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Antiretroviral Therapy: Current Drugs

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INTRODUCTION

The 1980s saw the devastation of the newly emerging and deadly disease of acquired immunodeficiency syndrome or AIDS. The identification of the retrovirus - now known as human immunodeficiency virus (HIV) - as the causative pathogen in the mid-1980s was the key milestone in the control of this disease. The discovery of the multi-step replicative life cycle of HIV in human CD4⁺ T-cells led to the identification of potential drug targets to halt or slow the replicative process (Figure 1). This resulted in unprecedented scientific progress in the drug discovery and drug development process.

Zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI), was the first approved antiretroviral agent for use in 1987 after it had shown to provide a dramatic survival benefit when compared with placebo in patients with advanced AIDS.¹ Although NRTI monotherapy showed a reduction in viral load, delayed disease progression and prolonged survival, the use of a single agent did not provide sustained viral suppression. Furthermore, it rarely reversed immune function. The approval of three HIV protease inhibitors (PI) in the mid-1990s dramatically changed the course of the HIV epidemic. The use of combination

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therapy consisting of a PI with 2-NRTI resulted in rapid reduction of HIV RNA, improved immune function,² regression of difficult to treat opportunistic infections such as Kaposi's sarcoma³ and progressive multifocal leukoencephalopathy⁴, and reduced mortality⁵. Since then, combination antiretroviral therapy became the mainstay of treatment. Table 1 provides a glimpse of the advances in antiretroviral therapy over the years.

As of early 2014, 28 antiretroviral drugs belonging to six different mechanistic classes have been approved for use in the US. Several of the older agents are no longer used in clinical practice, as they are replaced by newer drugs that are more potent, less toxic, with lower pill burden, and less dosing frequency. This large armamentarium of drugs provides the clinicians with ample options to individualize therapy. Despite the potency of current antiretroviral regimens, residual HIV remains in different sanctuary reservoirs. As a result, even temporary discontinuation of treatment results in viral rebound in almost all patients⁶, thus in order to maintain viral suppression with current treatment, therapy needs to be continued indefinitely. Maintaining strict adherence to long-term antiretroviral therapy is a challenge for many asymptomatic HIV-infected patients. Intermittent adherence may lead to selection of drug resistance mutations, limiting future options. This article will provide an overview of the goals and principles of antiretroviral treatment, factors to consider when selecting a regimen for an individual patient, with a main focus on the pharmacology of commonly used antiretroviral drugs in 2014.

GOALS AND PRINCIPLES OF ANTIRETROVIRAL THERAPY

The key goals of antiretroviral therapy are to:

- achieve and maintain suppression of plasma viremia to below the current assays' level of detection;
- improve overall immune function as demonstrated by increases in CD4+ T cell count;
- prolong survival;
- reduce HIV associated morbidity;
- improve overall quality of life; and
- reduce risk of transmission of HIV to others

In order to achieve these goals, the clinicians and patients must recognize several key principles:

- current antiretroviral regimens do not eradicate HIV, viral rebound occurs rapidly after treatment discontinuation, followed by CD4 decline, with potential for disease progression
- strict adherence to the prescribed regimen is essential in order to avoid viral rebound and the potential for selection of drug resistance mutations
- a combination regimen should consist of preferably 3 (but at least 2) active agents based on genotype resistance test results

HIV LIFE CYCLE AND TARGETS OF ANTIRETROVIRAL DRUG THERAPY

Figure 1 illustrates the different steps of the HIV life cycle and drug targets⁷ (adapted from <http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Biology/pages/hivreplicationcycle.aspx>). HIV virions enter the CD4+ T-cells and utilize the CD4 cells as the machinery for reproduction of new virions. The currently approved antiretroviral drugs aim at halting viral replication at 6 different stages of the HIV life cycle. Table 2 lists the drugs approved by the FDA within each drug class.

RATIONALE FOR COMBINATION ANTIRETROVIRAL THERAPY

As described above, HIV replication requires a multi-step process. Using a combination of different agents targeting different steps within the HIV life cycle provides either synergistic or additive antiviral effect, thus enhancing the efficiency in which viral replication is suppressed. Based on data from large, randomized clinical trials, four different combinations are commonly prescribed to treatment-naïve patients. All these combinations include a “backbone” of 2-NRTIs, plus one of these classes of drugs – a PI (usually boosted with ritonavir), an NNRTI, an INSTI, or the CCR5 antagonist maraviroc (for more detailed description of different regimens, please refer to the What to Start chapter of this series). Transmission of drug resistant HIV may occur, thus a genotypic resistance testing is generally recommended prior to initiation of therapy in order to avoid prescription of suboptimal therapy.⁸ Despite the efficacy of these antiretroviral regimens, some patients may experience treatment failure with HIV drug resistance. In these patients, therapy may be more complex and require the use of multiple drug classes, based on genotypic or phenotypic drug susceptibility testing (for more detailed discussion, please refer to Managing the Treatment Experienced Patients chapter).

Early generation antiretroviral agents have provided the evidence that viral suppression can be achieved. However, these earlier agents have largely fallen out of favor due to their large pill burden, frequent daily dosing, as well as intolerable side effects. Newer agents marketed in the past decade aim to provide some advantages including new mechanisms of action, greater virologic potency-especially towards multi-drug resistant HIV, fewer toxicities, less drug-drug interactions, lower pill burden or dosing frequency. The remainder of this article will describe the different currently used agents in each drug class. The accompanying tables provide a comparison of the characteristics of drugs in each class, to help the readers in selecting the most optimal drugs for each patient.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)

The NRTI is the first class of antiretroviral drugs approved for use in the United States, and remains as a key component of most combination regimens.⁸ The NRTIs are phosphorylated intracellularly to their active diphosphate or triphosphate metabolites, which then inhibit the enzymatic action of the HIV reverse transcriptase by incorporating into the nucleotide analogue causing DNA chain termination or by competing with the natural substrate of the virus. This in turn halts the conversion of viral RNA into double stranded DNA. Zidovudine was first approved in 1987 for patients with advanced HIV (CD4 count <200 cells/mm³) or with AIDS defining conditions,¹ followed by the approval of didanosine, zalcitabine,

stavudine, and lamivudine. These drugs were initially prescribed as monotherapy followed by combination of 2-NRTI (such as zidovudine + didanosine, zidovudine + zalcitabine, (zidovudine or stavudine) + lamivudine, or stavudine + didanosine). A combination antiretroviral regimen today typically consists of 2-NRTI as a “backbone” to be used in combination with a third or fourth drug, typically an NNRTI, a boosted-PI, an INSTI, or a CCR5 antagonist. The use of older NRTIs is limited by some serious toxicities, mostly related to their effects on human cellular mitochondrial DNA in different tissues.⁹ Some of these include bone marrow toxicities and myopathy associated with zidovudine; peripheral neuropathy with stavudine, didanosine, and zalcitabine; and pancreatitis with didanosine and stavudine. These older NRTIs are also associated with serious and sometimes fatal toxicities such as lactic acidosis and hepatic steatosis. Additionally, cosmetically disfiguring and mostly irreversible lipoatrophy has been associated with long-term use of the thymidine analogs stavudine and zidovudine. Newer NRTIs such as abacavir, tenofovir, lamivudine and emtricitabine appear to be weaker inhibitors of mitochondrial DNA polymerase gamma, and associated with much less toxicities that are associated with mitochondrial injury.¹⁰ NRTIs are not metabolized via the CYP450 enzyme system, thus have less potential for significant drug-drug interactions. Most NRTIs, except for abacavir, require dosage adjustment in patients with renal insufficiency. Dosing recommendations in patients with renal impairment can be found in the product labels and in the treatment guidelines.⁸

Today, the most commonly used NRTIs are tenofovir and abacavir, both used in combination of emtricitabine or lamivudine. These agents, along with zidovudine, will be discussed below. A comparison of the characteristics of the different agents can be found in Table 3.

Abacavir

Abacavir is a carbocyclic nucleoside analog which is converted to its active metabolite carbovir triphosphate, which in turn inhibits the effect of HIV reverse transcriptase (ZIAGEN 2013).¹¹ It is readily and extensively absorbed orally. It is metabolized by alcohol dehydrogenase and glucuronyl transferase. No dosage adjustment is needed in patients with renal insufficiency. Abacavir is commonly used in combination with lamivudine as a 2-NRTI backbone and it is available as a fixed dose combination with lamivudine (Epzicom™) or with zidovudine and lamivudine (Trizivir™). Although a 3-NRTI combination of abacavir + zidovudine + lamivudine has been approved as an initial regimen for antiretroviral-naïve patients, it is generally not recommended⁸ due to the inferior potency of this regimen¹². Abacavir + lamivudine can be given once daily without regard to food. Abacavir use has been associated with an immunologically-mediated systemic hypersensitivity reaction manifested by symptoms such as high fever, diffuse skin rash, flu-like syndrome, gastrointestinal disturbances, and respiratory compromise.¹³ These symptoms usually occur within the first few weeks of treatment initiation for which abacavir should be discontinued promptly. It is not recommended to re-challenge a patient who has experienced this hypersensitivity reaction as reintroduction of abacavir can lead to rapid onset of more severe symptoms such as profound hypotension and vascular collapse.¹³⁻¹⁵ This reaction has been found to be highly associated with the presence of the HLA-B*5701 allele.^{16,17} Testing of HLA-B*5701 should be done prior to initiation of abacavir and those

who test positive should not be given this agent.⁸ In some but not all prospective and retrospective studies, the current or recent use of abacavir was associated with cardiovascular events, such as acute myocardial infarction, especially in patients with significant history of cardiac diseases.^{18,19} To date, this association remains controversial. Because of concerns of lower rates of virologic suppression associated with abacavir + lamivudine as a NRTI backbone compared to tenofovir + emtricitabine in treatment-naïve patients with a baseline viral load > 100,000 copies/mL, some experts suggest that except when using with dolutegravir, abacavir + lamivudine use in patients with baseline HIV RNA > 100,000 copies/mL should be done with caution.⁸

Emtricitabine and Lamivudine

Emtricitabine and lamivudine share similar structure and activities. They possess similar HIV-1 resistance profiles, where the most frequently selected resistance mutation is M184V. They are both active against hepatitis B virus (HBV) and should be used as part of a regimen in patients with hepatitis B co-infection. Exacerbation of hepatitis may occur after initiation²⁰ (as a form of immune reconstitution) or discontinuation²¹ of these agents. These two agents are rapidly absorbed orally, with emtricitabine having a slightly longer intracellular half-life. They are both renally excreted, where dosage adjustment is necessary in patients with renal impairment. These drugs are generally very well tolerated, with skin discoloration being the most commonly reported side effect. Both agents are commonly used as part of a 2-NRTI backbone, together with abacavir, tenofovir, or zidovudine. They are both available in different fixed dose combination products on the market (see Table 3). As they provide similar antiviral activities without additive effect, there is no benefit in using these two drugs in combination.

Tenofovir Disoproxil fumarate (or tenofovir)

Tenofovir disoproxil fumarate is a nucleotide analog, which inhibits the reverse transcriptase of both HIV and HBV. It is approved for use as part of the treatment of HIV and HBV infection. Tenofovir with emtricitabine also has been approved for use as pre-exposure prophylaxis for individuals who are at high risk of acquisition of HIV.²² Tenofovir is available as part of a fixed dose combination product with various different antiretroviral drugs (see Table 2). It is rapidly absorbed orally and is eliminated renally by both glomerular filtration and active tubular secretion. It can be given as once daily therapy without regard to food. Dosage adjustment is necessary in patients with renal impairment. Use of tenofovir has been associated with new onset or worsening of renal dysfunction, primarily as a consequence of renal proximal tubulopathy (or Fanconi's syndrome), which may manifest as increase in serum creatinine, glycosuria, proteinuria, or hypophosphatemia.²³ These effects on the kidneys may be increased when tenofovir is used with a boosted PI.^{24,25} Renal function, electrolytes, and urinalysis should be monitored in patients receiving tenofovir, and particularly in those who have pre-existing renal dysfunction or who are receiving other nephrotoxic drugs. Tenofovir use has been associated with reduced bone mineral density and increases in biomarkers associated with bone metabolism, which may lead to increase in fracture risk.^{26,27} Osteomalacia and hypophosphatemia with symptomatic bone and muscular pain have been reported in patients that may have been a consequence of proximal renal tubulopathy.^{28,29} Tenofovir use with

emtricitabine or lamivudine and a third agent (either an NNRTI, a boosted PI, or an INSTI) have been found to result in potent antiretroviral effect, leading to durable viral suppression in the clinical trial participants. Because of its potency and ease of use, tenofovir is part of most preferred combination antiretroviral regimens for treatment-naïve patients.

Zidovudine

Zidovudine is a thymidine analog that is converted to its active triphosphate form intracellularly, which is then attached to the DNA polymerase of the reverse transcriptase leading to chain termination. It was the first NRTI approved, showing a survival benefit compared to placebo, in advanced HIV patients.¹ In 1994, zidovudine monotherapy was given to pregnant women after 14-week gestation, which included intrapartum intravenous zidovudine, and oral zidovudine given to the newborn. This resulted in a dramatic reduction in perinatal HIV transmission.³⁰ It is well absorbed orally, and undergoes glucuronidation in the liver and eventually elimination by the kidneys. Zidovudine is dosed at twice daily dosing without regards of food. It is commonly prescribed with lamivudine to form the 2-NRTI backbone of a combination regimen. It is available as co-formulated products with lamivudine (Combivir®) as well as with lamivudine and abacavir (Trizivir®). The side effects of zidovudine have led to its limited utility in today's treatment armamentarium. Some common side effects include bone marrow suppression (primarily macrocytic anemia and neutropenia), nausea and vomiting, nail pigmentation, and headache. Serious but less common side effects have also been reported, which include myopathy, cardiomyopathy, and lactic acidosis (often with hepatic steatosis). Because of its long-term efficacy and safety data for pregnant women and the fetus, zidovudine remains as one of the recommended antiretroviral drugs to be given during pregnancy. For non-pregnant patients, the utility of zidovudine is more limited, primarily due to its toxicity profile and the need for twice daily dosing.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are different from NRTIs in that they do not require intracellular phosphorylation to exert their pharmacologic action. NNRTIs are noncompetitive inhibitors of reverse transcriptase, which results in a conformational change and thus decreases the action of this enzyme.

NNRTIs are potent agents for virologic suppression but are limited by drug interactions, selected side effects, and overall low threshold for the emergence of resistant mutants (exception is etravirine). All of the NNRTIs are highly metabolized by CYP450 and are particularly potent inducers with the exception of rilpivirine. Caution should be exercised when prescribing concomitant agents that are also highly metabolized by CYP450. Clinicians should consult the prescribing information or other guidelines for information on the management of drug interactions. The description of the US FDA indications in HIV-1 infected adults and children, usual dose, formulations, daily pill burden, significant and/or common adverse effects, major drug interactions, primary resistance mutations, and special considerations are summarized in Table 4.

Efavirenz

Efavirenz is rapidly absorbed orally and the extent of absorption is increased in the setting of a high fat meal. It is therefore recommended to take efavirenz on an empty stomach to avoid excessive adverse effects. It is over 99% protein bound and is metabolized via oxidative metabolism primarily by CYP2B6 and CYP3A4. Efavirenz is a potent inducer of both these enzymes and should be used with caution when given with drugs which are metabolized by CYP2B6 and 3A4. It has a long half-life (40-55 hours) which allows for once daily dosing.³¹

Efavirenz is dosed at 600mg orally once daily and should be given preferably at bedtime due to the central nervous system (CNS) side effects, which include vivid dreams, dizziness, and hallucinations. More than 50% of patients experienced a myriad of CNS side effects.

Although less common, use of efavirenz has also been associated with psychotic disturbances such as depression, insomnia, mania³¹, and suicidality³². The incidence of these side effects is highest in the first 4 weeks of therapy and is known to resolve after this time period. Nevertheless, patients should be counseled on these potentially harmful side effects. Rash has been reported in approximately 26% of patients taking efavirenz in clinical trials and usually resolves within the first few weeks of therapy. Serious skin reactions such as Stevens-Johnson syndrome have been reported and should be promptly discontinued if suspected. Other reported side effects include hypercholesterolemia (up to 40%) and increase hepatic transaminases (up to 8%). It should be noted that efavirenz is a pregnancy category D where the use of this agent in the first trimester has been associated with neural tube defects in both primates and human.³¹ It is generally recommended to avoid efavirenz in women of childbearing age if possible. However, it may be continued in pregnant women already on an efavirenz containing regimen which produces virologic suppression.³³ This exception was made with the because neural tube defects occur most likely in the first 5-6 weeks of pregnancy and that pregnancy is usually not detected before 6 weeks.

Efavirenz is a preferred NNRTI for treatment naïve patients in the United States⁸ and worldwide³⁴ and is a popular treatment option given that it is co-formulated with NRTIs emtricitabine and tenofovir (Atripla ®). The long half-life of efavirenz allows for this one pill once a day ART regimen. Although the long half-life clearly represents a pharmacokinetic advantage, it should also be noted that HIV can rapidly develop resistance to this agent due to the relative ease of single amino acid substitutions, thus, patient adherence is especially important.

Etravirine

Etravirine is a viable treatment option in patients who have developed resistance to both efavirenz and nevirapine. Its oral bioavailability is increased in the setting of food and is recommended to be taken with food. It is metabolized in the liver via CYP3A4, 2C9, and 2C19 to its metabolites and primarily excreted into feces as unchanged drug (86%). Because its metabolism is mediated by multiple CYP450 enzymes for which it is a substrate, inducer, and inhibitor-caution should be exercised when giving this agent with drugs that are also highly metabolized via this enzyme system. Currently etravirine is dosed at 200mg orally twice daily. Unlike efavirenz, etravirine is not associated with CNS disturbances. Rash

occurred in 15% of patients in clinical trials and usually resolved within the first few weeks of therapy. Hyperglycemia and hypercholesterolemia have also been reported. It is only approved for use in treatment-experienced patients. In patients who experienced virologic resistance to other NNRTIs, etravirine should not be used with a 2-NRTI backbone alone. Instead other antiretroviral drugs such as a ritonavir-boosted PI or an INSTI or enfuvirtide should be added to the regimen.³⁵ In patients who fail a rilpivirine-based regimen with the emergence of the E138K mutation, use of etravirine should be avoided as this mutation also confers resistance to etravirine.³⁶

Nevirapine

The use of nevirapine has been largely limited by the development of resistance to this agent and its CD4 count dependent incidence of serious side effects. It is highly orally bioavailable and moderately protein bound (60%). It is extensively metabolized by CYP3A4 and 2B6 and undergoes entero-hepatic recirculation. It auto-induces its metabolism after the first 14 days of therapy for which a dosage adjustment from 200 mg once daily to 400mg daily dose (as 400mg extended release formulation once daily or 200mg twice daily) is required. Approximately 80% of the drug is eliminated into the urine.³⁷

Hepatotoxicity, often accompanied by systemic symptoms including fulminant hepatic failure has been reported in patients receiving nevirapine, with the highest incidence in women with a CD4 count of < 250 cells/mm³ and men with a CD4 count of < 400 cells/mm³.³⁷ Rash has also been frequently reported with this agent in up to 13% of patients often occurring within the first 6 weeks of therapy. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson Syndrome, and toxic epidermal necrolysis have all been reported with nevirapine use. Nevirapine is no longer one of the recommended NNRTI, however, it remains an option mainly in pregnant HIV positive women and for infant antiretroviral prophylaxis, especially in developing countries.^{8,33,34}

Rilpivirine

Rilpivirine is the most recently approved of the NNRTIs on the market which offers some distinct advantages over other agents in its class. Rilpivirine should be taken with food as its absorption is markedly increased in its presence and dependent on gastric pH. Acid suppressing agents should be separated by at least 2 hours of rilpivirine administration and proton pump inhibitors should be avoided entirely. It is highly bound to albumin (99%) and is metabolized by CYP3A4 – for which it is only a substrate for this enzyme. This represents an advantage over other NNRTIs as the drug interactions with this agent may be more predictable. Caution should be exercised when administering this agent with drugs that are potent inducers or inhibitors of CYP3A4 as these drugs may significantly alter the serum levels of rilpivirine. It has a long half-life of over 50 hours, which allows for convenient once a day dosing. It is primarily excreted into feces.³⁸

Rilpivirine is dosed 25mg orally once daily in both treatment naïve and experienced patients and is currently recommended as an alternative NNRTI in patients with a baseline viral load of $> 100,000$ copies/mL.⁸ Rilpivirine is not recommended in patients with a viral load $> 100,000$ copies/mL as it was shown to have inferior rates of virologic suppression compared

with efavirenz in treatment naïve patients.³⁹ Rilpivirine is co-formulated into a single tablet, once daily regimen (Complera®) with emtricitabine and tenofovir.

Rilpivirine is generally well tolerated. Like all NNRTIs, rilpivirine use has also been associated with rash (3%) although to a much lesser extent compared to nevirapine and efavirenz. CNS side effects including depression were reported in about 9% of patients in the double-blinded clinical trials comparing rilpivirine to efavirenz.³⁹ Elevations in hepatic transaminases have also been reported and therefore should be used with caution in patients with liver dysfunction. Rilpivirine is considered an alternative agent for the treatment of HIV and offers the advantage of a single tablet regimen, potentially fewer drug interactions, and is generally well tolerated, including fewer CNS side effects. Its use may be limited by its inferior efficacy rates in patients with high baseline viral loads and drug interactions with acid suppressing agents.

PROTEASE INHIBITORS

Protease inhibitors (PI) exhibit their pharmacologic action late in the HIV replication cycle by binding to HIV proteases, leading to blockage of the proteolytic activities of the enzyme, resulting in the inability of formation of mature, infectious virions. In combination with 2-NRTIs, certain ritonavir-boosted PI regimens are considered preferred therapies in treatment-naïve patients. PI plus NRTI combination regimens have shown to be effective not only treatment naïve patients, but also with other ART drug classes for patients who experience treatment failure.

Currently, nine PIs are available on the US market. Of these nine, only seven will be discussed in this review: ritonavir, saquinavir, lopinavir, fosamprenavir, tipranavir, atazanavir, and darunavir. Indinavir and nelfinavir will not be discussed as their role in therapy has diminished due to the large pill burden and intolerable side effects. The PIs remain an important class of antiretroviral drugs mainly because of their high barrier to resistance. These agents generally require an accumulation of multiple resistance mutations for resistance to occur. Class associated side effects include metabolic abnormalities including dyslipidemia (primarily triglycerides), insulin resistance, hyperglycemia, and lipodystrophy. The incidence of these side effects is augmented by the use of concomitant ritonavir, which is recommended to be given with most available PIs. Ritonavir, although it possesses anti-HIV activity, is not currently used as an active agent in the treatment of HIV, in part due to the high pill burden required as an active PI, and high rate of gastrointestinal side effects and lipid abnormalities. Instead its role is limited to “boosting” or enhancing the pharmacokinetic profile of other PIs. Being a potent CYP3A4 inhibitor (in both the liver and the gut lumen), low dose ritonavir inhibits the metabolism of most PIs resulting overall increase in drug exposure and plasma half-life, allowing for use of the active PI in lower dose and reduced dosing frequency. Currently, all PIs are given with ritonavir (100-400mg daily) as standard of therapy. The available protease inhibitors vary greatly in regards to their pharmacokinetics, dosing, virologic potency, pill burden, and side effect profile. Prescribers should be aware of these differences to individualize therapy for patients according to their concomitant medications, co-morbidities, and allergies/intolerances.

Virtually all of the available PIs are metabolized by CYP450. Caution should be exercised when prescribing concomitant agents that are also highly metabolized by CYP3A4. The description of the US FDA indications in HIV-1 infected adults and children, usual dose, formulations, daily pill burden, significant and/or common adverse effects, major drug interactions, primary resistance mutations, and special considerations are summarized in Table 5A and 5B.

Atazanavir

Atazanavir undergoes rapid oral absorption. When unboosted, the area under the concentration time curve (AUC) is increased by almost 70% when given with a light meal compared to approximately 35% with a high fat meal. When given with ritonavir, the AUC of atazanavir is increased by almost 2.5-fold. Atazanavir requires an acidic gastric environment to be optimally absorbed. Concomitant use with acid suppressants such as proton pump inhibitors and acid reducing agents such as histamine-2-receptor antagonists (H2RAs) and antacids significantly reduce atazanavir serum concentrations. Prescribing information provides recommendations on optimal dosage and/or timing adjustments for atazanavir when patients are also taking any acid reducing agents.⁴⁰ Atazanavir is extensively metabolized by CYP3A4. Because its metabolism is primarily mediated by CYP3A4, the potential for significant drug interactions is high. In addition, atazanavir is a moderate inhibitor of UGT1A1, which may increase the AUC of agents that are metabolized by this enzyme (e.g. certain integrase inhibitors). Despite this increase in concentration, dosage adjustments are not necessary as this interaction has not amounted to adverse responses. Unboosted atazanavir (at 400mg once daily dose) is only recommended for treatment-naïve patients who are not receiving tenofovir or a proton pump inhibitor. For most other patients, boosted atazanavir regimen of 300mg/100mg ritonavir orally daily is recommended.

Atazanavir is better tolerated when compared to patients treated with lopinavir, fosamprenavir, and efavirenz with lower rates of dyslipidemia and virtually no effect on glucose or insulin sensitivity.⁴⁰ The most common side effect is an increase in indirect bilirubin, which occurred in approximately 40% of patients in clinical trials. Although this indirect hyperbilirubinemia has not been correlated with hepatotoxicity, some patients may be adverse to this cosmetic side effect usually manifested by sclera icterus. Only 5% of patients in clinical trials experienced jaundice. Post marketing surveillance reported cases of cholelithiasis⁴¹ and nephrolithiasis⁴² which may be increased with cumulative exposure and in the presence of ritonavir boosting. Ritonavir boosting may also increase the overall incidence of dyslipidemia. Rash was also reported in about 20% of patients, with a median onset of 7 weeks. A less common but serious adverse reaction reported with atazanavir include PR interval prolongation which was largely limited to first degree atrioventricular (AV) block, thus, atazanavir should be used with caution in patients with a pre-existing cardiac conduction abnormality, especially in patients who are on concomitant medications which may also have PR prolongation effects. Boosted atazanavir is a preferred PI regimen primarily due to the overall lower pill burden (2 pills), its high barrier to drug resistance, and virologic potency demonstrated in treatment naïve and experienced patients.

Darunavir

Darunavir is the most recently approved PI on the market. Unlike atazanavir and fosamprenavir, darunavir must be boosted with ritonavir in all patients. It undergoes rapid absorption after oral administration and its AUC is significantly increased by up to 14-fold in the presence of ritonavir. Darunavir should also ideally be administered with food as the AUC is increased by 30%. It is highly protein bound (95%) to α_1 -acid glycoprotein and is metabolized by CYP3A4. When used with ritonavir, it is a potent CYP3A4 inhibitor, thus the potential for significant drug interactions is high. Its elimination half-life is approximately 15 hours when boosted with ritonavir.

Darunavir was initially FDA approved for treatment-experienced patients only, at a dose of 600mg with ritonavir 100mg both given twice daily. It was later approved in treatment naïve-patients and treatment-experienced patients with no darunavir associated mutations as a once daily regimen of 800mg/ritonavir 100mg.⁴³ The most common GI side effects (nausea, vomiting, diarrhea) associated with darunavir are likely attributed to the ritonavir. Like fosamprenavir, darunavir also contains a sulfonamide moiety and should be prescribed cautiously in patients with a known sulfa allergy. The overall incidence of rash was similar among patients with and without a reported history of sulfonamide allergy. Rash occurred in 10% patients treated with darunavir and occurred within the first 4 weeks of therapy. Hepatotoxicity, namely acute hepatitis has also been associated with darunavir use in both clinical trials (0.5%) and in post marketing reports. It should be used with caution in patients with underlying liver dysfunction. Like other PIs, darunavir is also associated with metabolic complications, which include dyslipidemia and hyperglycemia; however, a smaller percentage of patients experienced these side effects compared to lopinavir/ritonavir in clinical trial.⁴⁴ It has the highest barrier to resistance of the available PIs-requiring multiple primary mutations. It has also demonstrated superior virologic efficacy compared to lopinavir/ritonavir.⁴⁴ Like atazanavir, boosted darunavir is a preferred PI due to its low pill burden and tolerability profile.⁸

Fosamprenavir

Fosamprenavir is the phosphorylated pro-drug of amprenavir. The oral bioavailability of amprenavir is greatly increased by approximately 63% when given as the pro-drug. It is highly bound to α_1 -acid glycoprotein and primarily metabolized in the liver via CYP3A4, with a high potential for significant drug interactions. Even though fosamprenavir is approved to be used without ritonavir, it has less optimal virologic response, thus, in general, ritonavir-boosting is recommended. When given with ritonavir, the fosamprenavir may be reduced from 1400mg twice daily to (fosamprenavir 1400mg plus ritonavir 100 or 200mg) both given once daily or (fosamprenavir 700mg plus ritonavir 100mg) both given twice daily.⁸

The most common side effects associated with fosamprenavir include rash, nausea, vomiting, and diarrhea; and metabolic abnormalities including hypertriglyceridemia. Amprenavir contains a sulfonamide moiety which may increase the risk of rash in some patients. The overall incidence of rash varied in clinical trials between those who had a previous sulfa allergy versus those who did not (12-33%) and most often occurred within the

first two weeks of therapy. The potential for cross reactivity to other sulfonamide drugs is unknown and should be used with caution. Fosamprenavir is less favored overall compared to other PI based regimens due to the higher pill burden, and modest virologic efficacy compared to other boosted PI regimens.⁸

Lopinavir

Lopinavir is the only PI which is co-formulated with the ritonavir. The current formulation of lopinavir is absorbed rapidly when given via oral administration and is not affected significantly by the presence or absence of food. When given with ritonavir, the AUC is increased significantly potentiating a potent anti-viral pharmacologic effect. It undergoes significant oxidative metabolism mediated by CYP3A4, and along with ritonavir, is a potent CYP3A4 inhibitor, thus has the potential for significant drug interactions.

The typical dose in treatment naïve and experienced patients is lopinavir 400mg/ritonavir 100mg twice daily or lopinavir 800mg/ritonavir 200mg once daily. When given in combination with potent CYP3A4 inducers such as efavirenz, nevirapine, and amprenavir- the dose should be increased to lopinavir 500mg/ritonavir 125mg twice daily. It should be noted that the once daily regimen should not be prescribed for pregnant women³³ and for treatment-experienced patients with evidence of 3 or more of certain lopinavir associated-mutations.⁴⁵

Common adverse effects of lopinavir/ritonavir include metabolic abnormalities such as hypercholesterolemia, hypertriglyceridemia, hyperglycemia, and insulin resistance. In comparison to other PI agents on the market, the incidence of hypercholesterolemia and hypertriglyceridemia occur at higher rates with lopinavir/ritonavir, up to 39% and 36%, respectively. Pancreatitis has also been observed primarily in patients with marked elevations in triglycerides. GI side effects are also common-primarily nausea and diarrhea and likely attributed to the 200mg of concomitant ritonavir. Post-marketing cases of complete atrioventricular blockade and cardiomyopathy primarily in neonates receiving lopinavir solution which contains approximately 42% v/v of ethanol and 15% w/v of propylene glycol have been reported.⁴⁵ Furthermore, post-marketing cases of hepatotoxicity, PR and QT prolongation, and torsades de pointes have been reported with the use of lopinavir/ritonavir. It should be avoided in patients with congenital and structural heart diseases. Because of the higher pill burden, need for 200mg of ritonavir, higher incidence of metabolic abnormalities, and lower tolerability rates when compared to the newer PI agents, lopinavir/ritonavir is no longer recommended as preferred PI.⁸

Saquinavir

Saquinavir was the first approved PI. Oral bioavailability of saquinavir is poor as it undergoes significant first pass metabolism but is increased with a high fat meal.⁴⁶ Saquinavir should be given with a meal and always boosted with ritonavir. Common adverse effects include gastrointestinal disorders, with nausea being the most commonly reported (10%). Saquinavir was shown to cause PR interval and QT prolongation in a dose dependent manner in a healthy volunteer study.^{46,47} Cases of torsades de pointes have been reported. Patients with structural heart disease, pre-existing conduction abnormalities, and ischemic

heart disease are at an increased risk of cardiac conduction abnormalities. Baseline electrocardiogram (ECG) is recommended prior to initiation of saquinavir. Saquinavir is contraindicated in patients with prolonged long QTc, refractory hypokalemia or hypomagnesemia, and complete AV block.⁴⁶ Saquinavir is generally otherwise well tolerated but its use has fallen largely out of favor due to its high daily pill burden, need for twice daily dosing, and the potential cardiac toxicities.

Tipranavir

Tipranavir at a dose of 500mg twice daily given with 200mg twice daily of ritonavir, is a salvage option for treatment-experienced patients with documented resistance to one or more PIs. This is a total daily pill burden of 8 pills. Tipranavir is the only PI which requires 400mg of ritonavir daily to boost its concentrations.⁴⁸ This is primarily due to its very low oral bioavailability. In pharmacokinetic studies, 400mg daily of ritonavir boosted tipranavir trough concentrations by 29-fold compared to unboosted tipranavir. It is highly protein bound (99%) to both albumin and α_1 -acid glycoprotein and metabolized via CYP450 via 3A4 (substrate) and 2D6 (potent inducer). Tipranavir is different from other PIs in that it also induces p-glycoprotein, a major drug transporter- which poses an additional risk for significant drug interactions. Coupled with the higher dose of ritonavir which also poses its own drug interaction profile-this combination produces unpredictable drug interactions and should be used with caution when given concomitantly with other drugs.

Tipranavir is also associated with rare but serious life threatening side effects. Cases of clinical hepatitis and fatal hepatic decompensation have been reported.⁴⁹ Therefore, extreme caution should be used in patients with hepatitis B or C co-infection. Furthermore, both fatal and non-fatal cases of intracranial hemorrhage have been reported with the use of tipranavir.⁴⁹ Caution should be taken when prescribing tipranavir to individuals with medical conditions which may predispose them to intracranial bleed. Gastrointestinal side effects include nausea, vomiting, diarrhea, and abdominal pain are common, most likely because of the higher dosage of ritonavir used. Rash was also reported in up to 18% of patients in clinical trials accompanied by joint pain, fever, and myalgia. Tipranavir should be discontinued in the event of severe skin rash. Tipranavir contains a sulfonamide moiety, therefore it should be used with caution in patients with a known sulfa allergy. Boosted tipranavir can be used in select patients-namely treatment experienced patients with documented PI resistance but with demonstrated susceptibility to tipranavir. However, the pill burden, tolerability and toxicity profile preclude its widespread use.

Integrase Inhibitors—Almost 2 decades after the introduction of then novel compounds such as PI and NNRTI, raltegravir was introduced to the US market as the first integrase strand transfer inhibitors (INSTIs) with a novel mechanism of action (see Figure 1 step 4). Integrase inhibitors block the integrase enzyme from catalyzing the formation of covalent bonds between the host and viral DNA, this in turn prevents the incorporation of viral DNA into the host chromosome. Currently there are three licensed INSTIs (raltegravir, elvitegravir, dolutegravir) on the US market, each with its own unique characteristics. INSTI is particularly potent and can rapidly decrease the HIV RNA.⁵⁰ INSTIs are generally well tolerated. An ART regimen consisting of an INSTI + 2NRTI is now recommended a

preferred regimen in treatment naïve patients.⁵¹ Amongst the INSTIs, only elvitegravir is primarily metabolized by the CYP3A4 system and has potential for interacting with other drugs using the same metabolic pathway. All the INSTIs may bind to polyvalent cations, thus has the potential of interaction with products such as antacids containing magnesium, aluminum, and calcium, separating the dosage administration by several hours can reduce this interaction potential.⁵²⁻⁵⁴ The description of the US FDA indications in HIV-1 infected adults and children, usual dose, formulations, daily pill burden, significant and/or common adverse effects, major drug interactions, primary resistance mutations, and special considerations are summarized in Table 6.

Dolutegravir

Dolutegravir is the most recently approved INSTI on the US market. It is recommended to be given at a dose of 50mg po once daily in both treatment naïve and experienced patients (who do not harbor certain integrase associated mutations).⁵² It may be given without regard to meals but its absorption is increased in the setting of a high fat meal (area under the curve increased by 61%). It is over 99% protein bound and primarily metabolized by UGT1A1 and minimally by CYP3A.

When given with drugs that are inducers of UGT1A and CYP3A including efavirenz, rifampin, boosted fosamprenavir and tipranavir, dolutegravir should be dosed at a higher dose of 50mg twice daily. The 50mg twice daily dose is also recommended in patients with suspected INSTI resistance or with 2 or more of certain INSTI-associated resistance mutations.⁵² Dolutegravir is active against some HIV-1 strains that are resistant to elvitegravir and raltegravir, and thus can be a viable option in patients with prior or current virologic failure with elvitegravir or raltegravir containing regimens.⁵⁵

Dolutegravir is generally well tolerated, with headache (2%) and insomnia (3%) being the most common adverse effects reported in clinical trials. Dolutegravir decreases tubular secretion of creatinine, leading to increase in serum creatinine concentration, without having an effect on glomerular filtration. This serum creatinine increase is often seen within the first 4 weeks of therapy. Dolutegravir has several unique advantages over the available INSTIs including the tolerability profile and virologic potency in both treatment naïve and experienced patients (including patients failing elvitegravir- or raltegravir-based regimens), and its low potential for drug interactions. Although it is the newest agent on the market with the least clinical experience, dolutegravir shows promise to be the preferred INSTI for some patients.

Elvitegravir

Elvitegravir is only available within the fixed dose combination INSTI + NRTI one pill once a day regimen-Stribild®. Stribild® contains elvitegravir 150mg, cobicistat 150mg, emtricitabine 200mg, and tenofovir 300mg. Elvitegravir is a substrate of CYP3A4 and requires pharmacokinetic enhancement to increase its systemic exposure. Cobicistat is a new CYP3A4 inhibitor without antiretroviral activity. The absorption of elvitegravir is increased with food. It is highly protein bound (99%) and is metabolized not only by CYP3A but also undergoes glucuronidation via UGT1A1/3.⁵³

The drug interaction profile of Stribild® is an important consideration when given with other medications primarily due to the various enzymes and drug transporters which mediate the metabolism of components of Stribild®. Elvitegravir is a substrate of CYP3A4 and UGT1A1/3. Cobicistat, being a potent inhibitor of CYP3A4, a moderate inhibitor of CYP2D6, and an inhibitor of multiple drug transporters including P-gp, BCRP, OATP1B1 and OATP1B3, increases the overall potential for drug interactions.

Toxicities associated with Stribild® include those observed with tenofovir therapy including decreased bone mineral density and renal tubular damage, as well as diarrhea, nausea, and headache. Cobicistat may falsely increase serum creatinine and decrease creatinine clearance by inhibiting the tubular secretion of creatinine. This increase largely occurs early in treatment and does not affect glomerular function. Stribild® should only be initiated in patients with an estimated creatinine clearance of 70mL per minute or higher and be promptly discontinued in those whose creatinine clearance falls below 50mL per minute while on therapy. Stribild® is currently recommended as a preferred option in treatment naïve patients.⁵¹ It is available as a one pill once a day regimen which is attractive from a medication adherence standpoint. It is relatively well tolerated; however its potential effects on renal function when given with other renally eliminated medications and the high likelihood for significant drug interactions are some limitations.

Raltegravir

Raltegravir is the first INSTI to be introduced to the market.⁵⁴ It was initially studied and approved for use in treatment-experienced patients at a dose of 400mg twice daily.⁵⁶ It was later studied and approved for use in treatment naïve patients at the same dose.⁵⁷ The lower potential for drug interactions is attributed to raltegravir being principally metabolized via glucuronidation mediated by UGT1A1, and not via the CYP enzyme system. Its concentrations may increase/decrease if given with concomitantly with potent inhibitors or inducers of UGT1A1, such as rifampin. It is excreted into both feces (51%) and urine (32%) as unchanged drug.

Raltegravir is well tolerated with the most common side effects reported being headache, nausea, and fatigue. There have been case reports of creatinine kinase (CK) elevations, rhabdomyolysis, and myopathy in post-marketing surveillance.^{50,58} The exact mechanism as to how this occurs is unknown. It is also unclear what predisposes patients to a higher risk of developing these toxicities including factors such as age, gender, duration of raltegravir therapy, or background regimen. Raltegravir should be used with caution in patients who are increased risk of rhabdomyolysis or myopathy.

Raltegravir is an attractive option in both treatment naïve and experienced patients due to its potency and low potential for side effects and drug interactions. With the advent of newer once daily integrase inhibitors, raltegravir, which requires twice daily dosing, may be less preferred in patients who prefer a once daily regimen. Raltegravir remains as a preferred INSTI due to the longer clinical trial and post marketing experience compared to that of newer generation INSTIs.⁵¹

CCR5 ANTAGONIST

Maraviroc is the only CCR5 antagonist approved for use in treatment naïve or treatment experienced patients with CCR5 using virus. It selectively binds to human CCR5 receptor on the cell membrane, thus blocking the interaction of the HIV gp120 and the CCR5 receptor for CCR5-tropic HIV. However, it does not block viral entry of CXCR4 tropic HIV or HIV that uses both CCR5 and CXCR4 for cell entry. Prior to the prescription of maraviroc, viral tropism testing must be performed to confirm that the patient's virus only uses the CCR5 co-receptor.^{8,59} As co-receptor usage may change over time of HIV infection, it should be performed as close to the initiation of maraviroc as possible. Tropism testing should also be done in patients who fail to achieve viral suppression while receiving a maraviroc-based regimen, to assess whether there is a switch from CCR5 using to CXCR4 or dual-mix virus. Maraviroc is a substrate of CYP3A4, but does not cause enzyme induction or inhibition. The usual dose is 300mg orally twice daily, but the dose has to be modified if it is used with a CYP3A4 inhibitor or inducer. Hepatotoxicity (sometimes as a manifestation of a hypersensitivity reaction), upper respiratory tract infections, and fever have been reported in the clinical trials. Orthostatic hypotension has been reported, especially in patients with renal impairment. Because of the need for obtaining an expensive tropism testing prior to initiation, the drug interaction potential and twice daily dosing, maraviroc is not commonly used in clinical practice.

FUSION INHIBITOR

The fusion inhibitor enfuvirtide interferes with this fusion process by binding to the first heptad-repeat (HR1) in the viral envelope glycoprotein gp41, thus preventing conformational changes necessary for the fusion of the viral and cellular membrane.⁶⁰ Because of its unique mechanism of action, there is no cross resistance with other antiretroviral drugs, thus most patients who have not received enfuvirtide have found virologic benefit when enfuvirtide is added as part of a salvage regimen in patients with multiple drug class resistance. Enfuvirtide is only available in an injectable formulation, and needs to be given as a subcutaneous injection twice daily. Almost all patients experience some degree of injection site reaction, manifested as pain, erythema, induration, nodules, ecchymoses. Due to the profound loss of subcutaneous fat in some HIV-infected patients, some have found it difficult to locate and rotate the injection sites. Hypersensitivity reactions have also been reported. An increase in incidence of pneumonia was observed in clinical trials in subjects who received enfuvirtide, although the mechanism of this association is not known. Because of the need of twice daily injection, enfuvirtide is generally reserved for patients with multiple drug resistance where at least two or three orally active agents cannot be used. (Table 7)

CONCLUSION

The advances in antiretroviral drug development have dramatically changed the face of HIV infection in worldwide – from a deadly disease to a manageable chronic condition. Currently available antiretroviral drugs have greater potency, tolerability, and less pill burden than earlier agents. Understanding the potency of the drugs and drug regimens, toxicity profile,

drug interaction potential and resistance potential will help the clinicians to select a regimen most suitable for a specific patient.

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Key Points (outline)

- To date, 28 antiretroviral drugs have been approved by the FDA
- Effective combination antiretroviral therapy can durably suppress HIV viremia and has dramatically improved HIV-associated morbidity and mortality
- For antiretroviral treatment-naïve patients, a combination regimen typically consists of 2 nucleoside reverse transcriptase inhibitors (NRTI) + a third drug
- Because of increased number of options, selection of an ART regimen can be individualized, based on efficacy, adverse effects, co-morbidity, dosing frequency, pill burden, potential for drug interactions or drug resistance.
- Success and durable combination require strict adherence to long term therapy.
- This article will review the clinical pharmacology of antiretroviral drugs commonly used in the United States.

Synopsis

The rapid advances in drug discovery and development of antiretroviral therapy in the history of modern medicine. Administration of chronic combination antiretroviral therapy targeting at different stages of the HIV replicative life cycle allows for durable and maximal suppression of plasma viremia. This has resulted in dramatic improvement of patient survival. This article will review the history of antiretroviral drug development and discuss the clinical pharmacology, efficacy, and toxicities of the antiretroviral agents most commonly used in clinical practice to date.

Figure 1. HIV Replicative Life Cycle

Cell Entry –The first step of cell entry is the attachment of the HIV envelope glycoprotein gp120 onto human chemokine receptors (CCR5 or CXCR4) on the CD4 cell surface. After the initial attachment, the next step requires fusion of the viral and cell membranes, allowing the viral proteins to enter into the cytoplasm.

Reverse Transcription – After cell entry as HIV is a retrovirus, the virus's RNA template transcribes into a double-stranded viral DNA in the presence of the enzyme reverse transcriptase.

Integration – The viral double-stranded DNA produced after reverse transcription is then transported into the cellular nucleus. In the presence of the integrase enzyme, a multi-step process allows the integration of viral DNA into host genome, and ultimately formation of proviruses.

Formation of Infectious Virions by HIV Proteases – After successful integration of viral DNA into the host genome and formation of proviral proteins, the next step of the HIV-1 life cycle is the cleavage of these polyproteins and formation of infectious virions. The viral enzyme protease is the key element for this process.

Table 1
A Short History of Advances in Antiretroviral Therapy 1987-2014

Years	Advances in Antiretroviral Therapy	Comments
1987-1993	Nucleoside reverse transcriptase inhibitor (NRTI) monotherapy (zidovudine or didanosine)	Improved patient survival, slow disease progression, but does not halt CD4 decline
1993-1996	Dual NRTI therapy	Greater viral suppression than monotherapy, slow disease progression, with greater toxicities
1994	Prevention of mother to child HIV transmission (PMTCT) – with zidovudine monotherapy	The PACTG 074 trial showed dramatic reduction of PMTCT when zidovudine was given orally during pregnancy, with IV zidovudine given during labor and delivery, and oral zidovudine given to newborn.
1996	Protease inhibitor (PI) + 2NRTI regimens - ,highly active antiretroviral therapy or HAART-	PI + 2 NRTI was the first regimen shown to suppress HIV RNA to below lower limit of detection, improved CD4 cell count, and survival
1998	Non-nucleoside reverse transcriptase inhibitor (NNRTI) + 2NRTI regimens	efavirenz + 2NRTI found to be as potent as contemporary PI-based regimens. NNRTI-based regimen became a new HAART regimen option
1998	3-NRTI regimen	Approval of abacavir led to the hope of PI-sparing regimens (abacavir/zidovudine/lamivudine) to reduce PI-associated toxicities. However, this regimen was found to be less potent than PI or NNRTI-based regimens
Late 1990's early 2000's	Ritonavir-boosted PI	Ritonavir commonly used as a pharmacokinetic enhancer (instead of an active HIV PI) to increase bioavailability of other PIs – to reduce pill burden and dosing frequency
2003-2008	Approval of 2nd generation antiretroviral agents of existing drug classes for drug resistant HIV – tenofovir, tipranavir, darunavir, and etravirine	Increase in multiple drug class resistant HIV led to need of newer agents – resulting in approval of newer generation drugs from existing drug classes
2003	First fusion inhibitor (enfuvirtide) approved for multi-drug resistant HIV	T-20 added to an optimized background regimen can significantly reduce HIV RNA in patients with multiple drug class resistance. Need for subcutaneous injection and resultant injection site reactions limit its use.
2006	Atripla™ - fixed dose formulation of efavirenz, tenofovir, and emtricitabine approved	First fixed dose combination, one pill once daily product approved – to reduce pill burden and improve adherence.
2007	First CCR5 antagonist (maraviroc) approved for multi-drug resistant HIV	Use of maraviroc is limited by the need of performance of viral tropism testing before treatment. Later approved for treatment naïve patients
2007	First integrase strand transfer inhibitor (INSTI) (raltegravir) approved for multi-drug resistant HIV	Can significantly reduce HIV RNA in patients with multiple drug class resistance. Later approved for treatment naïve patients.
2011	Antiretroviral use as prevention of transmission to uninfected partners	The HPTN 052 study, the HIV-infected partners of serodiscordant couples were randomized to antiretroviral therapy or no therapy. HIV transmission was significantly reduced when antiretroviral therapy was used
2012	Pre-exposure prophylaxis with tenofovir + emtricitabine	FDA approval of tenofovir/emtricitabine for continuous pre-exposure prophylaxis for HIV-negative individuals who are at high risk of acquiring HIV infection. This marks the first

Years	Advances in Antiretroviral Therapy	Comments
		time approval of antiretroviral therapy for HIV-uninfected persons.

Table 2
US FDA Approved Antiretroviral Agents (listed in chronological order by year of drug approval) and Their Targets in the HIV Life Cycle

Drug Class	CCR5 Antagonist	Fusion Inhibitor	NRTI	NNRTI	INSTI	PI
FDA Approved Drugs	Maraviroc	Enfuvirtide	Zidovudine Didanosine Zalcitabine Stavudine Lamivudine Abacavir Tenofovir Emtricitabine	Nevirapine Delavirdine Efavirenz Etravirine rilpivirine	Raltegravir Elvitegravir ¹ Dolutegravir	Saquinavir Indinavir Ritonavir Nelfinavir Amprenavir Lopinavir ² Fosamprenavir Atazanavir Tipranavir Darunavir

Abbreviations – NRTI = nucleos(t)ide reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, INSTI = integrase strand transfer inhibitor, PI = protease inhibitor

¹ only approved as a fixed dose combination product with cobicistat (a pharmacokinetic enhancer), tenofovir, and emtricitabine

² only approved as a fixed dose combination product with low dose ritonavir as a pharmacokinetic enhancer

Table 3

Characteristics of Selected Nucleos(t)ide Reverse Transcriptase Inhibitors

	Abacavir (Ziagen®)	Emtricitabine (Emtriva®)	Lamivudine (Epivir®)	Tenofovir Disoproxil Fumarate (Viread®)	Zidovudine (Retrovir®)
Abbreviation	ABC	FTC	3TC	TDF	ZDV (or AZT)
US FDA Approval Year	1999	2003	2003	2001	1987
US FDA Indication(s) for HIV-1 infected adults	ART naïve and ART experienced patients	<ol style="list-style-type: none"> ART naïve and ART experienced patients Pre-exposure prophylaxis (use with tenofovir) 	<ol style="list-style-type: none"> ART naïve and ART experienced patients Hepatitis B infection 	<ol style="list-style-type: none"> ART naïve and ART experienced patients Hepatitis B infection Pre-exposure prophylaxis (when used with emtricitabine) 	<ol style="list-style-type: none"> ART naïve and ART experienced patients Prevention of perinatal HIV transmission
Approval for HIV-1 infected children	3 months and older	Newborn and older	3 months and older	2 years and older	Newborn and older
Generic Formulation	Yes	No	Yes	No	Yes
Fixed Dose Combination Product marketed in the United States	Epizom® (+lamivudine) Trizivir® (+lamivudine + zidovudine)	Truvada® (+tenofovir) Atripla® (+efavirenz +tenofovir) Complera® (+rilpivirine +tenofovir) Stribild® (+elvitegravir +cobicistat +tenofovir)	Epizom® (+abacavir) Combivir® (+zidovudine) Trizivir® (+abacavir + zidovudine)	Truvada® (+emtricitabine) Atripla® (+efavirenz +emtricitabine) Complera® (+rilpivirine +emtricitabine) Stribild® (+elvitegravir + cobicistat + emtricitabine)	Combivir® (+lamivudine) Trizivir® (+abacavir + lamivudine)
Usual Dose (Adult)	600 mg PO once daily or 300mg PO twice daily	200mg PO once daily Oral solution: 240mg daily	300mg PO once daily or 150mg PO twice daily	300mg PO once daily	300mg PO twice daily
Adjust Dose in Renal Insufficiency	No	Yes	Yes	Yes	Yes
Formulations (as individual drugs)	Oral tablet: 300mg Oral solution: 20mg/mL	Oral capsule: 200mg Oral solution: 10mg/mL	Oral tablets: 150mg and 300mg Oral solution: 10mg/mL	Oral tablets: 150, 200, 250, and 300mg Oral powder: 40mg/g	Oral tablet and capsule: 500mg
Significant and/or common adverse effects	Hypersensitivity reaction (primarily in patients with HLA-B*5701 allele)—perform HLA-B*5701 testing before prescribing abacavir	Skin pigmentation	Generally well tolerated Rarely reported – peripheral neuropathy	Renal insufficiency (proximal renal tubulopathy, manifested as increase in serum creatinine, hypophosphatemia, glucosuria) Decrease in bone mineral density	Bone marrow suppression (macrocytic anemia, neutropenia) Nausea, vomiting, headache Nail pigmentation Lactic acidosis, hepatic steatosis Cardiomyopathy

	Abacavir (Ziagen®)	Emtricitabine (Emtriva®)	Lamivudine (EpiVir®)	Tenofovir Disoproxil Fumarate (Viread®)	Zidovudine (Retrovir®)
					Lipoatrophy Myopathy
CYP3A4 interaction	None	None	None	None	None
Primary resistance mutations ⁶¹	K65R, L74V, Y115F, M184V	K65R, M184V	K65R, M184V	K65R, K70E	M41L, D67N, K70R, L210W, T215Y/F, K219Q/E
Other considerations	HLA-B*5701 testing should be performed before initiating abacavir; In some studies, lower virologic responses reported with pre-ART viral load > 100,000 copies/mL Some observation studies reported an association of abacavir use and increased cardiovascular events	Symptomatic hepatic flare has been associated with initiation or discontinuation of emtricitabine in patients with hepatitis B co-infection	Symptomatic hepatic flare has been associated with initiation or discontinuation of lamivudine in patients with hepatitis B co-infection	Symptomatic hepatic flare has been associated with initiation or discontinuation of tenofovir in patients with hepatitis B co-infection	Mitochondrial toxicities (such as lactic acidosis, lipoatrophy, cardiomyopathy, myopathy) – generally associated with long term use

Table 4
Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors

	Rilpivirine (Edurant ®)	Etravirine (Intelence ®)	Efavirenz	Nevirapine
Abbreviation	RPV	ETR	EFV	NVP
US FDA Approval Year	2011	2008	1998	1996
US FDA Indication(s) for HIV-infected adults	Antiretroviral (ART) naïve patients	ART experienced patients	ART naïve and experienced patients	ART naïve and ART experienced patients. For ART naïve patients – only recommended for female with CD4 count <250 cells/mm ³ and for male with CD4 count < 400 cells/mm ³
US FDA Indication(s) for HIV-infected children	Not recommended for children	6 years or older	Infants 3 months or older	Recommended in all ages
Generic Formulation	No	No	No	Yes
Fixed Dose Combination Product marketed in the United States	Complera ® (+emtricitabine + tenofovir)	None	Atripla ® (+emtricitabine + tenofovir)	None
Usual Dose (Adult)	25mg po once daily (taken with a ~500 calorie meal)	200mg po twice daily	600mg po once daily (take on empty stomach, at bedtime)	200mg po once daily × 14 days, then 200mg po BID or 400mg (extended release) po once daily
Adjust Dose in Renal insufficiency	No	No	No	No
Formulations (as individual drugs)	Tablet: 25mg	Tablet: 25mg, 100mg, 200mg	Capsule: 50mg, 200mg Tablet: 600mg	Oral suspension: 50mg/5mL Tablet: 200mg Extended release tablet: 100mg, 400mg
Daily Pill Burden	1	2	1	1-2
Significant and/or common adverse effects	Rash Elevations in hepatic transaminases CNS disturbances: depression	Rash Elevations in hepatic transaminases	Rash Hepatotoxicity CNS disturbances: vivid dreams, hallucinations, depression, suicidality	Rash (more frequent and more severe than other NNRTIs) Hepatotoxicity (can lead to fulminant hepatic failure)
Major drug interactions ^a	Substrate of CYP3A4: cautionary use with drugs that are strong CYP3A4 inhibitors or inducers Should not be co-administered with proton pump inhibitors	Substrate of CYP3A4, 2C19, 2C9; cautionary use with drugs that are strong inhibitors or inducers of these enzymes Moderate inhibition of 2C19, 2C9, P-gp	Substrate of CYP3A4, 2B6: cautionary use with drugs that are strong CYP3A4 or 2B6 inhibitors or inducers Moderate induction of CYP3A4, 2B6; cautionary use	Substrate of CYP3A4: cautionary use with drugs that are strong CYP3A4 inhibitors or inducers Potential induction of CYP3A4, 2B6: cautionary use with drugs that are major substrates for 3A4, 2B6

	Rilpivirine (Edurant ®)	Etravirine (Intence ®)	Efavirenz	Nevirapine
		glycoprotein: cautionary use with drugs that are major 2C19, 2C9 substrates Weak inducer of CYP3A4; cautionary use with drugs that are major CYP3A4 substrates	with drugs that are major 3A4, 2B6 substrates	
Primary resistance mutations ⁶¹	K101E/P, E138K, V179L, Y181I/V, Y188L, H221Y, F227C, M230I/L	L100I, K101P, E138K, Y181C/I/V	L100I, K101P, K103N, V106M, V108L, Y181C/I, Y188L, G190S/A, P225H, M230L	L100I, K101P, K103N, V106M, V108L, Y181C/I, Y188L, G190A, M230L
Special Considerations	Should be avoided in patients with a baseline viral load of 100,000 copies/mL and CD4 count < 200 cells/mm ³	Not recommended to be used with ritonavir-boosted atazanavir, fosamprenavir, or tipranavir	Alternative agent should be used for women who desire to get pregnant or who are not using effective contraception	Higher rate and more serious cutaneous events (including Stevens-Johnson syndrome and toxic epidermal necrolysis), reported with nevirapine use than with other NNRTI

^a Please refer to <http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-ary-guidelines/32/drug-interactions> for a comprehensive list of drug-drug interactions

Table 5A

Characteristics of Selected Protease Inhibitors

	Atazanavir (Reyataz ®)	Darunavir (Prezista ®)	Fosamprenavir (Lexiva ®)
Abbreviation	ATV	DRV	FPV
US FDA Approval Year	2003	2006	2003
US FDA Indication(s) for HIV-1 infected adults	Antiretroviral (ART) naïve and ART experienced patients	ART naïve and ART experienced patients	ART naïve and ART experienced patients
US FDA Indication(s) for HIV-1 infected children	6 to 18 years of age	3 years and older	2 to 18 years of age
Generic Formulation	No	No	No
Usual Dose (Adult)	ART naïve: 300mg po daily + ritonavir 100mg po daily; or 400mg po daily	ART naïve: 800mg po daily + ritonavir 100mg po daily	ART naïve: 1400mg + ritonavir (100-200) mg po daily; or 700mg po BID + ritonavir 100mg po BID
Adjust Dose in renal dysfunction	ART experienced: 300mg po daily + ritonavir 100mg po daily	ART experienced: 600mg po BID + ritonavir 100mg po BID	ART experienced: 700mg po BID + ritonavir 100mg po BID
Formulations	No	No	No
Daily Pill Burden	Oral capsules: 150mg, 200mg, 300mg	Oral tablets: 75mg, 150mg, 600mg, 800mg Oral suspension: 100mg/ml (200ml) ^a	Oral tablets: 700mg Oral suspension: 50mg/mL (225mL)
Significant and/or common adverse effects	2 pills; once daily administration Increased indirect bilirubin* Jaundice* Cholelithiasis* Rash Nephrolithiasis* Dyslipidemia*, ^a PR interval prolongation *Higher incidence observed with boosted ATV	2-4 pills; once or twice daily administration depending on ART naïve or experienced Rash (contains sulfonamide moiety) Dyslipidemia ^a Elevation of hepatic transaminases	3-4 pills; once or twice daily administration depending on ART naïve or experienced Rash (contains sulfonamide moiety) Dyslipidemia ^a Hyperglycemia Headache Nausea Diarrhea
Major drug interactions ^b	Potent CYP3A4 inhibition: cautionary use with drugs that are major CYP3A4 substrates Substrate of CYP3A4: cautionary use with drugs that are strong CYP3A4 inhibitor or inducer Atazanavir requires acidic gastric pH for optimal absorption; may be used with acid suppressive agents including antacids, H2RAs, and PPIs in some circumstances,	Potent CYP3A4 inhibition: cautionary use with drugs that are major CYP3A4 substrates Substrate of CYP3A4: cautionary use with drugs that are strong CYP3A4 inhibitor or inducer	Potent CYP3A4 inhibition: cautionary use with drugs that are major CYP3A4 substrates Substrate of CYP3A4: cautionary use with drugs that are strong CYP3A4 inhibitor or inducer

	Atazanavir (Reyataz ®)	Darunavir (Prezista ®)	Fosamprenavir (Lexiva ®)
	and with dosage separation. Refer to product label for recommendations.		
Primary resistance mutations ⁶¹	150L (most common), I84V, N88S	I47V, I50V, I54M/L, L76V, I84V	I50V, I84V

^a Dyslipidemia is observed with all boosted protease inhibitors, particularly hypertriglyceridemia: Boosted LPV=FPV> boosted ATV>DRV

^b Please refer to <http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/32/drug-interactions> for a comprehensive list of drug-drug interactions.

Table 5B

Characteristics of Selected Protease Inhibitors

	Lopinavir/ritonavir (Kaletra ®)	Saquinavir (Invirase ®)	Tipranavir (Aptivus®)
Abbreviation	LPV/r	SQV	TPV
US FDA Approval Year	2000	1995	2005
US FDA Indication(s) for HIV-1 infected adults	ART naïve and ART experienced patients	ART naïve and ART experienced patients	ART experienced patients
US FDA Indication(s) for HIV-1 infected children	14 days and older	Not approved for children	2 years of age
Generic Formulation	No	No	No
Usual Dose (Adult)	<i>All patients:</i> 400mg/100mg po BID <i>Once daily dosing (only in patients with < 3 LPV-associated resistance mutations):</i> 800mg/200mg po daily	<i>All patients:</i> 1000mg po BID + ritonavir 100mg po BID	<i>All patients:</i> 500mg po BID + ritonavir 200mg po BID
Adjust dose in renal dysfunction	No	No	No
Formulations	Oral tablet: 100/25mg, 200mg/50mg Oral solution: 80mg/20mg per 1 mL (160mL)	Oral tablet and capsule: 500mg tablet 200mg capsule	Oral capsule: 250mg Oral solution: 100mg/mL
Daily Pill Burden	4 pills	6 pills	8 pills
Significant and/or common adverse effects	Rash Dyslipidemia ^a Diarrhea Elevations in transaminases Hyperglycemia/Insulin resistance Pancreatitis PR & QT interval prolongation	Nausea, vomiting Dyslipidemia ^a Hyperglycemia PR & QT interval prolongation	Rash (contains sulfonamide moiety) Hepatitis Intracranial hemorrhage Headache Diarrhea
Major drug interactions ^b	Mediated by mainly CYP3A4 via Potent inhibition: cautionary use with drugs that are major CYP3A4 substrates	Mediated by mainly CYP3A4 via Potent inhibition: cautionary use with drugs that are major CYP3A4 substrates Substrate of CYP3A4: cautionary use with drugs that will strongly inhibit or induce CYP3A4 metabolism	Substrate of CYP3A4
Primary resistance mutations (generally requires multiple mutations to confer resistance) ^{c1}	V32I, I47V/A, L76V, V82A/F/T/S	G48V, L90M	I47V, Q58E, T74P V82L/T, N83D, 84V

^a Dyslipidemia is observed with all boosted protease inhibitors, particularly hypertriglyceridemia (↑TG); Boosted LPV=FPV> boosted ATV>DRV

Please refer to <http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/32/drug-interactions> for a comprehensive list of drug-drug interactions.

Table 6

Characteristics of Integrase Strand Transfer Inhibitors

	Dolutegravir (Tivicay ®)	Elvitegravir	Raltegravir (Isentress ®)
Abbreviation	DTG	EVG	RAL
US FDA Approval Year	2013	2012	2007
US FDA Indication(s) for HIV-infected adults	antiretroviral (ART) naïve and experienced patients	ART naïve patients	ART naïve and experienced patients
US FDA Indication(s) for HIV-infected children	12 years of age and older	Not recommended for children	4 weeks and older
Generic Formulation	t,h="c"Na	No	No
Usual Dose (Adult)	50mg po once daily; or 50mg po twice daily for the following situations: <ul style="list-style-type: none"> - For INSTI-naïve patients given with potent UGT1A1/CYP3A4 inducers^a; or - For INSTI-experienced patients with certain INSTI mutations (see product label) or with clinically suspected INSTI resistance 	EVG only available in a co-formulated single tablet regimen with cobicistat/emtricitabine/tenofovir: STRIBILD ® One tablet once daily Not recommended for patients with creatinine clearance (CrCl) < 70 mL/min	400mg po BID
Adjust dose in renal dysfunction	No	Yes	No
Formulations	Oral tablet: 50mg	Single tablet: Elvitegravir 150mg/cobicistat 150mg/emtricitabine 200mg/tenofovir 300mg	Oral tablet: 400mg Chewable tablets: 25mg, 100mg
Daily Pill Burden	1 pill; once daily administration	1 pill; once daily administration (full regimen)	2 pills, twice daily administration
Significant and/or common adverse effects	Insomnia Headache	Nausea Diarrhea Renal impairment (due to cobicistat and tenofovir)	Rash Nausea Insomnia CPK elevations
Major drug interactions ^b	Mediated mainly by UGT1A1 and to a lesser extent CYP3A; dosage adjustments required when given concomitantly with UGT1A1/CYP3A ^a inducers ^a Inhibits tubular secretion of creatinine via inhibition of OCT2; use with dofetilide contraindicated; use metformin with caution Chelation: administration should be separated (2 hours) when giving DTG with polyvalent cations containing Mg,	Mediated mainly by CYP3A and UGT1A1/3 Potent CYP3A4 inhibition (by cobicistat); cautionary use with drugs that are major CYP3A4 substrates Chelation: administration should be separated (2 hours) when giving EVG with polyvalent cations containing Mg, Al, Fe, Ca	Mediated mainly by UGT1A1; cautionary use with drugs which induce UGT1A1 including rifamycins Chelation: administration should be avoided when giving RAL with polyvalent cations containing Mg, Al, Fe. Antacids containing calcium carbonate may be given without dosage adjustment

	Dolutegravir (Tivicay ®)	Elvitegravir	Raltegravir (Isentress ®)
	Al, Fe, Ca		
Primary resistance mutations ⁶¹	E138A/K, G140S, Q148	T66A/I, E92G/Q, S147G, Q148R, N155H	Y143 C/H/R, Q148H/K/R, N155H
Special Considerations		Should be discontinued in patients with a CrCl <50ml/min while on therapy	

^a efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin

^b Please refer to <http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/32/drug-interactions> for a comprehensive list of drug-drug interactions.

Table 7

Characteristics of CCR5 Antagonist and Fusion Inhibitor

	CCR5 Antagonist	Fusion Inhibitor
Drug Name	Maraviroc (Selzentry™)	Enfuvirtide (Fuzeon™)
Abbreviation	MVC	T-20
US FDA Approval Year	2007	2003
US FDA Indication(s) for HIV-1 infected adults	ART naïve and ART experienced patients – with <u>only</u> CCR5-tropic HIV	ART experienced patients with HIV replication despite ongoing antiretroviral therapy
Approval for HIV-1 infected children	Not approved for children	6 years and older
Generic Formulation	No	No
Usual Dose (Adult)	Usual Dose - 300 mg PO twice daily With potent CYP3A4 inhibitor: <ul style="list-style-type: none"> - 150 mg PO twice daily With potent CYP3A4 inducer: - 600 mg PO twice daily 	90 mg subcutaneously injection twice daily
Adjust Dose in Renal Insufficiency	Yes	Yes
Formulations (as individual drugs)	Oral tablet: 150mg , 300mg	Lyophilized powder for injection – 108 mg per vial
Significant and/or common adverse effects	Hepatotoxicity with hypersensitivity reactions, may be in conjunction with severe systemic symptoms such as fever, rash, eosinophilia. Postural hypotension – reported in patients with renal insufficiency	Local injection site reactions (pain, induration, erythema, nodule formation) Hypersensitivity reaction Increased rate of pneumonia in clinical trials
CYP3A4 interaction	CYP3A4 substrate, dosage adjustment needed in patients receiving potent CYP3A4 inhibitor or inducer	None
Special considerations	Viral tropism testing should be done prior to initiation of maraviroc, this can only be performed if HIV RNA is > 1,000 copies/mL. Maraviroc should not be used if patients with CXCR4 using HIV-1, or with dual/mixed receptor usage. Tropism DNA assay may be useful in patients with HIV RNA < 1,000 copies/mL.	