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Sunlenca® (lenacapavir): A First-in-Class Capsid Inhibitor Injected into the Market

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Human immunodeficiency virus (HIV) is a virus that attacks the body's immune system; if left untreated, it can progress to acquired immunodeficiency syndrome (AIDS).[1] An estimated 38 million people worldwide are currently living with HIV.[2] If left untreated, AIDS predisposes patients to several opportunistic infections or other serious illnesses which can reduce the life expectancy of approximately three years.[1]

The use of antiretroviral therapy (ART) for HIV has skyrocketed in the past decade. By 2021, approximately 29 million people living with HIV globally were receiving ART.[2] Antiretroviral therapies work by interfering with the life cycle of the human immunodeficiency virus. The stages of the HIV life cycle include: (1) attachment onto a CD4 or T cell, (2) fusion into the cell, (3) reverse transcriptase/conversion of its RNA into DNA, (4) integration of the viral DNA into the cell's DNA, (5) replication, (6) assembly into new viruses, and (7) budding off the host cell.[3] Each medication class is designed to target a specific step in this process; combination therapy is optimal to target multiple steps of the lifecycle and prevent the virus from multiplying.[3] Current ART options for HIV-1 infection in the United States include nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), entry inhibitors (fusion inhibitors, CCR5 antagonists), and integrase strand transfer inhibitors (InSTI).[4] The US Centers of Disease Control and Prevention (CDC) recommends that initial antiretroviral therapy includes a combination of two NRTIs and one of either an InSTI, NNRTI, or a boosted PI. Per CDC guidelines, patients should be treated with the goal of reducing the plasma viral load to <50 copies/mL. Resistance to these medications should be assessed at diagnosis through genetic testing and during the course of treatment, especially for those patients with suspected treatment failure.[4,5]

While the use of these therapies has reduced HIV treatment failure, drug resistance to ART has remained a common issue.[2,6] An estimated 2% of adults living with HIV who are on treatment are considered heavily treatment-experienced, having tried and failed at least two regimens of ART.[7] Patients who are treatment-experienced are unable to suppress viral load due to resistance or intolerance to current therapies, suboptimal adherence, or safety considerations. Multidrug-resistant HIV (MDR-HIV) is defined as HIV that contains mutations causing reduced susceptibility to antiretroviral drugs.[8] Patients with a drug-resistant virus will require a change in therapy if they fail to suppress the viral load after 24 weeks, which can be challenging and expensive for the patient. Up to 10% of adults starting HIV treatment have drug resistance to NNRTIs, a common drug class for HIV treatment. The rate of resistance can further increase while on treatment.[2] Of the current antiretrovirals on the market, PIs and INSTIs have the lowest rates of resistance among HIV drug therapies; medications from these classes will typically be used as a backbone in therapy for heavily treatment-experienced patients in combination with two or more other medication classes.[2,9] Due to the high resistance rates, new therapies for heavily treated HIV patients are being studied. Sunlenca® (lenacapavir) was approved on December 22nd, 2022 as a first-in-class capsid inhibitor indicated for the treatment of multi-drug resistant HIV-1 infection in heavily treatment-experienced adults.[10]

Mechanism of Action

Lenacapavir is a multistage, selective inhibitor of HIV-1 capsid function that directly binds between capsid protein (p24) subunits.[11,12] By binding to these subunits of the capsid protein, lenacapavir can interfere with multiple stages of the viral replication cycle, including nuclear uptake and transport of the viral complex, virus assembly and production, and capsid core formation when the virus is about to bud off the host cell.[11,12]

Pharmacokinetics

A summary of the pharmacokinetic properties of lenacapavir can be found in **Table 1**. Lenacapavir is a highly-protein-bound compound. Oral lenacapavir has a T_{max} of 4 hours and a half-life of 10-12 days, allowing it to be used as an initial loading dose prior to subcutaneous administration biannually.[11] Subcutaneous administration of lenacapavir has a much slower release, with a T_{max} of 77-84 days and a half-life from 8 to 12 weeks.[11]

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Table 1 | Table 1: Pharmacokinetic Properties of Lenacapavir[11]

	Oral Tablets	Subcutaneous Injection
Absorption		
T_{max}[a]	4 hours	77 to 84 days
Distribution		
Vd[b] (L)	19240	9500 to 11700
% Bound to plasma protein	>98.5	
Metabolism		
Metabolic pathways	CYP3A (minor) UGT1A1 (minor)	
Elimination		
$T_{1/2}$[c]	10 to 12 days	8 to 12 weeks
Major route of elimination	Unchanged into feces	

[a]Time to maximum plasma concentration, [b]Volume of distribution, [c]Half-life

Clinical Trials

The safety and efficacy of lenacapavir were evaluated in two major clinical trials prior to its approval in December 2022. The CAPELLA and CALIBRATE trials were designed to evaluate the antiviral activity and safety of lenacapavir compared to other antiretroviral agents.

CAPELLA (NCT04150068)

CAPELLA is a phase III trial evaluating the safety and efficacy of lenacapavir in combination with other antiretroviral agents in HIV-positive patients.[13] This was a randomized, open-label, active-controlled study conducted in patients with MDR-HIV who had received a stable failing drug therapy (HIV-1 RNA level of at least 400 copies per milliliter) for at least eight weeks with resistance to at least two ART regimens.

Cohort 1 included the first 36 patients who had a decrease of fewer than 0.5 $\log_{10}$ copies per milliliter between screening and cohort -selection visits and an HIV-1 RNA level of 400 copies or more per milliliter. Patients in this cohort after undergoing randomization received either oral lenacapavir (Cohort 1a) (600 mg on Days 1 and 2 and 300 mg on Day 8) or a matching placebo while continuing their failing therapy (Cohort 1b). Starting on Day 15, patients in group 1a received lenacapavir injections (927 mg in two 1.5 mL injections) with optimized background therapy, while patients in 1b received oral lenacapavir (600 mg on Days 15 and 16, and 300 mg on Day 22), followed by lenacapavir injections with optimized background therapy.

Cohort 2 included patients with a decrease of at least 0.5 $\log_{10}$ copies per milliliter between screening and cohort-selection visits, an HIV-1 RNA level of 400 copies or more per milliliter, or both. Patients that would have been eligible to participate in Cohort 1 after enrollment closure were also included. All cohort 2 patients received open-label oral lenacapavir (600 mg on Days 1 and 2 and 300 mg on Day 8) followed by lenacapavir injection. Optimized background therapy was initiated on Day 1 and patients began to receive subcutaneous lenacapavir every 6 months starting Day 15. Participants in Cohort 2 were not taking a failing ART regimen during the treatment study (in contrast to Cohort 1a). Cohort 2 was not included in the analysis for the primary outcome for the reduction of viral load; data was collected on its secondary outcomes and adverse effect profile.

Table 2 displays the results of the CAPELLA trial. The primary outcome that was evaluated was the percentage of patients who had a reduction from baseline of at least 0.5 $\log_{10}$ copies per milliliter in plasma HIV-1 RNA viral load by Day 15. Cohort 1a was directly compared to 1b; 87.5% of patients in 1a were found to have a reduction in viral load compared to 16.7% of patients in 1b (percentage difference between the two treatment groups 70.8, 95% CI 34.9-90, $p < 0.0001$).

Evaluations were also performed at the 26-week mark during the maintenance period. A viral load of less than 50 copies per milliliter was reported in 87.5% (95% CI 67.6-97.3, $p < 0.0001$) of patients in Cohort 1a and 66.7% (95% CI 34.9-90.1, $p < 0.0001$) of participants in 1b. A viral load of less than 200 copies per milliliter was detected in 95.8% (95% CI 78.9-99.9, $p < 0.0001$) of participants in 1a and 75.0% (95% CI 42.8-94.5, $p < 0.0001$) in 1b. The mean change in viral load was -2.58 ± 1.04

Table 2 | Summary of Primary Outcome of the CAPELLA Trial[13]

Treatment Arms	Primary Endpoint	Results (%)	Difference between Treatment Groups (%) (95% CI)	P-Value
LEN[a]/failing ARV[b]/OBR[c] (n=24)	Percentage of Participants in Cohort 1 Achieving a Reduction of ≥ 0.5 log10 Copies/mL in HIV-1 RNA at Day 15 (end of monotherapy period)	87.5	70.8 (34.9-90.0)	< 0.0001
Placebo LEN[a]/failing ARV[b]/OBR[c] (n=12)		16.7		
LEN[a]/OBR[c] (n=36)	*Primary Outcome not evaluated*	*Primary Outcome not evaluated*	*Primary Outcome not evaluated*	*Primary Outcome not evaluated*

[a]Lenacapavir therapy defined as oral lenacapavir 600 mg tablet on Days 1 and 2 and 300 mg tablet on Day 8 followed by subcutaneous lenacapavir 927 mg on Day 15 and at Week 26 or 28 (CAPELLA and CALIBRATE, respectively); [b]Failing antiretroviral regimen defined by lack of efficacy; [c]Optimized background regimen as individually prescribed

Table 3 | Summary of Primary Outcome of the CALIBRATE Trial[14]

Treatment Arms	Primary Endpoint	Results (%)	Difference between Treatment Group and Active Comparator (B/F/TAF) (%) (95% CI)	P-Value
LEN[a]/ F/TAF[b] / TAF[c] (n=54)	Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 54	90.4	-2.6 (-18.4 to 32)	0.7178
LEN[a]/ F/TAF[b] / BIC[d] (n=53)		84.9	-7.1 (-23.4 to 9.3)	0.3900
LEN[a] / F/TAF[b] (n=52)		84.6	-7.2 (-23.5 to 9.1)	0.3797
B/F/TAF[e] (n=25)		92.0	-	-

[a]Lenacapavir therapy defined as oral lenacapavir 600 mg tablet on Days 1 and 2 and 300 mg tablet on Day 8 followed by subcutaneous lenacapavir 927 mg on Day 15 and at Week 26 or 28 (CAPELLA and CALIBRATE, respectively); [b]Descovy® (emtricitabine/tenofovir alafenamide) 200/25mg; [c]tenofovir alafenamide 25mg; [d]bictegravir 75mg; [e]Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide) 50/200/25 mg

log10 copies per milliliter. In cohort 2, a viral load of less than 50 copies per milliliter was reported in 30 of 36 patients (83%) and a viral load of less than 200 copies per milliliter in 31 of 36 patients (86%). The mean change from baseline was −2.49±1.34 log10 copies per milliliter. Overall, the percentage of patients with a CD4+ count of less than 50 cells per cubic millimeter decreased from 24% to 0%. The authors concluded that the efficacy of lenacapavir was similar regardless of optimized background therapy or whether subjects had resistance to integrase inhibitors.[13]

CALIBRATE (NCT04143594)

At the time of this writing, lenacapavir is being further evaluated in the CALIBRATE study, an open-label, Phase II, active-controlled study of treatment-naïve patients with HIV.[14] Participants in the study were randomized and placed in one of four treatment groups. Patients in Group 1 and 2 received oral lenacapavir and emtricitabine/tenofovir/alafenamide (F/TAF), also known as Descovy®. On Day 15 of treatment, patients began receiving subcutaneous lenacapavir, and then every 26 weeks onward. Participants discontinued F/TAF at Week 28 and took only oral daily TAF (Group 1) or bictegravir (B) (Group 2) with subcutaneous lenacapavir injections. Group 3 received only oral lenacapavir and F/TAF throughout the study, while Group 4, the active comparator, received only B/F/TAF, also known as Biktarvy®.

A summary of the results from CALIBRATE is found in **Table 3**. The primary outcome was the percentage of participants with HIV-1 RNA less than 50 copies per mL at week 54. Between all four groups, percentages of participants who met this endpoint ranged from 84-92%; Group 1 had 90.4% suppression (difference in percentage from Group 4 –2.6, 95% CI –18.4-13.2, p-value of 0.7178), Group 2 achieved 84.9% suppression (difference in percentage from Group 4 –7.1, 95% CI –23.4-9.3, p-value of 0.3900), Group 3 achieved 84.6% suppression (difference in percentage from Group 4 –7.2, 95% CI –23.5-9.1, p-value of 0.3797), and the active comparator Group 4 achieved 92% suppression. Evaluations were performed at the 28-week mark; a secondary outcome was determined as a viral load of less than 50 copies per milliliter. All participants in the active comparator group, Group 4, achieved this suppression. Lenacapavir-based therapies in Groups 1-3 still lead to high rates of viral suppression, achieving load suppression in 92.5-94.2% of their participants.[14]

Adverse Effects, Drug Interactions and Precautions

The most commonly reported adverse effects associated with lenacapavir are injection-site reactions. These events include pain, swelling, erythema, and nodule formation. Most injection reactions were considered mild and of short duration by participants.[13,14] Other side effects include nausea, diarrhea, and headache. A summary of these reactions can be found in **Table 4.** Lenacapavir interacts with strong CYP3A inducers.[11] These medications can significantly decrease the plasma concentration of lenacapavir, which could result in ineffective treatment and potential treatment resistance. As a moderate inhibitor of CYP3A itself, lenacapavir can increase drug exposure of medications heavily metabolized by CYP3A.[11]

Currently, there is insufficient data on the use of lenacapavir in pregnancy and lactation, pediatric patients, and geriatric patients. Additionally, lenacapavir has not been studied in patients with end-stage renal disease (creatinine clearance less than 15 mL per minute) or severe hepatic impairment.[11,13,14]

Table 4 | Commonly Reported Adverse Effects[13,14]

Adverse Effect	Incidence Rate (%)
Injection Site Reactions	33 - 62
Nausea	11 - 12
Constipation	2 - 11
Diarrhea	7 - 11
Headache	8 - 13
Pyrexia	6 - 8
Fatigue	5 - 6

Dosage and Administration

Lenacapavir is currently available in two dosage forms: 300 mg tablets and 463.5 mg/1.5 mL injections in single-dose vials.[11] An initiation phase (of which there are two options) will be followed by once every 6-month maintenance dosing. A summary of the recommended dosing schedule can be found in **Table 5.** Tablets can be taken without regard to food. Lenacapavir injec-

tion is administered into the abdomen by a healthcare provider. During the maintenance period, if more than 28 weeks have elapsed since the last injection and it is clinically appropriate to continue treatment, the treatment must be restarted using either initiation phase option.[11]

Many antiretroviral therapies are associated with high costs for patients as most are not available as generic medications. Sunlenca® injections and tablets are expected to cost $42,250 in the first year of therapy, with injections costing $39,000 annually after.[15] Gilead, the manufacturing company for Sunlenca® has a program where eligible patients can be covered for up to $9600 in co-pays per year for Sunlenca®.[16]

Table 5 | Recommended Treatment Regimen for Sunlenca® Initiation and Maintenance[11]

Initiation Option 1	
Day 1	927 mg subcutaneous injection (2 x 1.5 mL injections) AND 600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Initiation Option 2	
Day 1	600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Day 8	300 mg orally (1 x 300 mg tablets)
Day 15	927 mg subcutaneous injection (2 x 1.5 mL injections)
Maintenance	
927 mg subcutaneous injection (2 x 1.5 mL injections) every 6 months (or 26 weeks) from the date of the last injection +/- 2 weeks.	

Clinical Implications

The CAPELLA trial was the major study used by the FDA to assess lenacapavir's safety and efficacy and bring it to market. Patients in this study were placed into two cohorts: participants in cohort 1 were randomized to receive either lenacapavir therapy or placebo (with their current treatment regimen) while all patients in cohort 2 received open-label lenacapavir.

In this study, patients were on individualized ART treatment which was called "optimized background therapy (OBT)". Each participant in the study was on a specific antiretroviral regimen based on their own personal history and resistance patterns/ mutations. While the CAPELLA trial found that patients saw similarities in reduction of viral load regardless of what OBT they were on, individualized treatment in the study could confound those results and limit the strength of this study. Different regimens in combination with lenacapavir therapy could be more or less effective in reducing viral load. However, the inclusion for optimized background therapy was ethically necessary in this study due to these patients having already failed treatment and the nature of MDR-HIV. The smaller patient sizes in both the CAPELLA and CALIBRATE trials (72 and 183, respectively) also limit the strength of these studies. Smaller sample sizes can limit both the external and internal validity of the trial.

Lenacapavir was shown in these trials that it is effective against HIV-1 infection in treatment-experienced patients; however, there was limited data on whether it was more effective than current agents on the market currently. In CAPELLA, lenacapavir was studied against placebo with participants' current failing regimens and optimized background regimens as a backbone. The active comparator group, Lenacapavir alone combined with a patient's OBT, was not evaluated for its reduction in HIV viral load. Neither CAPELLA nor CALIBRATE compared lenacapavir against placebo long-term with a standardized optimized regimen as the backbone. The CALIBRATE trial used Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide) as an active comparator but found no statistically significant difference in efficacy in treatment-naïve patients. More studies need to be conducted to show the benefit of lenacapavir compared to an active comparator in treatment-experienced patients.

Lenacapavir was well-tolerated in both studies. Common side effects patients reported were injection site reactions and less commonly nausea, diarrhea, and constipation. This favorable side effect profile may make lenacapavir a desirable option for patients who have severe gastrointestinal side effects while on the other failed ART regimens.

Four tablets of lenacapavir currently cost $3432. With the biannual injections, the price of Sunlenca® therapy is roughly $42,000. To compare, dolutegravir (Tivicay®), an integrase strand inhibitor used for MDR-HIV, has a cash price of $458 for a 30-tablet quantity. At the time of this writing, patients on federally funded insurance, such as Medicaid, are not eligible for the patient assistance programs sponsored by Gilead, which could severely limit the accessibility of this medication.[16] Sunlenca® is currently severely limited by its cost and will likely only be used as a last-line option for patients with multiple resistances to known ARTs.

On March 23, 2023, lenacapavir was added to Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.[17] It is recommended currently if there have been multiple treatment failures with extensive drug resistance to current therapies.[18] Longer-term data will need to be evaluated in the CAPELLA and CALIBRATE trials before it is more commonly used.

Lenacapavir is currently being studied as an option for pre-exposure prophylaxis (PrEP) in the PURPOSE 2 trial which could help expand the market for this therapy.[19] As resistance rates are rising among HIV-positive patients, new antiretrovirals such as lenacapavir can be used for patients who have tried and failed multiple treatment options. New mechanisms of action can be utilized to counter resistance mechanisms in HIV and lenacapavir, as a first-in-class capsid inhibitor, is a prime example of new treatment mechanisms for this patient population.

Conclusion

Sunlenca® (lenacapavir) is a first-in-class HIV capsid inhibitor approved by the FDA in December 2022 for the treatment of multidrug resistance HIV-1 infections in heavily treatment-experienced patients. While there is no current place for lenacapavir in HIV therapy due to its recent approval and high cost, patients who have failed traditional combination antiretroviral therapy and have known resistance could benefit from this new medication. Additional studies need to be done to assess the efficacy of lenacapavir compared to current therapies in treatment -resistant patients before its place in therapy can be determined.

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Prevention of HIV Transmission through Post Exposure Prophylaxis (PEP) and Pre-Exposure Prophylaxis (PrEP)

Christie Monahan, PharmD

According to the Centers for Disease Control (CDC), there is an estimated 1.2 million people in the United States living with human immunodeficiency virus (HIV), while only 87% of those knew their status.[1] Routine HIV testing and prophylactic measures to guard against infection, including barrier contraception methods, use of clean needles and medication therapy are advised for those at high risk of contracting HIV.[1] Those at highest risk include men who have sex with men (specifically those engaging in anal sex) and persons who inject drugs (though sharing of unclean needles). In addition, other factors may increase the risk of transmitting HIV including a high detectable viral load, co-infection with other sexually transmitted diseases (STDs), and co-occurring substance use.[1] Patients at risk of contracting HIV should be advised of prophylactic options and continued non-stigmatized discussion of repeat HIV testing to minimize risk of transmission.[1]

Multiple pharmacologic methods for prevention of transmission exist today, and center around the time of anticipated HIV exposure - either prior to or immediately after point of contact (Figure 1).[1]

Pre-exposure prophylaxis (PrEP) is defined by the National Institutes of Health Office of AIDS Research as a prevention method for people who are HIV negative, but at high risk of HIV infection.[2] This method involves taking a specific combination of medications daily and is most effective when combined with condoms and other prevention tools, such as limiting number of sexual partners and routine testing for HIV and STDs.[2] Current medication regimens available consist of both oral and injectable formulations (Table 1).[3]

Table 1 | Pre-Exposure Prophylaxis (PrEP) FDA-Approved Medications[4-6]

Brand Name	Components/Dosing	Indication for Use
Truvada® (oral)	Emtricitabine 200mg + Tenofovir disoproxil fumarate 300mg	Those at risk through sex or injection drug use
Descovy® (oral)	Emtricitabine 200mg + Tenofovir alafenamide 25mg	Those at risk through sex who are not assigned female at birth
Apretude® (injection)	Cabotegravir 600mg	Those at risk weighing at least 35 kilograms (77 pounds)

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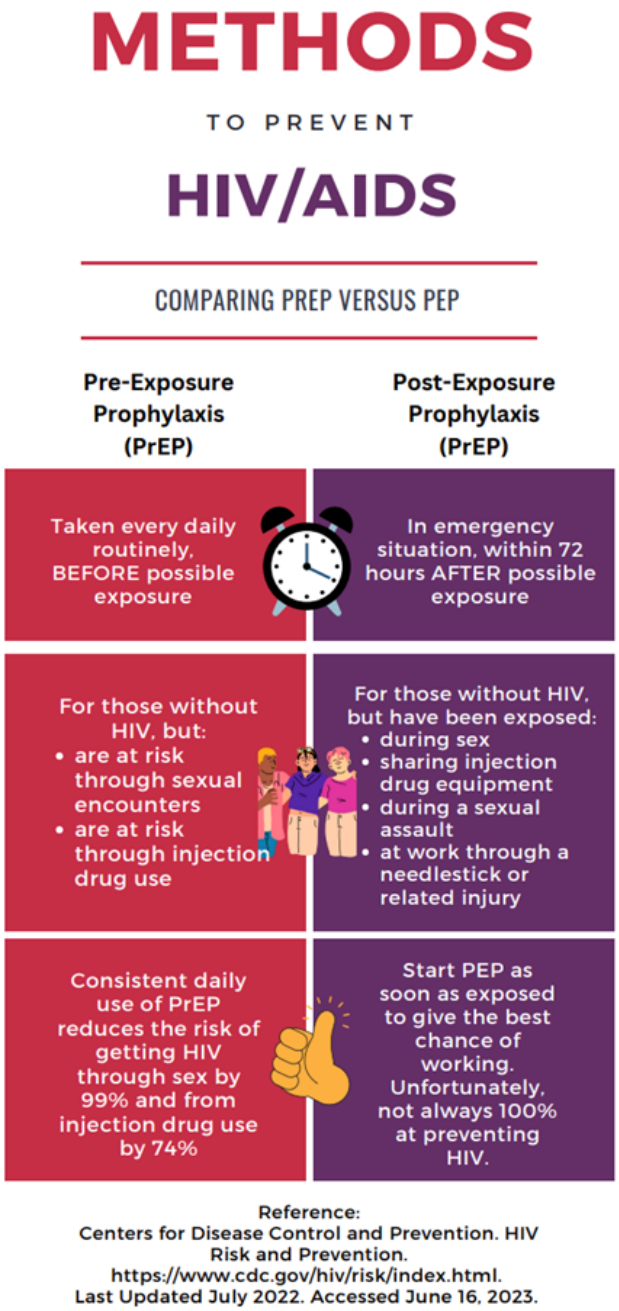
Truvada® (emtricitabine/tenofovir disoproxil fumarate) is FDA-approved for the prevention of HIV transmission through sex or injection drug use for all people at risk, whereas Descovy® (emtricitabine/tenofovir alafenamide) is approved for only those sexually active men and transgender women at risk of getting HIV.[3] Both oral medications consist of a once daily combination pill to be taken with or without food and should be stored in the original container.[4,5] For patients concerned about medication adherence, the FDA has approved the use of Apretude® (cabotegravir), an injection given in the providers office every 2 months instead of daily pills. Apretude® has only been approved for patients weighing over 77 pounds but can be used regardless of gender identification.[6] Patients should be screened for hepatitis B and HIV prior to starting any PrEP medication as a sudden stop in antiretroviral therapy may cause worsening of hepatitis B infection.[4-6] Routine lab monitoring for kidney, liver, and bone loss should be performed. Patients with plans to become pregnant, or with frequent changes to their medications should consult a physician prior to starting PrEP as many drug interactions occur with antiretroviral therapy.[4-6] In addition, patients using the injectable formulation of Apretude® should be advised to monitor for depressive symptoms as worsening of depression symptoms have been reported.[6] Providers are encouraged to use oral cabotegravir tablets for the first month prior to use of the long-acting injectable formulation to assess patient tolerability, but is not required.[6]

Patients should be advised of the need for routine HIV testing while on PrEP and reevaluation for continued need for therapy if risk of HIV becomes low due to life changes or inability to tolerate the medication.[1] PrEP can also be restarted following drug holiday if repeat HIV test prior to starting therapy is negative.[1] While PrEP is 99% effective at preventing the spread of HIV, patients should be counseled on the continued use of barrier contraception, need for daily administration, and routine monitoring for HIV infection and STDs.[1] Currently the US Food and Drug Administration (FDA) and CDC do not recommend PrEP on-demand use immediately prior to anticipated exposure.[1]

While these medications are highly effective when used

Figure 1 | Methods to Prevent HIV/AIDS



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appropriately, patients may experience a barrier to care secondary to cost. Several national organizations exist, such as The Ryan White Foundation®, and manufacturer patient assistance programs to make drug costs affordable or covered free-of-charge for eligible patients.[7-10] The CDC has a helpful figure to help navigate the financial aspects of PrEP (https://www.cdc.gov/stophivtogether/library/hiv-prevention-resources/fact-sheets/cdc-lsht-factsheet-paying-for-prep.pdf).[9] All patients should be able to receive PrEP, regardless of ability to pay, to prevent the spread of HIV within the community.

In contrast to PrEP, post-exposure prophylaxis (PEP) is a short-term treatment that should be started as soon as possible, but no

Table 2 | Preferred antiretroviral medication 28-day regimens for PEP[13]

Age Group	Medication	Total Number of Medications
Age ≥ 13 years with creatinine clearance ≥ 60 mL/min	tenofovir DF 300 mg + fixed dose combination (emtricitabine 200 mg once daily with raltegravir 400 mg twice daily ***or*** dolutegravir 50 mg once daily)	3
Age ≥ 13 years with creatinine clearance ≤59 mL/min	zidovudine* + lamivudine* + raltegravir 400 mg twice daily ***or*** dolutegravir 50 mg once daily	
Children aged 2–12 years	tenofovir DF[f] + emtricitabine[f] + raltegravir[f]	
Children aged 4 weeks–< 2 years	zidovudine oral solution + lamivudine oral solution + raltegravir[f] ***or*** lopinavir/ritonavirb[f] oral solution	
Birth–27 days old	Consult pediatric HIV specialist	

*dose adjusted to degree of renal function; [f]drug dose adjusted to age and weight

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later than 72 hours, after high-risk exposure to an infectious sources.[11] The purpose of PEP use is to reduce the risk of infection development post-exposure, but unfortunately is not 100% effective and should only be used in emergency situations.[12] Emergency situations warranting use includes unprotected sex with infected partner, use of shared needles or equipment to inject drugs, or possible workplace exposure through needlestick injury.[12] Time to medication use is most important with PEP and should be started within 72 hours to reduce likelihood of disease transmission.

Currently there are many options for use of PEP on the market with most consisting of multi-drug regimens to provide broad antiviral coverage in the setting of unknown exposure risk. Each medication regimen should be taken for 28 days following possible exposure with routine testing for HIV at the 4-6 week and 3-month mark to ensure medication efficacy.[12] Type of medication selection is dependent on patient-specific, including age and kidney function (Table 2).[13] Workplace procedures may differ from guideline recommendations dependent on type of exposure and clinic policy, but advised to contact immediate supervisor urgently if concerned about possible transmission. In addition to a wide range of medications available, patients should be counseled on medication side effects and a drug interaction assessment performed prior to starting PEP due to known drug-drug interactions with antiretroviral medications.[13]

For patient engaging in behaviors that result in frequent repeated use of PEP, guidelines recommend transitioning patients to PrEP at the conclusion of the 28-day PEP course to provide better antiretroviral coverage consistently.[13] Currently no evidence exists to support a gap in PEP and PrEP therapy, routine monitoring for change in HIV status is recommended.[13] In addition, if patients are on current PrEP therapy, with daily medication adherence and practicing mitigation of risk factors, no use of PEP is indicated.[13] If patients are taking PrEP sporadically or have missed doses within the week prior to possible exposure, PEP may indicated for 28 days, then resumption of previous PrEP therapy thereafter.[13] Healthcare providers are encouraged to contact the PrEPline 855-448-7737 at the National Clinician Consultation Center or go to their website at http://nccc.ucsf.edu/clinician-consultation/prep-pre-exposure-prophylaxis/ for questions regarding PrEP/PEP medication use and risk of transmission.[13]

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Over-the-Counter

At Home HIV Tests

Angelina Vascimini, PharmD, BCACP

Over the last few years, during the COVID-19 pandemic, patients have become accustomed to use of at-home tests. Given the increase in at-home tests for COVID-19, patients may desire testing for other diseases or infections at home. Aside from patient interest, the US Department of Health and Human Services (HHS) has created an initiative titled *Ending the HIV Epidemic in the U.S. (EHE) by 2030*.[1] The EHE initiative has two major goals: Reduce incidence of new HIV infections in the US and increase knowledge of HIV status. In order to increase knowledge of HIV status and to help prevent the spread, providers and patients may turn to home HIV testing.[2]

What at home HIV tests are available?

There are two major types of at home HIV tests: a rapid self-test versus a self-collection test. A rapid self-test is completed within the patient's home and results are available within 15-20 minutes from the completion of the test.[2,3] A self-collection test or mail-in test is when a patient collects the sample and sends it to a company for further analysis of the results.[3] Results can take anywhere from 2 to 5 days depending upon the test used.[2-4] In addition, it is important to note that the OraQuick at home HIV test is the only FDA approved at home HIV test.[8] Other available tests are completed within a CLIA certified lab but have not submitted testing to the FDA for approval.[4] More information about these types of tests can be found in Table 1.

Table 1 | Types and Availability of at Home HIV Tests[(2–4)]

	Rapid Self-Test	Self-Collection/ Mail-In Test
Who can order	Patient	Patient
Testing Location	Entirely at home	Sample collect at home and sent to a lab
Result Timing	15-20 minutes	2-5 days
Available at pharmacy?	Yes	No
Cost	Low (Sometimes free from local health department)	High
Tests Available	OraQuick – available OTC at most community pharmacies	Testing.com Everlywell LetsGetChecked MyLAB Box

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When should a patient use an at home HIV test?

According to the US Centers for Disease Control and Prevention (CDC), patients should be screened for HIV at least once in their lifetime if they are between the age of 13-64.[2] In addition, patients at an increased risk of HIV should be tested more frequently, with recommendations for at least once a year.[3,5] Patients are considered to be at an increased risk if they fall into one of the following categories: men who have sex with men, injectable drug users or use of shared needles/syringes with others, and have had sex with someone with a known HIV diagnosis etc.[3,5] The testing

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window will vary depending upon the type of test completed. At home HIV self-tests are typically antibody tests and can detect an HIV infection from 23-90 days after exposure.[6] A self-collection or mail-in test is usually a rapid antigen/antibody test and can detect HIV infection from 18-90 days after exposure.

What should a patient do if their at home test is positive?

For patients that test positive with either a self-test or self-collection/main-in test should make an appointment with their primary care physician for additional testing.[7,8] It is important to note that positive result from an at home HIV test does not confirm a diagnosis of HIV. Confirmatory blood work will need to be obtained prior to physician diagnosis. This is because the at home HIV tests have the potential to produce a false positive test. The OraQuick at home HIV test has a 0.02% chance of resulting in a false positive (1 out of 5000 tests).[8]

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ADMINISTRATION ADVICE

Tips and Tricks for HIV Medication Administration

Angelina Vascimini, PharmD, BCACP

The first reported case of Human Immunodeficiency Virus (HIV) was in 1981.[1] Over the last forty years there have been large research advancements not only in the pathophysiology, diagnosis, and clinical presentation of HIV but also in medications used for treatment. Due these advancements, patients with HIV have an improvement in quality and length of life, with the life expectancy for patients with HIV similar to those patients without.[2] One of the main goals for HIV treatment is to reduce a patient's viral load so that it is undetectable.[3] The best way to do this is to initiate and remain adherent to Antiretroviral Therapy (ART). [3]

Prior to selecting ART for patients, providers will need to assess adherence barriers for patients. For example: the use of a single tablet regimen versus multi-tablet regimen, drug interactions with other medications a patient is currently taking, side effects, which medications need to be taken in conjunction with food, and which medications need to be kept in their original container versus a pill box. The following tables can be utilized by providers when selecting ART.

Table 1 | Common Drug Interactions[4–11]

Drug Interaction	Mechanism of Interaction	HIV Medications Potentially Effected
Acid Reducing Agents Proton Pump Inhibitors H2 Antagonists Antacids	These medications can increase the pH within the stomach, reducing absorption of ART that requires an acidic environment for absorption	Atazanavir Rilpivirine Fosamprenavir Tipranavir Delavirdine
Agents with polyvalent cations Iron products Antacids	These medications can bind to integrase strand transfer inhibitors (INSTIs) cause an overall decrease in absorption	INSTIs – "tegravir" Bictegravir Cabotegravir Dolutegravir Elvitegravir Raltegravir
HMG-CoA Reductase Inhibitors Atorvastatin Fluvastatin Lovastatin Pravastatin Rosuvastatin Simvastatin	Lipophilic statins such as simvastatin and lovastatin are CYP3A4 substrates. Hydrophilic statins such as pravastatin and rosuvastatin are not affected by CYP enzyme metabolism.	Avoid lipophilic statin use with protease inhibitors ("navir) Atazanavir Darunavir Lopinavir Nelfinavir Ritonavir
CYP3A4 Inducers Carbamazepine Phenytoin Rifampin Saint John's wort Nevirapine Etravirine Efavirenz	A CYP3A4 inducer will decrease the AUC of a CYP3A4 substrate	CYP3A4 Substrates NNRTI (Efavirenz, Rilpivirine, Neviraine,, Eravirine) Methadone Protease Inhibitors ("navir) (Atazanavir, Darunavir,, Nelfinavir, Ritonavir) Maraviroc Warfarin
CYP3A4 Inhibitors Clarithromycin Cobicistat Protease Inhibitors Ketoconazole Efavirenz	A CYP3A4 inhibitor will increase the AUC of a CYP3A4 substrate	
CYP2C9 Inducers Rifampin Carbamazepine Ritonavir	A CYP2C9 inducer will decrease the AUC of a CYP2C9 substrate	CYP2C9 Substrates Etravirine Warfarin
CYP2C9 Inhibitors Amiodarone Fluconazole Efavirenz Etravirine	A CYP2C9 inhibitor will increase the AUC of a CYP2C9 substrate	
UGT 1A1 Enzyme Inducers/Inhibitors Anticonvulsants	Many medications used to treat HIV are metabolized by or effect UGT 1A1 and can cause an increase or decrease in absorption	INSTIs – "tegravir" Bictegravir Cabotegravir Dolutegravir Elvitegravir Raltegravir

The University of Liverpool has a HIV Drug Interaction Checker that can be used for additional information: https://www.hiv-druginteractions.org

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Table 2 | General Side Effects by Class of HIV Medications[12]

HIV Drug Class	General Side Effects (not all inclusive)
Capsid Inhibitor	Headache, nausea, diarrhea
CCR5 Antagonists	Rash, abdominal pain
Fusion Inhibitors	Rash, injection site reactions
INSTIs	Insomnia, depression, and suicidality (typically for patients with PMH of psychiatric conditions), rash
NNRTIs	Decrease bone mineral density, rash, lipohypertrophy, weight gain
NRITs	Lactic acidosis, weight gain, headache
PIs	Nausea, vomiting, diarrhea, hyperlipidemia, hyperglycemia, lipohypertrophy, weight gain
Post Attachment Inhibitor	Rash, diarrhea, nausea

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Table 3 | HIV Combination Pills and Food Intake[13,14]

HIV Medication	Food Consideration
Atripla® (efavirenz/emtricitabine/tenofovir)	Take on an empty stomach
Biktarvy® (bictegravir/emtricitabine/tenofovir)	Take with or without food
Cabenuva ®(cabotegravir/rilpivirine)	Take with or without food
Cimduo® (tenofovir/lamivudine)	Take with or without food
Complera® (emtricitabine/rilpivirine/tenofovir)	Take with food
Delstrigo® (doravirine/lamivudine/tenofovir)	Take with or without food
Descovy® (emtricitabine/tenofovir)	Take with or without food
Dovato® (dolutegravir/lamivudine)	Take with or without food
Epzicom® (abacavir/lamivudine)	Take with or without food
Genvoya® (elvitegravir/cobicistat/emtricitabine/tenofovir)	Take with food
Juluca® (dolutegravir/rilpivirine)	Take with food
Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir)	Take with food
Symfi® (efavirenz/lamivudine/tenofovir)	Take on an empty stomach
Symfi Lo® (efavirenz/lamivudine/tenofovir)	Take on an empty stomach
Symtuza® (darunavir/cobicistat/emtricitabine/tenofovir)	Take with food
Triumeq® (abacavir/dolutegravir/lamivudine)	Take with or without food
Truvada® (emtricitabine/tenefovir)	Take with or without food

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Strategies to Improve Adherence

Once ART is initiated for a patient it is vital to ensure the patient remains adherent to this regimen in order to reach treatment goals, as well as to prevent treatment failure and develop resistance to ART.[15] See Figure 1 for some adherence strategies.

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Figure 1 | Adherence Strategies

Evaluate patient's understanding [16]

- When patients understand the importance of taking their medications and understand "the why" they are more likely to be adherent to their medication regimen[17]
- Use the "teachback method" when counseling patients on how to take their medications[17]

Lightbulb Idea – search "idea". *PowerPoint*, *Microsoft Office Professional Plus*, version 16.0.10401.20025, Microsoft, 2019.

Follow Up

- After initially prescribing ART, healthcare providers should follow up with the patient to ensure that the medication prescribed is affordable and at each office visit, affordability should be assessed[16]
- Patients should have frequent follow up with their healthcare providers and adherence should be assessed at every clinic visit [16]
- At each follow up appointment, patients should be asked about potential side effects and evaluate if they are currently experiencing any[15,16]
- A large portion of patients with HIV also suffer from depression and this may affect adherence to ART. Assess patients for depression and treat when appropriate.[15,16]

Calendar – search "calendar". *PowerPoint*, *Microsoft Office Professional Plus*, version 16.0.10401.20025, Microsoft, 2019.

Couple medication administration with daily activities [18]

- Review with patients their daily routine and help identify tasks or activities that are done everyday; counsel patients to couple these daily activities with medication administration to help reduce forgotten doses.

Toothbrush—search "toothbrush". *PowerPoint*, *Microsoft Office Professional Plus*, version 16.0.10401.20025, Microsoft, 2019.

Pill box [18]

- Sometimes patients find it helpful to use a pillbox to keep track of their medications and to help remember doses. However, there are some ART regimens that need to remain in the container they are dispensed in. If patients would like to use a pill box, have the patient reach out to their local pharmacist to ensure it is safe to keep their medication inside a pillbox instead of the dispensed container.

Pill Bottle—search "pill". *PowerPoint*, *Microsoft Office Professional Plus*, version 16.0.10401.20025, Microsoft, 2019.

Alerts/reminders on phone [18]

- Patients may set alarms or reminders on their smart phones or other devices at the time they are suppose to take their medication

Alarm—search "alarm clock". *PowerPoint*, *Microsoft Office Professional Plus*, version 16.0.10401.20025, Microsoft, 2019.

Support system [18]

- A support system may consistent of healthcare providers, friends, family and/or support groups. [16]
- Rapport built between healthcare providers and patients may be vital if the patient is experiencing adherence barriers and needs help resolving those barriers
- Family and friends may be able to provide assistance with reminding to take medications when prescribed and assisting in other ways.

Family of Four—search "family". *PowerPoint*, *Microsoft Office Professional Plus*, version 16.0.10401.20025, Microsoft, 2019.

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Personalized Medicine Corner

CYP2B6 Genotype-Guided Efavirenz Dosing to Reduce the Risk of CNS Adverse Effects

Madeline Norris, PharmD

Background

Efavirenz is a first-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) commonly used for the treatment of human immunodeficiency virus type 1 (HIV-1) infections (**Figure 1**). For many years, efavirenz-based regimens were considered to be the cornerstone of HIV-1 treatment. This is largely due to its desirable efficacy profile, availability as a generic formulation, and the availability of combination pills with other antiretrovirals allowing for the first one pill once daily dosing regimen. In 2015, the United States Department of Health and Human Services downgraded efavirenz-based regimens from "recommended" to "alternative" options in their guidelines for antiretroviral therapy for adults and adolescents with HIV-1.[1] This change in classification was largely due to the discovery of integrase strand transfer inhibitors (INSTI), as well as an undesirable tolerance profile.

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Efavirenz is often associated with adverse effects including those involving the central nervous system (CNS). The incidence of neuropsychiatric adverse effects (e.g., abnormal dreams, dizziness, anxiety, depression) in patients taking efavirenz has been reported to be upwards of 50%.[2] Despite its unfavorable adverse effect profile, efavirenz is still a commonly used medication in many parts of the world. In fact, the World Health Organization describes efavirenz as a "safe and effective alternative for women of childbearing potential desiring pregnancy".[3]

Efavirenz is primarily metabolized in hepatocytes by the cytochrome P450 2B6 (CYP2B6) isoenzyme into inactive metabolites (**Figure 1**). CYP2B6 is considered to be highly polymorphic with 49 named allele variants.[4] Decreased or no function variants of CYP2B6 impact the metabolism of CYP2B6 substrates, including efavirenz. One single nucleotide polymorphism (SNP) at position 516 of CYP2B6 (516G>T) is associated with decreased enzyme activity and is identified in many decreased function variants, most commonly the *6 allele. Patients who carry at least one decreased or no function CYP2B6 allele are shown to have decreased efavirenz clearance compared to CYP2B6 normal metabolizers and may be at an increased risk of CNS-related adverse effects (**Figure 2**). One study showed that a dose reduction to 400 mg/day or 200 mg/day in 516G>T carriers taking efavirenz 600 mg/day who had supratherapeutic plasma levels (> 4 µg/mL) and adverse effects improved adverse effects in all included patients. This dose reduction did not result in subtherapeutic efavirenz plasma levels in any patient.[5] The Clinical Pharmacogenetics Implementation Consortium (CPIC) have published guidelines available to help guide safe and effective efavirenz dosing in patients with CYP2B6 genotype results available.[6]

Interpretation of pharmacogenetic results

Individuals with two normal function alleles (e.g., CYP2B6*1/*1) have a CYP2B6 normal metabolizer phenotype. The presence of one normal function allele and one decreased or no function variant allele (e.g., CYP2B6*1/*6, CYP2B6*1/*18) results in a CYP2B6 intermediate metabolizer phenotype. Individuals who carry two decreased function (e.g., CYP2B6*6/*6) or two no function (e.g., CYP2B6*18/*18) alleles have a CYP2B6 poor metabolizer phenotype. On the other end of the spectrum, individuals with one (e.g., CYP2B6*1/*4) or two (e.g., CYP2B6*4/*4) increased function alleles have a CYP2B6 rapid and ultrarapid metabolizer phenotype, respectively.[6]

Therapeutic Recommendations

The Clinical Pharmacogenetics Implementation Consortium (CPIC) published updated efavirenz pharmacogenetic guidelines in 2019.[6]

For patients who have CYP2B6 normal, rapid, or ultrarapid metabolizer phenotype it is appropriate to use the standard efavirenz dose (600 mg/day). The increase in CYP2B6 enzyme activity in rapid and ultrarapid metabolizers appears to be minimal.[7] There is currently no substantial evidence that increased function alleles (e.g., *4, *22) result in a decrease in antiretroviral efficacy. Those who have a CYP2B6 intermediate metabolizer phenotype should consider a lower starting dose of efavirenz 400 mg/day. A lower dose of efavirenz 400 mg/day was shown to be noninferior to the standard dose of 600 mg/day when used in combination with emtricitabine and tenofovir in treatment naïve patients regardless of genotype.[8] Due to its potential to decrease the incidence of adverse effects, while not decreasing the efficacy of efavirenz, it is reasonable to reduce the daily dose in CYP2B6 intermediate metabolizer in addition to CYP2B6 poor metabolizers. A lower starting dose of 200 mg/day to 400 mg/day should be considered in patients who have a CYP2B6 poor metabolizer phenotype. If therapeutic drug monitoring is available, intermediate and poor metabolizers should be monitored to ensure reduced doses achieve an efavirenz steady state plasma concentration within the recommended therapeutic range (1-4 µg/mL).

Enzyme inducers (e.g., carbamazepine, phenytoin) are thought to significantly decrease efavirenz plasma concentrations.[9] Although co-administration of enzyme inducers with efavirenz is generally not recommended, it may be unavoidable in some patients. In these cases, careful consideration and therapeutic drug monitoring should be used when evaluating the appropriateness of efavirenz dose reductions.

Patient Case

AM is a 32 yo Caucasian female with a PMH significant for generalized anxiety, MDD, and HIV-1. Her doctor would like to start the antiretroviral medication Atripla (efavirenz 600 mg; emtricitabine 200 mg; tenofovir disoproxil fumarate 300 mg). Before starting Atripla, AM mentions she previously received panel-based pharmacogenetic testing to help guide selection of an antidepressant. She is curious if any of the genes from her testing may be relevant to her new medications.

Her pharmacogenetic test results include the following:
CYP2B6 genotype: *6/*6
CYP2B6 phenotype: Poor metabolizer (!)

AM's pharmacogenetic results indicate that she has decreased CYP2B6 enzyme activity. Her specific genotype is associated with decreased efavirenz oral clearance and plasma concentrations above the recommended therapeutic range of 1-4 µg/mL.[6,10] This increase in efavirenz plasma concentrations may subsequently put AM at an increased risk of CNS-related adverse effects.

Recommendation

Consider switching to Symfi Lo (efavirenz 400 mg, lamivudine 300 mg, and tenofovir disoproxil fumarate 300 mg). This would decrease AM's risk of efavirenz related adverse effects, while not increasing her pill burden as it is also a one pill once daily regimen.

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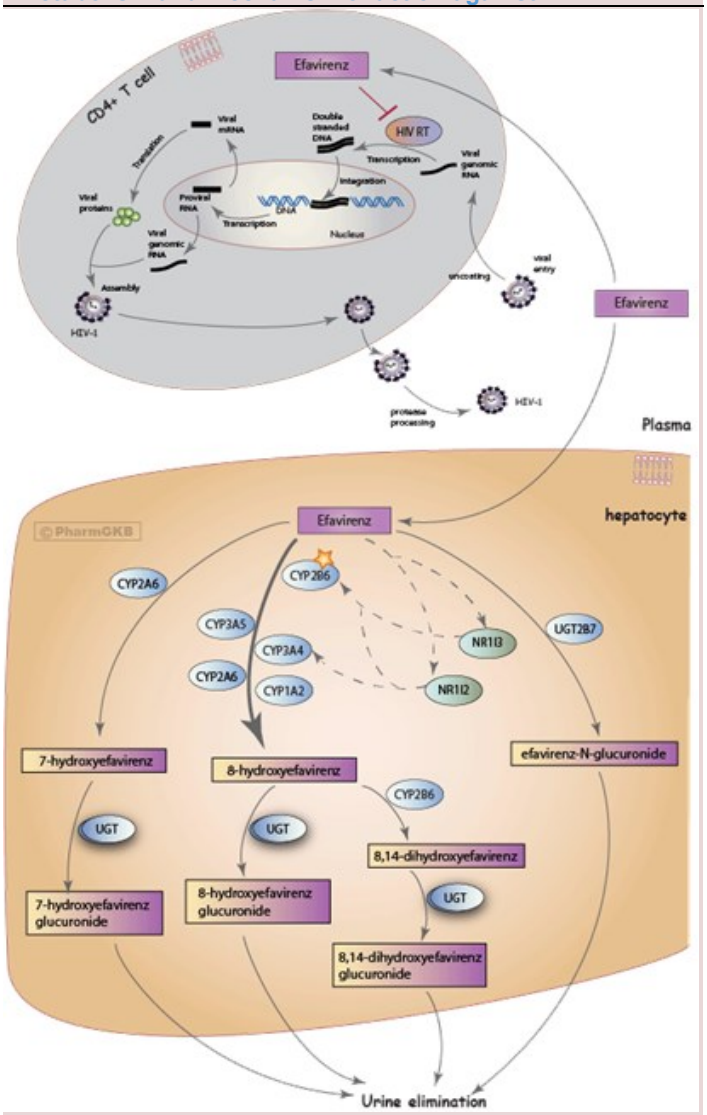
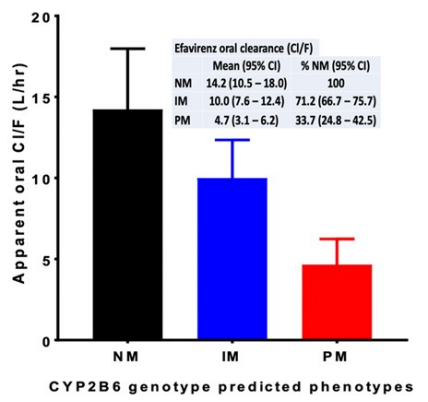
Figure 1 | Schematic representation of efavirenz metabolism and mechanism of action against HIV



Pathway accessed at: https://www.pharmgkb.org/pathway/PA166123135 (8/13/2023). Image reproduced and is licensed under CC BY-SA 4.0 from PharmGKB.

CYP, cytochrome P450; NR1, Transcription factors pregnane X receptor (PXR, NR1I2) and constitutive androstane receptor (CAR, NR1I3); RT, reverse transcriptase; UGT, UDP-glucuronosyltransferase.

Figure 2 | Apparent oral clearance (CL/F) of efavirenz (600 mg/day) in HIV-positive individuals genotyped for CYP2B6 variants.[6]



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