called CCR5 co-receptor antagonists, that selectively binds to the host chemokine CCR5 receptor found on the cell membrane of CD4 cells. HIV can express either co-receptor CCR5 or CXCR4 or both co-receptors that are used to bind to host cells. This is a required step for HIV to enter the CD4 cell. Maraviroc only inhibits entry of CCR5 containing viruses (referred to as CCR5-tropic), not CXCR4-tropic viruses or dual/mixed tropic (both CCR5 or CXCR4) viruses.(14) Thus, testing for CCR5 containing HIV is suggested prior to initiation of maraviroc. Virologic failure has been associated with outgrowth of low level pre-existing virus CXCR4 or dual/mixed-tropic HIV virus, therefore not suggested for individuals with dual-tropic virus either. The use of maraviroc is limited to treatment-experienced patients with multi-class experience and resistance,

and more recently approved for the treatment of naïve patients. In patients with documented CCR5-tropic virus receiving either optimized therapy (OT) or maraviroc, the proportion of patients with HIV RNA < 400 was 56% in the maraviroc group versus 22% in the OT arm at 48 weeks. In addition, the maraviroc group had a significant CD4 increase. In clinical trials, the most common side effects included upper respiratory tract infections, cough, pyrexia, rash and dizziness. There have been reports of serious reactions including hepatotoxicity with allergic features in healthy volunteers, increased risk of cardiovascular events (i.e. myocardial ischemia and/or infarction) in at-risk populations, and symptomatic postural hypotension in treatment naïve patients. The use of maraviroc should be limited to treatment experienced patients and monitored closely for side effects. **See Table 1 on our website for dosing & storage requirements.**

## INDICATIONS FOR ANTIRETROVIRAL AGENTS

Recently the Department of Health and Human Services (DHHS) published guidelines for the use of antiretroviral agents in HIV-infected patients that recommended starting therapy in patients with higher CD4 counts than previously published.(5) According to these guidelines, all patients with advanced HIV disease (AIDS) or with CD4 count less than 350 cells/$mm^3$ should be treated with HAART, due to high risk of opportunistic diseases, non-AIDS morbidity and death. In addition, certain patients with co-morbid conditions should be considered for antiretroviral treatment regardless of CD4 count. These include patients that are pregnant, have HIV associated nephropathy, or have hepatitis B virus (HBV) requiring HBV treatment.(5) Antiretroviral therapy is now recommended for patients with CD4 counts from 350 to 500 cell/$mm^3$ due to recent data from observational studies suggesting higher rates of death when treatment was deferred. For patients with CD4 counts above 500 cells/$mm^3$, the panel members of the DHHS guideline committee are divided in their recommendation. The strength of the recommendation must be evaluated based on the readiness of the patient for lifelong therapy, the benefits and risks of antiretroviral therapy and the patient's understanding of the importance of adherence.(2) Advanced stage patients being maintained on an antiretroviral regimen should not have the HAART therapy discontinued during an acute opportunistic infection or other HIV complication, unless there are significant concerns regarding drug toxicity, intolerance, or drug interactions. (5)

## DEVELOPING THE REGIMEN

Combining three or more antiretroviral agents has become the standard of care in treatment of HIV infection. These therapies achieve goals more effectively than previous one or two drug combinations. The first antiretroviral regimen used has the greatest chance of success; subsequent regimens are often more complicated and have higher failure rate.(5) Recently, resistance testing has been recommended prior to initiating antiretroviral therapy in acute and chronically infected patients to assist with the selection of antiretroviral agents. **Table 2 on our website provides a guide to the use of available treatment regimens for individuals with no prior, or with limited experience to HIV therapy.(5) That table is also a resource & reference. None of that information appears on the quiz.**

Regimens should be individualized based on the advantages and disadvantages of each combination such as number of pills, dosing frequency, adverse effects and drug-drug interactions. Also, considerations to patient specific variables should be made prior to selecting the regimen such as pregnancy potential, potential drug interactions and co-morbid conditions (cardiovascular disease, liver disease, psychiatric disease, etc).

Some potential advantages to NNRTI regimens include less dyslipidemia than PI-based regimens, and reserving the PI and Integrase options for future use. The disadvantages of the NNRTI class include: low genetic barrier to resistance, cross-resistance among the NNRTI class, central nervous system adverse effects, skin rash and the potential for drug-drug interactions.(4,5) Another advantage of the NNRTI-based regimen is low pill burden because efavirenz, tenofovir and emtricitabine are co-formulated into a single tablet as Atripla®. In contrast, the recommended PI regimens are multiple tablets once daily.

For the PI-based regimens, the advantages include: saving the NNRTI-class for future use and the longest prospective study data, including data on survival benefit, and higher genetic barrier to resistance. The disadvantages include metabolic complications such as dyslipidemia and insulin resistance, gastrointestinal side effects and the potential for multiple drug-drug interactions.

Lastly, the integrase inhibitors regimen is now recommended for naïve patients. The combination of tenofovir, emtricitabine and raltegravir has similar virologic efficacy and tolerability when compared to efavirenz, emtricitabine and tenofovir. Clinical trials comparing safety and efficacy with PI based regimens are ongoing. The advantages of an integrase-inibitor based regimen include: fewer drug-related adverse effects and lipid changes compared to efavirenz, no food effect and fewer drug interactions. Unfortunately, the integrase inhibitors lack long-term data for treatment naïve patients, require twice daily dosing and have a low genetic barrier to resistance.

The NRTI backbone of the preferred regimens include tenofovir and emtricitabine (or lamivudine). Tenofovir with either emtricitabine or lamivudine given with efavirenz in treatment naïve patients demonstrated superior virologic efficacy over the zidovudine/lamivudine with efavirenz. In addition, less patients developed loss of limb fat (lipoatrophy) and anemia in the tenofovir treated group.(5) The availability of the fixed combination of tenofovir/emtricitabine and tenofovir/emtricitabine/efavirenz as one tablet improves adherence.

Abacavir with lamivudine (or emtricitabine) is considered an alternative NRTI backbone for several reasons. When compared to tenofovir/emtricitabine with either efavirenz or atazanavir/ritonavir, abacavir patients with a viral load greater than 100,000 copies at initiation had virologic failure in a shorter time period. The data and safety board terminated this arm of the study due to these results. These results were not reproducible in a smaller study (HEAT) comparing abacavir/lamivudine and tenofovir/emtricitabine given with lopinavir/ritonavir. A subanalysis of the patients with a baseline viral load greater than 100,000 demonstrated no difference in virologic response.(5)

In addition, there have been concerns about the cardiovascular risks associated with abacavir containing regimens. In a large, multi-national, observational cohort study, abacavir use (within 6 months of current use) predicted an increased risk of myocardial infarction. This risk was not seen with tenofovir treated patients. The DHHS guideline committee recommends using abacavir/lamivudine with

caution in patients with a higher risk of cardiovascular disease and/or patients with baseline viral loads greater than 100,000 copies. Abacavir and lamivudine (Epzicom®) is available as a co-formulated tablet.(5)

Although zidovudine/lamivudine have substantial safety, tolerability and efficacy data, the DHHS consider this combination an alternative NRTI option due to greater toxicity compared to tenofovir/emtricitabine. The toxicities include bone marrow suppression (macrocytic anemia and/or neutropenia), gastrointestinal, fatigue and mitochondrial toxicities (lactic acidosis/hepatic steatosis and lipoatrophy). (5) Zidovudine and lamivudine are still recommended for pregnant women. They are available as a co-formulated tablet Combivir®.(5)

## INDICATIONS FOR CHANGING THERAPY

Therapeutic goals of HAART include maximum viral suppression, optimum immunologic response, minimum adverse effects of antiretroviral medications, and the highest adherence. It is expected that first-line regimens should suppress the virus indefinitely, as long as the optimal regimen is selected and consistent adherence is maintained. Change in therapy is warranted when any of these goals are not achieved. (5) Common reasons for altering therapy include: drug intolerance, non-adherence, emergence of resistance, or failure to achieve sustained viral suppression. It is estimated that suboptimal adherence and toxicity account for up to 40% of treatment failures and discontinuations.(5) Changes based on inadequate virologic response should be confirmed using at least two measurements of viral loads. Testing for antiretroviral resistance is recommended for virologic failure during combination antiretroviral therapy, or when suboptimal suppression of viral load after antiretroviral therapy initiation, or during acute HIV infection if therapy is initiated. Changing between drugs or classes with documented cross-resistance is not recommended. Single agent substitution is only recommended in case of drug toxicity. Based on the above recommendations, the decision to change therapy must be carefully evaluated, because delaying a switch in therapy may severely limit future therapeutic options due to selection of resistance mutations.(5)

## ADVERSE DRUG REACTIONS

With successful viral control and immune repair in patients taking HAART, **complications due to therapy** have become more prevalent than opportunistic infections and malignancies.(4) Most frequent adverse effects reported with all antiretrovirals remain to be GI related including nausea, vomiting, diarrhea and flatulence. Several class-related adverse events have been recognized with antiretroviral drugs during the post-marketing period. These are vast and range from mild to life-threatening. The following highlights some key adverse effects. Detailed information about side effects can be found in the prescribing information and the DHHS guidelines (www.aidsinfo.nih.gov).(5)

### NRTIs

Lactic acidosis, with hepatomegaly and hepatic steatosis including fatal cases, has been reported with the use of NRTIs alone (especially stavudine, didanosine and zidovudine) or in combination with other antiretroviral agents. The onset generally occurs after months of therapy with GI symptoms such as nausea, anorexia, abdominal pain, vomiting, and weight loss. Subsequent symptoms can rapidly progress with tachycardia, tachypnea, hyperventilation, jaundice, muscle weakness, and mental status changes. This is a rare side effect (less 1 case per 1000 patient-years) and depends on the regimen and the gender of the patient.(5)

Abacavir can cause a hypersensitivity reaction which can be characterized by several of the following symptoms: 1. fever 2. rash 3. gastrointestinal (nausea, vomiting, diarrhea or abdominal pain) 4. constitutional (malaise, fatigue, or achiness) 5. respiratory symptoms. Abacavir should be discontinued if a hypersensitivity reaction is suspected.(15) Screening patients for the presence of the MHC class I allele (HLA-B*5701) predicts those at risk for developing this hypersensitivity reaction. Screening is recommended prior to initiation of abacavir. In addition, abacavir and didanosine use have been associated with an increased risk of myocardial infarctions in an observational study. Patients with underlying cardiac risk factors (hyperlipidemia, hypertension, etc) may require lifestyle modifications to prevent cardiovascular events, or switching to an agent with less propensity for increasing risk of cardiovascular disease.

Zidovudine (AZT) can cause a reversible anemia (usually macrocytic) and neutropenia. This can develop a few weeks after therapy is initiated; therefore, close monitoring of a complete blood count is necessary during this time period. Some patients may require an alternate NRTI or factors such as erythropoietin or filgrastim.

Stavudine and didanosine can cause peripheral neuropathy and pancreatitis when given individually, but the incidence is greatly increased when given together. This combination should be avoided if possible.

Tenofovir has been associated with nephrotoxicity due to its structural similarity to adefovir and cidofivir. In clinical trials, tenofovir-associated renal dysfunction was rare in antiretroviral-naïve patients. Tenofovir-induced acute renal failure (known as Fanconi syndrome) is associated with proteinuria, hypophosphatemia, euglycemic glycosuria, hypouricemia, hypokalemia, and metabolic acidosis.(5) Concomitant use of nephrotoxic agents should be avoided. Patients with history of renal disease should be closely monitored.

Lipoatrophy, the loss of peripheral fat in the face, extremities, and buttocks, can occur after prolonged therapy with NRTIs. The NRTIs with the highest incidence of lipoatrophy are stavudine and zidovudine (thymidine analogs). In general, tenofovir, abacavir, emtricitabine and lamivudine can cause lipoatrophy, but this a less frequent side effect and are often used to treat patients with lipoatrophy caused by the thymidine analogs.

### PIs

Hyperglycemia, diabetes mellitus, insulin resistance, lipodystrophy with and without serum lipid abnormalities have been associated with PI use. All PIs can cause hyperlipidemia except atazanavir without ritonavir, as indicated by increases in LDL, total cholesterol and triglycerides. Fasting lipid profile must be monitored at baseline, and after 3-6 months of therapy. Pharmacologic and lifestyle modifications are imperative to management after hyperlipidemia has been identified. The HIV Medicine Association and the National

Cholesterol Education Program ATP III guidelines provide recommendations on appropriate treatment. In addition, PIs have been associated with cardiovascular effects including myocardial infarctions and cerebrovascular accidents (CVA) in cohort studies. Early diagnosis and management of cardiovascular risk factors (hyperlipidemia, hypertension, insulin resistance, and diabetes) should be a priority in these patients. It is important to assess cardiac risk factors prior to therapy and emphasize lifestyle modifications such as smoking cessation, heart-healthy diet and increased physical activity. (5)

The tipranavir/ritonavir combination and other PIs have been associated with increased bleeding episodes in patients with hemophilia. There have been reports of Intracranial hemorrhage (ICH) with the tipranavir/ritonavir combination. This combination should be avoided in patients with additional risk factors for ICH. (5) Hepatotoxicity has been associated with PI use. The tipranavir/ritonavir combination seems to be the most frequent culprit. Patients at the highest risk for hepatoxicity include those with HBV/HCV co-infection, a history of alcoholism, and concomitant administration of hepatoxic drugs. (11)

Fosamprenavir and Darunavir should be used cautiously in patients with known sulfonamide allergy because they contain a sulfonamide moiety.(17,18)

Lipodystrophy, an increase in abdominal girth, breast size and development of buffalo hump, is associated with PIs and NNRTI use when given with thymidine analogs (zidovudine and stavudine). The development of lipodystrophy can be gradual but difficult to treat. Treatment options include: plastic surgery, a rigorous diet/exercise program, and a regimen change.

**NNRTsI**

Rash and skin reactions are relatively common events encountered during use of NNRTIs. A minority of these rashes is severe; potentially fatal cases of Stevens-Johnson's syndrome have been reported. Average time of onset is 1-3 weeks. In clinical studies, severity sufficient to require discontinuation is 7% with nevirapine and 2% with efavirenz.(5)

Central nervous system effects have been associated with the initiation of efavirenz, including drowsiness, somnolence, abnormal and vivid dreams, impaired concentration, and exacerbation of psychiatric illnesses. Most of these symptoms will subside after 2-4 weeks of therapy and may be lessened if taken on an empty stomach at bedtime. An alternate agent may be necessary if symptoms persist and cause disruption in daily activities. Nevirapine can cause hypersensitivity reactions with hepatic effects in 4% of patients. Women with CD4 counts > 250 cells/$mm^3$ and men with CD4 counts > 400 cells/$mm^3$ are at a higher risk for this reaction; therefore, the DHHS guidelines do not recommend nevirapine in these patients. The symptoms include an abrupt flu-like illness, abdominal pain, jaundice or fever with or without a skin rash. This may progress to fulminant hepatic failure, so patients should seek medical attention immediately and discontinue all the antiretroviral agents. Patients who are initiated on nevirapine should have liver function tests monitored frequently during the first 6 weeks of therapy, but this reaction may happen up to 18 weeks after the initiation of therapy.

**ALL AGENTS**

Osteopenia and Osteoporosis have been associated with many antiretrovirals, including: tenofovir, stavudine, efavirenz and lopinavir/ritonavir. It can manifest after months to years of HAART. It is generally asymptomatic, but bone pain and increased fractures can occur. The frequency of osteopenia and osteoporosis is higher in HIV populations compared to the general population. The HIV population at risk for these complications are patients with a low CD4 count, prolonged HIV infection, lipoatrophy, increased lactic acid levels and prolonged tenofovir exposure.

**Immune reconstitution inflammatory syndrome (IRIS)** has been reported with combination antiretroviral therapy in the setting of an opportunistic infection. Initiation of HAART would logically improve immune function and, therefore, leads to faster resolution of the opportunistic infection (OI), but a paradoxical worsening can occur. IRIS refers to a group of clinical syndromes associated with immune reconstitution and concurrent OI. The symptoms of IRIS are diverse and have not been precisely defined. They can be characterized by fever and worsening of clinical manifestations of the underlying OI. The clinical manifestations may be at the site of the previously known pathogen, may unmask disease at a new site, or represent an unrecognized additional pathogen. The majority of patients develop IRIS within the first 4 to 8 weeks after starting antiretroviral therapy.(5)

**DRUG INTERACTIONS**

Antiretroviral therapy has become increasingly more complex due to the propensity for drug-drug interactions. Drug(s) affecting plasma concentrations of concurrent medication(s) may result in reduced efficacy or increased toxicity. Most interactions with antiretroviral agents revolve around the hepatic enzyme system, cytochrome P450 (CYP450). NRTIs, including nucleotide RTIs, do not undergo extensive CYP450 metabolism. They are eliminated predominantly through renal mechanisms. Therefore, drug interactions are less common with these two classes. Nonetheless, there are a few clinically significant drug interactions involving the NRTIs.(4,5)

Zidovudine and stavudine appear to compete for phosphorylation; therefore, they are not recommended in combination with each other. (5) When atazanavir and tenofovir are combined, atazanavir levels are decreased so atazanavir must be combined with low dose ritonavir to boost the levels of atazanavir.(8,20)

Unlike NRTIs, protease inhibitors are extensively metabolized by CYP450. All protease inhibitors are competitive inhibitors of cytochrome P-450, predominantly the CYP3A4 isoform. PIs increase plasma drug levels of concurrent medications metabolized by this enzyme system.(4,5) Of the protease inhibitors, ritonavir is the most potent enzyme inhibitor; saquinavir is the least potent inhibitor; while indinavir, nelfinavir, atazanavir, darunavir, fosamprenavir and lopinavir fall in between those two.(4) In fact, ritonavir has been utilized

extensively with other PIs to increase blood levels of the concurrent agent. (4,5) Tipranavir can induce and inhibit CYP450 resulting in a complex drug-drug interaction profile.(11) Drugs that should not be used in combination with PIs include simvastatin, lovastatin, cisapride, rifampin, midazolam, triazolam, astemizole, terfenadine, dihydroergotamine (DHE) & other ergotamines, and St. John's Wort. Furthermore, concurrent use of amiodarone, flecainide, propafenone, quinidine, bepridil, meperidine, rifabutin, diazepam, and bupropion should be avoided with ritonavir.(5)

Like protease inhibitors, NNRTIs are associated with several significant drug interactions.(4,5) The NNRTIs have complex metabolic pathways. Delavirdine inhibits, while nevirapine induces, CYP450 (3A4 and 2D6 isoforms). Efavirenz both induces and inhibits CYP450 (3A4 and 2D6 isoforms) lending to multiple drug-drug interactions. Nevirapine and efavirenz both induce their own metabolism, while delavirdine may inhibit its own metabolism.(2) Due to their effects on CYP450, NNRTIs have potential to alter plasma concentrations of concurrent drugs metabolized by some isoforms of CYP450. Drugs that should not be used with efavirenz include: astemizole, terfenadine, cisapride, midazolam, triazolam, DHE & other ergotamine derivatives.(5)

Maraviroc is a substrate of CYP 3A4; therefore, concentrations are modulated by inhibitors and inducers of CYP 3A4.(14) A significant dose reduction (150mg twice daily) is required when concomitant protease inhibitor therapy is given; whereas, significant dose escalation (600mg twice daily) is required with potent CYP 3A4 inducers (e.g. efavirenz and etravirine.) Prescribing information should be consulted for detailed information regarding maraviroc drug interactions.(14) Raltegravir is not metabolized by, nor an inhibitor/inducer of the cytochrome system; rather raltegravir is eliminated by a UGT1A1-mediated glucuronidation pathway. Rifampin is an inducer of the UGT1A1 pathway and significantly reduces concentrations of raltegravir, requiring a dose escalation. (13) Raltegravir drug interactions are less cumbersome than those with other antiretroviral agents.

In addition to the drugs to avoid with these agents, there are many other clinically significant drug-drug interactions that require careful evaluation and monitoring by the pharmacist to avoid adverse drug reactions or inadequate drug concentrations. Some examples include: methadone, oral contraceptives, inhaled fluticasone, erectile dysfunction agents like sildenafil, and antifungals like fluconazole and voriconazole. In addition, several over the counter acid suppressant agents (such as ranitidine, omeprazole, etc) can decrease concentrations of atazanavir resulting in subtherapeutic concentrations. (20) In short, with the knowledge of current nomenclature of drug interactions with the CYP450 system, clinicians should be able to predict most of these interactions. For specific details regarding other potentially significant drug-drug interactions, consult www.aidsinfo.nih.gov/guidelines or other pertinent references.

## TREATMENT DURING PREGNANCY

Treatment guidelines during pregnancy have also been developed for HIV-infected pregnant women and prevention of vertical transmission.(21) If these women satisfy criteria for therapy, DHHS guidelines should be followed for treatment like any other HIV infected patient. Pregnant women should be offered the standard combination antiretroviral therapy to prevent perinatal transmission. The most significant data on prevention for perinatal transmission comes from the Pediatric AIDS Clinical Trial Group Protocol 076 (PACTG 076). This pivotal trial demonstrated that AZT reduced the rate of perinatal transmission by 66%.(21) As per AZT 076 protocol, zidovudine chemoprophylaxis is a three part regimen consisting of maternal AZT therapy from week 14 to delivery, followed by intrapartum IV AZT administration, which is then followed by 6 weeks of AZT for the newborn. When combination therapy is administered to pregnant women, zidovudine should be included in the regimen unless substantial zidovudine-related toxicities occur. Due to the risk of lactic acidosis, stavudine and didanosine should not be used in combination in pregnant women. (5,21)

Not much is known about the use of antiretroviral agents in pregnant women and their effect on the developing fetus. The data, to date, supports the safety of antiretroviral agents in pregnancy except for ddI + d4T, efavirenz, and hydroxyurea.(21) The pregnant HIV–infected women should be extensively counseled on the risks and benefits of antiretroviral therapy for the mother and the newborn infant. Some authorities recommend HAART therapy be delayed or interrupted during the first trimester, as safety of these agents is sometimes questioned during this, the most vulnerable, part of the pregnancy. This involves a risk-benefit decision, and recommendations should be based on theoretical concerns as well as on clinical findings (CD4+ T cell count, viral load, symptoms, etc.).(5,21) Women with CD4+ T cell counts > 250 cells/$mm^3$, including pregnant women receiving chronic nevirapine are at risk for fatal hepatotoxicity (i.e. cholestatic hepatitis, hepatic necrosis and hepatic failure.) Patients with signs or symptoms of hepatitis and associated symptoms (i.e rash) must discontinue nevirapine and seek medical attention. In contrast to nevirapine, efavirenz is not recommended during the first trimester of pregnancy due to case reports of neural tube defects . Efavirenz is now considered as pregnancy catergory D. In addition, women of child-bearing age on efavirenz should be counseled about using appropriate and reliable birth control to prevent exposure should they become pregnant. (21)

## CONCLUSION

Treatment of HIV is complex and requires a full understanding of both the disease state and the medications associated. Pharmacists can play an important role in HIV treatment by assessing adherence to treatment regimens, educating patients about drug toxicity and educating clinicians to avoid interacting drugs.

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**Table 1. The Dosing /Administration and Food Requirements for Antiretroviral Agents** [2]

| **Generic Name, *Brand Name*** | **Class** | **Usual Adult Dose** | **Food Effect** |
|---|---|---|---|
| Abacavir (ABC) *Ziagen®*<br><br>• 300mg tablets<br>• 20 mg/mL oral solution | NRTI | 300 mg po q12h<br>600mg po daily | Without regard to meals; alcohol increases ABC levels 41%; no effect on alcohol |
| Available as:<br>• Trizivir ® (ABC/ZDV/3TC)<br><br>• Epzicom ® (ABC/3TC) | | 1 tablet po q12h<br><br>1 tablet daily | |
| Didanosine (ddI),<br><br>Videx EC delayed release capsules®<br>• 125, 200, 250, 400mg<br>• 10mg/ml oral solution | NRTI | >60kg<br><br>• 400mg capsule QHS<br>• With Tenofovir: 250mg daily<br><br><60kg<br>• 250 mg capsule QHS<br>• w/ tenofovir 200mg daily | Take half hour before or 1 hour after meals<br><br>Videx buffered tablet® distribution discontinued in 2006.<br><br>Dosing with oral solution is BID (same total daily dose) |
| Emitricitabine (FTC)/Emitriva ®<br><br>200mg capsule<br><br>10mg/ml oral solution | NRTI | 200mg capsule daily<br><br>240 (24mL) oral solution daily | Without regard to meals |
| Available as:<br><br>Atripla ® (EFV/TDF/FTC)<br><br>Truvada ®(TDF/FTC) | NRTI/NNRTI | EFV: 600mg +<br>TDF: 300mg +<br>FTC: 200mg – once daily<br><br>TDF: 300mg + FTC 200mg – once daily | Give at bedtime on an empty stomach<br><br>Without regard to meal |
| Lamivudine (3TC), *Epivir®*<br><br>• 150, 300mg tablets<br>• 10mg/mL solution | NRTI | 150 mg q12h<br><br>300mg QD | Without regard to meals |
| Available as:<br>• Combivir ® (ZDV/3TC)<br>• Epzicom ®(see Abacavir)<br>• Trizivir ®(See Abacavir) | | ZDV: 300mg +<br>3TC: 150mg – 1 tablet q12h | Without regard to meals |
| Stavudine (d4T),<br><br>*Zerit®*<br>• 15, 20, 30, 40mg capsules<br>• 1 mg/mL solution | NRTI | ≥60kg = 40 mg q12h<br><br><60 kg = 30 mg q12h | Without regard to meals |

| | | | |
|---|---|---|---|
| Zidovudine (AZT),<br><br>Retrovir®<br>• 100mg capsules, 300mg tablets<br>• 10mg/mL IV solution<br>• 10mg/mL oral solution | NRTI | 300 mg q12h | Without regard to meals |
| Available as:<br>Combivir ® (see Lamivudine)<br>• Trizivir ® (see abacavir) | | | |
| Tenofovir(TDF)<br><br>Viread®<br>300mg tablet | Nucleotide RTI | 300 mg QD | Without regard to meals |
| Available as:<br>Truvada ® (see Emtricitabine)<br>Atripla ® (see Emtricitabine) | | | |
| Delavirdine (DLV),<br><br>Rescriptor®<br>• 100, 200mg tablets | NNRTI | 400 mg q8h | Without regard to meals |
| Efavirenz (EFV),<br><br>Sustiva ®<br>• 50, 100, 200mg capsules<br>• 600mg tablet<br>• Available as: Atripla ® (see Emitricitabine) | NNRTI | 600 mg QHS | For tablets: avoid taking after high fat meals, levels increase 50% |
| Etravirine (ETR)<br><br>*Intelence ®*<br><br>• 100mg tablets | NNRTI | 200mg q12h | Following a meal |
| Nevirapine (NVP)<br><br>*Virammune ®*<br><br>• 200mg tablet<br>• 50mg/5mL oral suspension | NNRTI | 200 mg QD x 14days then 200mg q12h | Without regard to meals |
| Atazanavir (ATZ)<br><br>*Reyataz®*<br><br>• 100,150, 200, 300mg capsules | PI | 400mg QD<br><br>300mg + 100mg ritonavir | Food enhances bioavailability<br>Take with food |
| Darunavir (DRV)<br><br>Prezista ® | PI | Naïve: 800mg + 100mg ritonavir QD<br><br>Experienced: 600mg q12 + 100mg ritonavir q12h | Take with food |

| | | | |
|---|---|---|---|
| Fosamprenavir (fAPV)<br><br>*Lexiva®*<br><br>700mg tablets | PI | Naïve pts:<br>• 1400 mg q12h<br>• 1400 mg QD + ritonavir 100 to 200mg QD<br>• 700mg q12h + ritonavir 100mg q12h<br>Experienced pts:<br>• 700mg q12h + ritonavir 100mg q12h<br><br>• 1400mg + ritonavir 300mg once daily | Take without regard to meals |
| Indinavir (IDV), *Crixivan®*<br><br>• 200, 333, 400mg capsules | PI | 800mg q12 + ritonavir 100 – 200mg q12 | Levels decrease 77%, take 1 hour before or 2 hours after meals; drink plenty of fluids |
| • Lopinavir/Ritonavir (LPV/r), *Kaletra®*<br>• 200mg/50mg tablets<br>• 80mg/20mg oral solution | PI | 2 tablets q12h | Take without regard to food |
| Nelfinavir (NFV),<br><br>Viracept®<br>• 250mg tablet<br>• 625mg tablets'<br>• 50mg/g oral powder | PI | 750 mg q8h or<br><br>1250 mg q12h | Levels increase 2-3 fold, take with meal or snack |
| Saquinavir (SQV)-HGC,<br><br>Invirase®<br>• 200mg capsules<br>• 500mg tablets | PI | • not recommended without ritonavir<br>• 1000mg q12h + ritonavir 100mg q12h | No food effect when taken with ritonavir |
| Tipranavir<br><br>Aptivus ®<br><br>• 250mg capsules | PI | 500mg + 200mg ritonavir po q12h | Take without regard to meals<br><br>Capsules should be refrigerated |
| Ritonavir (RTV)<br><br>Norvir ®<br><br>• 100mg capsules and tablets<br>• 600mg/7.5mL solution | PI | Not generally used as a full dose but as a pharmacokinetic booster for other PIs from 100-400mg per day | Capsules should be refrigerated<br><br>Tablets now available |
| Raltegravir (RAL)<br><br>Isentress ®<br><br>• 400mg tablets | INSTi | 400mg q12h | Without regard to food |

| | | | |
|---|---|---|---|
| Maraviroc (MVC)<br><br>Selzentry ®<br><br>• 150mg, 300mg tablets | CCR5 inhibitor | 150mg q12h ( with CYP 3A4 inhibitors)<br><br>300mg q12h<br><br>600mg q12h (with CYP 3A4 inducers) | Without regard to food |
| Enfuvritide, Fuzeon ®<br><br>• 90mg vials | Fusion inhibitor | 90mg SC q12 | |

**Table 2. Recommended Antiretroviral Agents for Initial Treatment**

**PREFERRED REGIMENS IN BOLD**

| | |
|---|---|
| **NNRTI-based regimen** | |
| **Preferred regimen** | **Efavirenz +(lamivudine or emtricitabine) +( tenofovir) – except pregnant women or women with pregnancy potential** |
| alternatives | Efavirenz + (lamivudine or emtricitabine) +(abacavir or zidovudine) - except pregnant women or women with pregnancy potential |
| | Nevirapine + (emtricitabine or lamivudine) + (zidovudine); should not be used in patients with CD4<250 cells/mm3 or men with CD4>400 cells/mm3 |
| **PI-based regimen** | |
| **Preferred regimen** | **Atazanavir/ritonavir + (lamivudine or emtricitabine) + (tenofovir)**<br><br>**Darunavir/ritonavir (once daily) +(lamivudine or emtricitabine) + (tenofovir )** |
| alternatives | Atazanavir/ritonavir + (emtricitabine or lamivudine) + (zidovudine or abacavir) |
| | Fosamprenavir/ritonavir (once or twice daily) + either [(abacavir or zidovudine) +(emtricitabine or lamivudine)] OR [(emtricitabine or lamivudine ) + tenofovir ] |
| | Lopinavir/ritonavir (once or twice daily) + either [(zidovudine or abacavir) +(emtricitabine or lamivudine)] OR [(emtricitabine or lamivudine) + tenofovir] |
| | Saquinavir/ritonavir + (emtricitabine or lamivudine) + (tenofovir) |
| **Integrase Inhibitors-based regimen** | **Raltegravir + tenofovir + (emtricitabine or lamivudine)** |
| **Pregnant women** | Lopinavir/ritonavir (twice daily) + zidovudine + (emtricitabine or lamivudine) |

Fill in the information below, answer questions and return **Quiz Only** for certification of participation to: *CE PRN*®, 400 Lake Cook Road, Suite 207, Deerfield, IL 60015.

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**LESSON EVALUATION**

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

| | | |
|---|---|---|
| Describe indications for initiating antiretroviral therapy | Yes | No |
| Differentiate between classes of antiretroviral agents | Yes | No |
| Describe antiretroviral agents-pharmacology; adverse effects; drug interactions | Yes | No |
| List preferred 1st line & alternative therapies for HIV | Yes | No |
| Discuss antiretroviral therapy in pregnancy | Yes | No |

2. Was the program independent & non-commercial Yes No

| | Poor | | Average | | | Excellent | |
|---|---|---|---|---|---|---|---|
| 3. Relevance of topic | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

4. What did you like most about this lesson?_____

5. What did you like least about this lesson?_____

**Please Select the Most Correct Answer(s)**

1. Emtricitabine is a cytidine analogue, so it cannot be used with:
   A. AZT
   B. Lamivudine
   C. Ziagen®
   D. Zerit®
2. Which of these has recently been approved to treat Hepatitis B?
   A. Emtricitabine
   B. Lamivudine
   C. Neupogen®
   D. Tenofovir
3. The first non-peptidic protease inhibitor (NPPI) is:
   A. Tipranavir
   B. Zidovudine
   C. Chloriprazine
   D. All of these
4. Which of these is administered SubQ
   A. Efavirenz
   B. Epzicom®
   C. Enfuvirtide
   D. Saquinavir
5. The only approved antiretroviral that targets HIV-1 integrase is:

A. Ralcicom®
B. AZT
   C. Isentress®
   D. Enfuvirtide

6. Selzentry® is the only approved:
   A. CCR5 inhibitor
   B. PI
   C. NRTI
   D. Integrase inhibitor
7. A co-formulated tablet of zidovudine and lamivudine is:
   A. Combivin®
   B. Adecoline®
   C. Reznicol®
   D. Hivzicom®
8. Drug interactions are least common with:
   A. NRTIs & Nucleotide RTIs
   B. NNRTIs
   C. PIs
   D. FIs
9. Which of these SHOULD NOT be used in combination with PIs?
   A. Simvastatin
   B. Rifampin
   C. Lovastatin
   D. St. John's Wort
   E. All of these
10. Why should the combination of stavudine & didanosine NOT be used in pregnant women?
    A. Too expensive
    B. Risk of lactic acidosis
    C. Requires larger doses
    D. Postural hypotension

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