Updates in Human Immunodeficiency Virus Infection Treatment

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EDUCATIONAL OBJECTIVES

After the completion of this activity pharmacists will be able to:

• Discuss updated guidelines in the treatment of HIV.
• Discuss two new HIV therapies and potential drug interactions, side effects and warnings.

INTRODUCTION

In August 2012 the FDA approved the new Human Immunodeficiency Virus infection (HIV) drug Stribild™ which is a single tablet taken once a day.1 Also in August 2012 the FDA approved a new indication for Truvada® for pre-exposure prophylaxis. In February 2013 the Use of Antiretroviral Agents in HIV infected Adults and Adolescents guidelines were updated by the Department of Health and Human Sciences. The objective of this manuscript is to discuss new developments in HIV therapy pertaining to Stribild™ and Truvada®.

BACKGROUND

The estimated prevalence of HIV is 1.2 million patients in the United States with approximately 25% of this population unaware of their infection.2 Comprehending the treatment of HIV requires an understanding how an HIV infection occurs. HIV is transmitted in three ways: sexual intercourse; parenterally through contact of blood; and mother to child vertical transmission. Sexual intercourse accounts for approximately 80% of all transmissions.3 Once transmission occurs the virus will bind to CD4 receptors on T cell, monocytes, and macrophages.4,5 The virus also attacks the immune cell by binding to coreceptors CCR5 and CXCR-4 on the immune cell membrane. After binding to the CD4 receptor and coreceptors fusion of the cell membranes is mediated by gp41 on the virus cell membrane. The fusion process allows virus genes access to the immune cell genes. The HIV virus contains two copies of ribonucleic acid (RNA) and a reverse transcriptase enzyme. Once inside the immune cell the reverse transcriptase enzyme will make a complementary strand of deoxyribonucleic acid (DNA) from the viral RNA. Ribonuclease H will remove the RNA from the complementary strand of DNA and allow the reverse transcriptase to complete a double strand of DNA. This is the completion of the reverse transcription process the next step is integration of the viral DNA to the immune cell DNA. The viral DNA travels to the nucleus where an integrase enzyme will insert or integrate the viral DNA into the immune cell DNA. The newly infected immune cell will undergo cell replication by starting with transcription, translation, and production of proteins. A virion will bud off from the infected immune cell containing the viral RNA, proteins and enzymes. The HIV protease enzyme located inside the virion will cleave large polypeptides into functional proteins which allows for maturation of the virion. The mature virion is now able to go infect another immune cell and the cycle continues. An illustration of the HIV life cycle described above can be seen in Figure 1.

Medications used in HIV are designed to target the steps in the infection and replication process of the virus.10 HIV medications fall into one of six classes: the nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); fusion inhibitors; CCR5 inhibitors; and integrase inhibitors. The NRTIs compete with endogenous nucleotides to be incorporated into the DNA strand made by HIV virus. If a NRTI is used instead of endogenous nucleotides this stops the production of viral DNA. NNRTIs bind directly to reverse transcriptase and cause a conformational change in the enzyme preventing reverse transcriptase from binding to RNA and DNA. The conformational change of reverse transcriptase prevents the formation of viral DNA. Integrase inhibitors bind to integrase enzyme and prevent integrase from inserting the viral DNA into the immune cell DNA. PIs inhibit the protease enzyme from forming functional proteins for the virion core and produce a noninfectious virion. The CCR5 inhibitor binds directly to the CCR5 coreceptors and blocks HIV from binding to and entering CD4 cells. The fusion inhibitors bind to the gp41 subunit on the virus and prevent the virus cell membrane fusing with the immune cell. For a list of medications in each of these categories see Table 1.

CURRENT APPROACHES TO TREATMENT

Each year guidelines are updated for the treatment of HIV with the latest guidelines being published in February 2013.45 The goals of treating HIV have remained the same and they are to reduce morbidity and prolong the duration and quality of life while restoring and preserving immune function by maximally suppressing the HIV viral load and preventing HIV transmission. To achieve these goals there are basic standards that have been developed. First, to achieve viral suppression the antiretroviral regimen requires at least one active drug from two or more drug classes. Having three active drugs from two or more drug classes is preferred. Second, adherence is key. As the number of missed doses increases the ability for the HIV virus to mutate and become resistant increases too. Finally, early initiation of therapy helps CD4 counts stay high and viral load to stay low.

Identifying HIV infected patients can be difficult. The typical symptoms patients experience are fever, lymphadenopathy, skin rash, fatigue, headache, diarrhea, and oral ulcers.14 The signs of HIV include low white blood cells, decreased platelets, and elevated transaminase levels. Most of these symptoms are mistaken for a cold or other common infection. HIV is diagnosed by using a HIV antibody enzyme immunoassay (EIA). If this initial screen is positive then a Western blot test is required to confirm the diagnosis. If a patient has both negative EIA and Western blot but suspected to be in the acute phase, meaning the body has not produced enough antibodies to be detected, a virologic test measuring the viral load of HIV can be conducted.3

A current debate regarding HIV therapy is when should patients start treatment. The Health and Human Services panel, who developed the guidelines, agrees that patients who are experiencing an AIDs defining illness, have a CD4 count less than 350 cells/mm³, HIV-associated nephropathy, or hepatitis B virus
co-infection requiring treatment should be started on antiretroviral therapy (ART). AIDS defining illnesses include opportunistic infections including cryptococcosis infection, mycobacterium infection, pneumocystis infection and certain cancers such as Kaposi sarcoma and non-Hodgkin lymphoma. HIV associated nephropathy is a kidney disease with large amounts of protein in the urine due to the HIV infection. It is also recommended for nephropathy is a kidney disease with large amounts of protein in those patients with CD4 less than 500 cells/mm³ and who are pregnant to start an ART regimen. Most debate is in regard to patients with CD4 counts above 500 cells/mm³ with 50% of the panel in support of starting ART at this stage while the other half believes treatment should wait until the CD4 count falls below 500 cells/mm³. Once ART is indicated all patients should be assessed for willingness and commitment for adherence and understand treatment once initiated is lifelong. If the patient meets these criteria for ART then a regimen should be selected. The following regimens are recommended as first line therapy for treatment naïve patients. Typically regimens consist of two NRTIs in combination with either an NNRTI, PI boosted with ritonavir, fusion inhibitor, or a CCR5 antagonist.

- Preferred regimens include:
  - Efavirenz/tenofovir/emtricitabine
  - Ritonavir-boosted atazanavir + tenofovir/emtricitabine
  - Ritonavir-boosted darunavir + tenofovir/emtricitabine
  - Raltegravir + tenofovir/emtricitabine

- Preferred pregnancy regimen is:
  - Ritonavir-boosted lopinavir + zidovudine/lamivudine

Some ART regimens should never be used together. Monotherapy, dual therapy or triple therapy with NRTIs alone should not be used because these treatments do not sustain antiviral activity. Additional combinations that should not be used together in a ART regimen are listed in Table 2.

The use of two NNRTIs in a ART regimen together will have an increase in adverse events. Efavirenz is teratogenic and because of this effect its use is not recommend in women of childbearing potential. Emtricitabine and lamivudine have been shown to have minimal antiviral activity and similar resistance. The following medications should not be used with etravirine because appropriate dosing has not been established.

- Any unboosted PI
- Boosted atazanavir
- Boosted fosamprenavir
- Boosted tipranavir

Nevirapine if started in women with CD4 counts greater that 250cells/mm³ and men with CD4 counts greater than 400 cells/mm³ have a greater risk of hepatic complications which can be life threatening. Unboosted darunavir, saquinavir, or tipranavir should not be used because efficacy has not been established without boosting. Stavudine and zidovudine showed an antagonistic effect on HIV when used together in an ART regimen.

At initiation of therapy patients are monitored monthly for safety and efficacy of the ART regimen until treatment goals are reached. Patients are then monitored every 3 months. Efficacy parameters monitored are CD4 and viral load. For safety basic chemistry, ALT, AST, total bilirubin, and complete blood count with differential are monitored every 6 to 12 months. Annual safety monitoring includes fasting lipid profile, and fasting glucose however, if an abnormality is found increased monitoring is recommended. Finally, whenever there is a change in treatment the patient should be monitored more frequently for the first 3 months after the modification in treatment.

HIV is an intricate disease with even more complexity in regards to its treatment. A basic understanding of how HIV utilizes our immune system is essential in understanding the treatment and management of HIV.

**STRIBILD™ (ELVITEGRAVIR, Cobicistat, EMTRICITABINE, AND TENOFOVIR)**

In August 2012 the U.S. Food and Drug Administration approved a new HIV antiviral therapy developed by Gilead Sciences Incorporated. Stribild™ is a quadruple therapy containing a dual nucleoside/nucleotide reverse transcriptase inhibitor regimen (emtricitabine/tenofovir) in combination with two new agents, elvitegravir (an HIV integrase inhibitor), and cobicistat (a “boosting” agent). To date, Stribild™ is the only combination product that has been approved before each individual component. Stribild™ is indicated for treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients. Current Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents consider Stribild™ to be an alternative therapy, defined as regimens that are effective and tolerable, but have potential disadvantages such as increased risks for renal failure when compared with preferred regimens.

Similar to other integrase inhibitors, elvitegravir interferes with the HIV enzyme called integrase. This inhibition prevents insertion of pre-viral genes into human DNA, thus preventing replication of viral DNA. Similar to the role of ritonavir in HIV treatment regimens, cobicistat is mechanism-based inhibitor of the cytochrome 3A family. By inhibiting CYP3A enzymes found in the intestine and liver, cobicistat enhances the systemic exposure of CYP3A substrates, such as elvitegravir, thus increasing bioavailability and half-life. The resulting increased plasma half-life allows for daily dosing of elvitegravir. Emtricitabine is a nucleoside reverse transcriptase inhibitor that interferes with HIV viral RNA dependent DNA polymerase resulting in inhibition of viral replication. Tenofovir, a nucleotide reverse transcriptase inhibitor, interferes with the HIV viral RNA dependent DNA polymerase resulting in inhibition of viral replication. Stribild™ is available only in tablet form containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir. Patients will be instructed to take one tablet by mouth daily with food, with monthly costs estimated to be $2800.

**EVIDENCE**

The FDA approval of Stribild™ was based upon the results of two 48 week, double blind, randomized, controlled trials termed “Study 102” and “Study 103”. In both studies, subjects were stratified by baseline HIV-1 RNA levels. The primary endpoint
was virologic success defined as HIV-1 RNA < 50 copies/mL at 48 weeks. In Study 102, treatment-naïve, HIV-1 infected subjects (N=700) were randomized to receive either Stribild™ (N=348) once daily or Atripla® (efavirenz 600 mg/emtricitabine 200 mg/tenofovir DF 300 mg, N=352) once daily. The primary endpoint (HIV-1 RNA < 50 copies/mL at 48 weeks) was reached by 88% in the Stribild™ arm and 84% in the Atripla® arm. The mean increase from baseline in CD4+ cell count at week 48 was 230 cells/mm³ in the Stribild™-treated subjects and 193 cells/mm³ in the Atripla®-treated subjects.1.11.12 For reference, an adequate CD4 response for most patients on therapy is defined as increases in CD4 count between 50-150 cells/mm³ per year.1 In Study 103, treatment-naïve, HIV-1 infected subjects (N=715) were randomized to receive either Stribild™ (N= 353) once daily or atazanavir 300 mg + ritonavir 100 mg + Truvada® (emtricitabine 200 mg/tenofovir DF 300 mg, N=355) once daily. The primary endpoint (HIV-1 RNA < 50 copies/mL at 48 weeks) was reached by 90% in the Stribild™ arm and 87% in the atazanavir + ritonavir + Truvada® arm. The mean increase from baseline in CD4+ cell count at week 48 was 207 cells per mm³ in the Stribild™ treated subjects and 211 cells per mm³ in the Truvada + atazanavir/ritonavir treated subjects.12 These studies suggest that the overall efficacy of Stribild™ appears to be non-inferior to both Atripla® and atazanavir 300 mg + ritonavir 100 mg + Truvada® in the suppression of HIV viral RNA. In the two trials, adherence was similar in all treatment groups with the majority of patients being >95% compliant, with roughly a 4% increased adherence rate in the Stribild™ treated patients.1.11.12

SAFETY

The most common adverse events reported with the use of Stribild™ include diarrhea (22.4%), nausea (20.3%), headache (14.6%), upper respiratory tract infections (14.6%), abnormal dreams (9.3%), insomnia (8.4%), depression (7.6%), skin rash (6.7%), dizziness (6%), and flatulence (3.6%).6,8,11,12 These effects were reported as being mild to moderate in severity and occurring early during treatment.8,11,12 The FDA reports several adverse reactions that lead to discontinuation of therapy in both trials 102 and 103 including diarrhea, nausea, fatigue, pyrexia, hepatitis C, increases in serum creatinine, and renal failure. The last three (hepatitis C, increases in serum creatinine, renal failure) where only reported in the Stribild™ treatment arms of the trials.6,8,11,12 The tenofovir component of Stribild™ has been associated with severe hepatomegaly and lactic acidosis, causing a black box warning to be issued. A black box warning has also been issued for acute exacerbations of hepatitis B. This is due to reports of patients co-infected with HIV-1 and HBV experiencing acute exacerbations of hepatitis B when using emtricitabine or tenofovir, two of the components of Stribild™.6,10 Renal impairment, including cases of acute renal failure and Fanconi syndrome (a renal tubular injury that prevents the kidneys to reabsorb phosphorous and other substances), has been reported with the use of tenofovir and with the use of Stribild™.6,11 In the clinical trials of Stribild™, 8 subjects in the Stribild™ group and 1 subject in the combined comparator groups discontinued the study drug due to a renal adverse event.10,11 Additionally, the cobicistat component appears to inhibit tubular creatinine secretion without affecting glomerular filtration, which may lead to declines in estimated renal function early in therapy.4 Due to these renal effects, the manufacturer recommends against the initiation of therapy in patients with creatinine clearance <70 mL/minute, and suggests that Stribild™ be discontinued in patients who reach creatinine clearance <50 mL/minute.5 Patients experiencing >0.4 mg/dL increase of serum creatinine from baseline should be monitored closely.6 For liver impairment, no dosage adjustment is required in mild or moderate (Child-Pugh Class A or B) hepatic impairment but the manufacturer recommends against the use in severe hepatic impairment (Child-Pugh Class C) since this population has not been studied.4 Decreased bone mineral density and osteomalacia has been associated with use of tenofovir.6 In Study 103, bone mineral density was assessed by a DEXA scan in a subset of 120 subjects. Mean percentage decreases in BMD from baseline to week 48 were similar to the atazanavir + ritonavir +Truvada® group in the hip (-3.1% versus -3.9%, respectively) and the lumbar spine (-2.6% versus -3.3%, respectively).11 Due to these findings, bone density should be evaluated prior to initiation of therapy. Although occurrence was rare, fat redistribution was noted in the facial area, extremities, torso, and breast. Similar in occurrence, immune reconstitution syndrome was reported in one patient.4,6 This is a condition that can occur during the initial phase of treatment with antiretroviral agents. Patients whose immune system responds after the initiation of therapy may develop an inflammatory response to idle or residual opportunistic infections.4,6

PREGNANCY

Stribild™ currently has a pregnancy category B rating. There are no adequate and well-controlled studies in pregnant women using Stribild™.6,10 No birth defects were reported in animal studies; however, animal studies are not always predictive of human response, so the FDA recommends that Stribild™ only be used during pregnancy if the prescribing physician determines the potential benefit outweighs the potential risk to the fetus.

DRUG INTERACTIONS

Cobicistat is an inhibitor of CYP3A and CYP2D6, therefore coadministration of Stribild™ with drugs that are primarily metabolized by CYP3A or CYP2D6 may result in increased plasma concentrations of such drugs.6,9,10 Due to these effects, concurrent use of drugs that are highly dependent upon CYP3A4 for metabolism (alfuzosin, cisapride, ergot derivatives, lovastatin, simvastatin, midazolam, pimozide, rifampin, sildenafil, St John’s wort, triazolam) are contraindicated.4 Cobicistat is a substrate of P-glycoprotein transporters, and organic anion transporters (OATS) that contribute to the uptake of drugs from the circulation into cells and excretion of drugs at the kidneys.6,6,9 Coadministration of other drugs utilizing these transporters can result in increases in plasma concentrations of both drugs.6 Elvitegravir is a modest inducer of CYP2C9 that may decrease the plasma concentrations of CYP2C9 substrates. Examples of CYP2C9 substrates include, losartan, phenytoin, prasugrel, and glyburide.6,20 Lastly, it should be noted that Stribild™ is indicated for use as a complete regimen for
the treatment of HIV-1 infection and should not be administered with other antiretroviral products.6

In summary, Stribild™ is a complete HIV-1 treatment indicated for use in antiretroviral-naïve adult patients. Results from two clinical trials suggest that Stribild™ has similar efficacy to that of Atripla and Truvada®, and side effects appear to be similar as well. However, the use of Stribild™ is limited to patients without renal impairment and may in fact cause acute renal failure in otherwise healthy patients. For this reason kidney function should be evaluated prior to initiation and throughout the duration of therapy. Stribild™ has an increased potential for drug interactions, particularly with substrates of the CYP3A family. All medications should be reviewed prior to initiation of Stribild™ and patients should be counseled on the potential for interactions.

TRUVADA® (EMTRICITABINE/TENOFOVIR) FOR PRE-EXPOSURE PROPHYLAXIS

Truvada® contains 200mg of emtricitabine with 300mg of tenofovir in one tablet. Truvada® (emtricitabine/tenofovir) was originally approved by the food and drug administration (FDA) in July 2004 for patients infected with HIV-1. In July 2012 the FDA approved Truvada® (emtricitabine/tenofovir) for the pre-exposure prophylaxis (PrEP) for prevention of HIV infection in uninfected high risk individuals. This is the first marketed medication for the prevention of an HIV infection.

Truvada® safety and efficacy for PrEP was demonstrated in two large, randomized, double-blind, placebo-controlled clinical trials. The Pre-exposure Prophylaxis Initiative (iPrEx) trial evaluated Truvada® in 2,499 HIV-negative men or transgender women, who have sex with men, and are at high risk for HIV infection.6 High risk was deemed to be inconsistent or no condom use during sex with a partner of positive or unknown HIV status, a high number of sex partners, and exchange of sex for commodities. At each scheduled visit participants received a comprehensive prevention package that included HIV testing, risk-reduction counseling, condoms, and diagnosis and treatment of symptomatic sexually transmitted infections. Compliance was measured according to pill bottle counts, pill dispensing dates, self-report and drug level assays. Self-report and pill bottle counts indicated a high rate of compliance (89-95%) whereas pill dispensing dates and drug levels assays indicated a lower level of compliance. In the treatment arm, only 8% of subjects who developed an HIV infection and 54% of those without an HIV infection had detectable plasma study drug levels. HIV seroconversion was observed in 110 participants (36 in the Truvada® arm and 64 in the placebo arm) of these, 10 participants had detectable plasma HIV RNA at enrollment (2 in the Truvada® arm and 8 in the placebo arm). Pre-exposure prophylaxis with Truvada® resulted in a relative risk reduction of 44% (95% CI: 15-63; P=0.005). Efficacy was strongly correlated with drug adherence; participants with a detectable study drug level had a relative risk reduction of 92% (95% CI: 40-99; P<0.001) as compared to those without a detectable level. Medication resistance was not detected in the 34 participants who developed HIV after enrollment; however the 2 participants who were HIV RNA positive at enrollment did develop resistance to Truvada®.

The Partners Pre-exposure Prophylaxis trial was conducted in 4,758 heterosexual couples where one partner was HIV-infected and the other was not.7 The trial evaluated the efficacy and safety of Truvada® and tenofovir versus placebo in preventing HIV infection in the uninfected male or female partner. The uninfected partner received regular screening, couples risk-reduction counseling, condoms, and screening and treatment for sexually transmitted infections. Compliance was measured by monthly pill counts and patients were chosen at random to have tenofovir plasma levels tested. According to pill counts, study medication was in use 92.1% of the total follow-up time. HIV seroconversion occurred in 96 participants (22 in the tenofovir arm, 16 in the Truvada® arm and 58 in the placebo arm) and of these, 13 participants had detectable plasma HIV RNA levels at enrollment (5 in the tenofovir arm, 3 in the Truvada® arm and 6 in the placebo arm). Tenofovir reduced the risk of an HIV infection by 67% (95% CI: 44-81: P<0.001) versus placebo, and Truvada® reduced the risk of an HIV infection by 75% (95% CI: 55-87: P<0.01) versus placebo. Not all participants received plasma tenofovir level testing, but of those that did, a detectable tenofovir plasma level was associated with a relative risk reduction of 86% with tenofovir and 96% with Truvada®. Medication resistance was not observed in any of the participants who acquired HIV-1 after randomization; however 2 of the 8 participants who had detectable HIV RNA levels at enrollment did develop resistance (1 in the tenofovir arm and 1 in the Truvada® arm).

Some concerns have been raised about this new FDA indication for Truvada®.14 Some experts are afraid that non-compliance will lead to resistance to the medication. Compliance did prove to be an issue in the iPrEx trial but resistance was not observed in any of the patients who were HIV negative at enrollment and used Truvada® for prophylaxis. There are also concerns that this medication will give healthy individuals a false sense of complete protection, which will lead to more risky behavior; however, patients enrolled in these studies received monthly counseling and were provided with condoms, which resulted in study participants reporting a decrease in sexual partner’s overtime and an increase in condom usage. The counseling was likely a contributor to a more responsible sex behavior in these participants and further emphasizes the need for continued counseling by healthcare providers that are providing participants with Truvada® for prophylaxis purposes.

Compliance and safe sex practices should be taken seriously by all patients using Truvada® for PrEP; healthcare providers involved in the patients care will be responsible for providing patient education. The dispensing pharmacists have the advantage of being able to track how often the patient fills the prescription and will therefore play a key role in monitoring patient compliance. The following information should help community pharmacists as they anticipate an influx of questions from a curious public and as they encounter prescriptions for Truvada® for PrEP.

Truvada® one tablet daily is the recommended dose for PrEP in high risk individuals. Patients considered to be high risk would be:5,10,19

- Those with partners known to be HIV-1 infected
Prior to initiating Truvada* for PrEP patients need to obtain a negative HIV-1 test and patients’ needs to be retested every three months while on Truvada*. Prior to HIV-1 testing patients’ should refrain from potential HIV-1 exposure events for at least one month. If the patient becomes infected with HIV, Truvada* would not be sufficient in treating the HIV and would likely cause resistance. Truvada* is meant to be used as a comprehensive HIV prevention plan that includes counseling, condoms usage, regular HIV testing along with testing for other sexually transmitted diseases. Patients should be counseled on the importance of adhering to a strict dosing schedule, because adherence was strongly correlated with effectiveness in clinical trials.9,10,19

SAFETY:

No new side effects were identified in the clinical trials evaluating Truvada* for the PrEP indication. The most common side effects that patients should be aware of with Truvada* include diarrhea, nausea, abdominal pain, headache, and weight loss.9,10,21 Although uncommon Truvada* has been associated with a 5-7% decrease in bone mineral density; patients at risk for osteopenia or with a history of fractures should consider supplementing with calcium or vitamin D. Due to the tenofovir component, Truvada* has also been associated with rare cases of renal toxicity. Patients should have their renal function monitored with serum BUN and creatinine prior to initiation, three months after initiation and then every six months. If the CrCl falls < 60ml/min, Truvada* should be discontinued for PrEP. Truvada* is also associated with the following black box warnings:

• Black Box Warning (due to tenofovir component): lactic acidosis and severe hepatomegaly with steatosis; Truvada* should be used cautiously in patients with factors for liver disease or those who experience elevated transaminase levels during treatment.

• Black Box Warning: Drug resistant HIV-1 variants have been identified in participants who used Truvada* for prophylaxis and had an acute HIV-1 infection at the time of initiation. Do not initiate Truvada* PrEP if signs or symptoms of acute HIV-1 infection present unless negative infection status is confirmed.

CONCLUSION

In conclusion, the first HIV diagnosis was in 1981; in a little over 30 years it has already affected the lives of millions of people. Due to its growing resistance to medications, new guidelines have to be developed every year and there is a continued need for new therapies. With each new therapy comes new side effects, warnings and drug interactions, therefore it is very important that pharmacists stay up to date on new HIV recommendations and therapies because patient education is key in increasing patient compliance. In the past, therapies typically consisted of at least two medications, but newer therapies like Stribild™ (elvitegravir/ cobicistat/emtricitabine/tenofovir) contain multiple active drugs in one tablet, making HIV therapy less complicated for patients; however they also come with increased drug interactions, side effects and warnings. Pharmacists need to be aware of the drug interactions, side effects and warnings associated with each medication in these combination products. Although our newer therapies are very effective in decreasing viral load and increasing CD4 counts they are not able to cure HIV. Prevention is the most effective way to control this epidemic. Truvada* (emtricitabine/ tenofovir) is the first medication brought to market for pre-exposure prophylaxis, however there are multiple limitations that affect its efficacy. Patients need to be counseled on the importance of compliance with therapy and that Truvada* is to be used as part of comprehensive HIV prevention plan. Pharmacists dispensing HIV medications play an active role in treating and preventing HIV infections; it is very important to stay up to date on new therapies and continue to educate patients about their therapy and monitor for patient compliance.

DRUG INTERACTIONS:

Drug interactions with Truvada* are mainly with other anti-retroviral agents and the only ones of concern in patients using Truvada* for PrEP would be acyclovir/ valacyclovir which can decrease tenofovir elimination and increase the risk of renal toxicity. Truvada* is a P-glycoprotein inducer and can increase elimination of dabigatran and should therefore be avoided in patients who require dabigatran therapy.9,10,19

In summary, Truvada* does provide added protection for patients who put themselves at high risk for HIV infection. This added protection comes at a high price of about $1500.00 for a one month supply. Before starting therapy patients need to be committed to a strict dosing regimen and regular testing. The healthcare professionals that are prescribing and dispensing Truvada* for PrEP will be responsible for monitoring compliance and holding patients accountable to regular HIV testing. Patients should be reminded of the following points on a regular basis:

• Truvada* is not a substitute for safe sex practices
• Truvada* needs to be part of a comprehensive prevention plan that includes condoms and regular testing
• 100% compliance with Truvada* is necessary in order to assume efficacy

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• Black Box Warning: Drug resistant HIV-1 variants have been identified in participants who used Truvada* for prophylaxis and had an acute HIV-1 infection at the time of initiation. Do not initiate Truvada* PrEP if signs or symptoms of acute HIV-1 infection present unless negative infection status is confirmed.
REFERENCES


7. Stribild® [Internet]. Foster City (CA): Gilead Sciences Incorporated; c2013. Safety Information; 2013 [cited 2013 April 7]; [about 5 screens]. https://www.stribild.com/


18. Truvada approved to reduce the risk of sexually transmitted HIV in people who are not infected with the virus [Internet]. Silver Spring (MD): U.S Food and Drug Administration; [updated 2012 Nov 07, cited 2012 April 9]. Available from: http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/hivandAidsactivities/ucm312264.htm

Figure 1.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</td>
<td>Abacavir (ABC)</td>
<td>Ziagen</td>
</tr>
<tr>
<td></td>
<td>Didanosine (ddI)</td>
<td>Videx</td>
</tr>
<tr>
<td></td>
<td>Videx EC (enteric-coated)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emtricitabine (FTC)</td>
<td>Emtriva</td>
</tr>
<tr>
<td></td>
<td>Lamivudine (3TC)</td>
<td>Epivir</td>
</tr>
<tr>
<td></td>
<td>Stavudine (d4T)</td>
<td>Zerit</td>
</tr>
<tr>
<td></td>
<td>Tenofovir (TDF)</td>
<td>Viread</td>
</tr>
<tr>
<td></td>
<td>Zidovudine (ZDV, AZT)</td>
<td>Retrovir</td>
</tr>
<tr>
<td>Non-nucleoside Reverse Transcriptase Inhibitors</td>
<td>Delavirdine (DLV)</td>
<td>Rescriptor</td>
</tr>
<tr>
<td></td>
<td>Efavirenz (EFV)</td>
<td>Sustiva</td>
</tr>
<tr>
<td></td>
<td>Etravirine (ETR)</td>
<td>Intelence</td>
</tr>
<tr>
<td></td>
<td>Nevirapine (NVP)</td>
<td>Viramune</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine (RPV)</td>
<td>Edurant</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td>Atazanavir (ATV)</td>
<td>Reyataz</td>
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<tr>
<td></td>
<td>Darunavir (DRV)</td>
<td>Prezista</td>
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<tr>
<td></td>
<td>Fosamprenavir (FPV)</td>
<td>Lexiva</td>
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<tr>
<td></td>
<td>Indinavir (IDV)</td>
<td>Crixivan</td>
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<td></td>
<td>Nelfinavir (NFV)</td>
<td>Viracept</td>
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<td></td>
<td>Ritonavir (RTV)</td>
<td>Norvir</td>
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<td></td>
<td>Saquinavir (SQV)</td>
<td>Invirase</td>
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<td></td>
<td>Tipranavir (TPV)</td>
<td>Aptivus</td>
</tr>
<tr>
<td>Fusion Inhibitors</td>
<td>Enfuvirtide (T-20)</td>
<td>Fuzeon</td>
</tr>
<tr>
<td>CCR5 Antagonists</td>
<td>Maraviroc (MVC)</td>
<td>Selzentry</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td>Raltegravir (RAL)</td>
<td>Isentress</td>
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<tr>
<td>Combination Products</td>
<td>Abacavir, Lamivudine</td>
<td>Epzicom</td>
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<tr>
<td></td>
<td>Abacavir, Lamivudine, Zidovudine</td>
<td>Trizivir</td>
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<td>Efavirenz, Emtricitabine, Tenofovir</td>
<td>Atripla</td>
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<td>Elvitegravir, Cobicistat, Emtricitabine, Tenofovir</td>
<td>Stribild</td>
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<td>Emtricitabine, Rilpivirine, Tenofovir</td>
<td>Complera</td>
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<td>Lamivudine, Zidovudine</td>
<td>Combivir</td>
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<tr>
<td></td>
<td>Lopinavir, Ritonavir</td>
<td>Kaletra</td>
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</tbody>
</table>
Table 2.

<table>
<thead>
<tr>
<th>ART Combinations to Avoid</th>
<th>Side effects due to combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir and indinavir</td>
<td>Grade 3 or 4 hyperbilirubinemia</td>
</tr>
<tr>
<td>Didanosine and stavudine</td>
<td>Peripheral neuropathy, pancreatitis, lactic acidosis, possible death</td>
</tr>
<tr>
<td>Didanosine and tenofovir</td>
<td>Lactic acidosis, virologic failure and immunology non response</td>
</tr>
</tbody>
</table>

**Abbreviations**

- Antiretroviral therapy: ART
- Deoxyribonucleic acid: DNA
- Enzyme immunoassay: EIA
- Human Immunodeficiency Virus Infection: HIV
- Non-nucleoside reverse transcriptase inhibitors: NNRTIs
- Nucleoside or nucleotide reverse transcriptase inhibitors: NRTIs
- Organic anion transporters: OATS
- Pre-exposure prophylaxis: PrEP
- Pre-exposure Prophylaxis Initiative: iPrEx
- Protease inhibitors: PIs
- Ribonucleic acid: RNA