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Cabenuva® (cabotegravir/rilpivirine): Injecting New Life into Treatment of Human Immunodeficiency Virus

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Human immunodeficiency viruses (HIV) belong to a class of viruses known as lentiviruses.[1] Lentiviruses are a type of retrovirus, and the principle genomic component is positive-sense, single-stranded ribonucleic acid (RNA). Like other lentiviruses, HIV relies on the enzyme reverse transcriptase to convert its genome from RNA to complementary deoxyribonucleic acid (cDNA).[1] The genome of HIV encodes for several proteins which are directly involved in virulence, cellular entry, viral replication, and, importantly, integration into the host genome. HIV can be transmitted via sexual intercourse, infected blood products, and sharing of needles in intravenous drug use.[1]

Two types of HIV have been characterized, with the more prevalent and virulent type of HIV being HIV-1. The HIV-2 subtype is less prevalent (<0.1% of infections in the US), virulent and transmittable, being largely limited to West Africa.[2] Both HIV-1 and HIV-2 display tropism for immune cells and have the ability to cause acquired immunodeficiency syndrome (AIDS), which is characterized by a CD4+ T-cell count < 200 cells/mm3 or the presence of so-called AIDS-defining illnesses. Such illnesses include various opportunistic infections (e.g., *Pneumocystis jirovecii* pneumonia, *Mycobacterium* avium complex, *Toxoplasma gondii*), Kaposi's sarcoma, and various lymphomas.[1] Individuals infected with HIV are often unaware of the infection, as the virus may lay dormant for months-to-years before causing symptoms. Often, when symptoms occur in acute infection, they mimic signs and symptoms of other viral infections such as mononucleosis: malaise, fever, rash and gastrointestinal upset.[1] This acute period is characterized by high viral loads and massive decreases in CD4+ count. Following acute infection, a period of dormant infection occurs marked by an increase in CD4+ cell counts and decrease in viral load.[1]

Centers for Disease Control and Prevention (CDC) models report that approximately 1.2 million people are infected with HIV in the United States. Of those infected, as many as one-in-seven are unaware of their infection status. In 2018, 37,968 individuals were diagnosed, a 7% decline since 2014.[2] Sixty-nine percent of new HIV diagnoses in 2018 were in gay, bisexual, and other men who have sex with men. Heterosexuals account for 24% of all HIV diagnoses. Ethnic minorities, specifically Blacks and Hispanics, made up the majority of new infections.[2]

Diagnosis of HIV occurs through a multi-step process. Enzyme-linked immunosorbent assay (ELISA) has been a mainstay in the detection of circulating HIV antibodies. Great advancements have been made in ELISA tests, shortening the length of time required for test validity, thus leading to prompter diagnoses and treatment. Modern ELISA (third and fourth generation) techniques detect anti-HIV antibodies [immunoglobulin G (IgG), immunoglobin M (IgM)] and p24 antigens.[1] ELISA tests display high sensitivity (>99%) and specificity (>99%). The CDC recommends screening for HIV for everyone between ages 13 and 64. Annual screening is recommended for those with major risk factors for transmission.[1, 2]

Current pharmacotherapeutic options for the treatment of HIV-1 infection in the US 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).[3] The CDC recommends that antiretroviral therapy (ART) include a combination of two NRTIs in combination with a third ARV drug: an InSTI, NNRTI, or ritonavir/cobicistat boosted-PI. Per CDC guidelines, patients should be treated with the goal of reducing the plasma viral load to <50 copies/mL. Resistance profiles should be assessed genotypically upon diagnosis and throughout the course of treatment, especially in the case of suspected treatment failure.[2,3] Strategies to minimize resistance should be utilized, and drugs with high barriers to resistance such as InSTIs and PIs make up the backbone of most ART regimens. Antiretrovirals with lower barriers to resistance such as NNRTIs and NRTIs should not be used alone in the treatment of HIV.[2, 3] The administration of most modern ART regimens requires daily, oral dosing and strict adherence to ensure effectiveness. Poor compliance with ART regimens leads to a greater propensity for the development of resistance regardless of which oral ART regimen is utilized.

Cabenuva®(cabotegravir/rilpivirine) was approved by the Food and Drug Administration (FDA) in January 2021 for the maintenance of viral suppression in treatment-experienced adult patients with viral RNA load of <50 copies/mL, who are on a

IN THIS ISSUE

stable ART regimen, have not experienced treatment failure, and do not have known or suspected resistance to cabotegravir or rilpivirine. Cabenuva® (cabotegravir/rilpivirine) is the first long acting intramuscular injectable approved in the fight against HIV. A four-week trial of oral, lead-in therapy is required to assess patient tolerance of cabotegravir and rilpivirine.[4] This article will discuss cabotegravir/rilpivirine pharmacology, pharmacokinetics, pharmacodynamics, dosing and administration, evidence on safety and efficacy, and its clinical implications.

Pharmacology

Mechanism of Action

Cabotegravir/rilpivirine is a combination product containing an InSTI (cabotegravir) and an NNRTI (rilpivirine). Cabotegravir inhibits HIV integrase and upon binding, cabotegravir inhibits the insertion of linear viral cDNA into the host genome - an essential feature of the HIV life-cycle.[4,5] Rilpivirine is a diarylpyrimidine NNRTI that binds directly to reverse transcriptase at the active site. Binding of rilpivirine induces a conformational change in the active site of reverse transcriptase, which greatly reduces the polymerase activity. As a class, NNRTIs are effective only against subtype HIV-1 and not other lentiviruses.[4, 6]

Pharmacokinetics

When cabotegravir is administered orally, the median time (T_{max}) to a peak plasma concentration (C_{max}) of 8 mcg/mL is three hours.[4] Cabotegravir is >99.8% bound to plasma proteins. The drug is metabolized primarily by uridine diphosphate (UDP)-glucuronosyl transferase (UGT1A1) and excreted in the feces (59% of dose) and urine (27% of dose). Following oral administration of rilpivirine, the time to peak plasma concentrations is roughly four to five hours. The area under the curve (AUC) for rilpivirine is increased by 40% when administered with meals. Metabolism occurs primarily through hepatic cytochrome p450 3A. The terminal elimination half-life of rilpivirine is approximately 50 hours, and excretion occurs primarily through the feces. About 25% of the administered dose is excreted unchanged.

In contrast, the T_{max} of intramuscular (IM) cabotegravir is 7 days. The distribution and metabolism of IM cabotegravir do not vary greatly from orally administered cabotegravir.[4,5] The largest difference between oral and IM cabotegravir pharmacokinetics is seen in terminal half-life. Administration intramuscularly extends the half-life of cabotegravir to 5.6-11.5 weeks.[4] Similarly, the IM administration of rilpivirine extends the terminal half-life to 13-28 weeks. **Table 1** provides a detailed summary of the pharmacokinetic data collected from clinical studies of cabotegravir and rilpivirine. In two phase III trials, plasma concentrations did not significantly vary between oral and IM administration.

Table 1 | Select Cabenuva® Component Pharmacokinetics[4]

Absorption	Cabotegravir[a]	Rilpivirine[b]
T_{max}[c]	7 days	3-4 days
SS_t[d]	4.2 mcg/mL	116 mcg/mL
Distribution		
Blood-to-Plasma Ratio	0.52	0.7
Protein Binding	>99.8%	99.7%
Metabolism		
	UGT1A1 UGT1A9 (minor)	CYP3A
Elimination		
$T_{1/2}$[e]	5.6-11.5 days	13-28 days
Fecal	59%	85%
Urine	27%	6%

[A]400mg IM monthly injection; [B]600mg IM monthly injection; [C]Time to maximum concentration; [D]Time to steady state; [E]Half-life

Clinical Trials

Cabotegravir/Rilpivirine was approved for use based on two phase III randomized, multicenter, active controlled, parallel-arm, open-label, non-inferiority trials known as the First Long-Acting Injectable Regimen (FLAIR) study and the Antiretroviral Therapy as Long-Acting Suppression (ATLAS) study. The following sections will summarize these trials with the results displayed in **Table 2**.

FLAIR (NCT02938520) Trial[7]

The authors of the FLAIR trial sought to determine whether long-acting injectable therapy with cabotegravir/rilpivirine was noninferior to oral therapy for maintenance of viral suppression following an oral ART induction regimen.[7] Included subjects were those older than 18 years of age with a baseline HIV RNA ≥1,000 copies/mL.[7] Excluded subjects were pregnant or breastfeeding women, those with severe hepatic impairment, those with evidence of Hepatitis B (HBV) infection or evidence of Hepatitis C (HCV) infection, those presenting evidence of resistance to NNRTIs, and those with an estimated creatinine clearance <50 mL/min/1.73m2.[7]

At the beginning of the study, 629 treatment-naïve patients received oral induction therapy with an oral combination of dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg or dolutegravir 50 mg plus two other NRTIs (if HLA-B*5701 positive) over a period of 20 weeks. Following induction therapy, 566 subjects had confirmation of viral suppression (HIV RNA levels <50 copies/mL).[7] This cohort (n=566) was randomized (1:1) to either continue the initial regimen (n=283) or receive cabotegravir 600mg/rilpivirine 900mg (n=283). Initially, subjects in the cabotegravir and rilpivirine group received oral lead-in therapy with doses of 30mg and 25mg once daily, respectively for approximately four weeks. Depending on tolerability and safety of lead-in therapy, the long-acting injectable therapy-consisting of loading doses (cabotegravir 600 mg IM once and rilpivirine 900 mg once) and maintenance doses (cabotegravir 400 mg IM every four weeks and rilpivirine 600 mg every four weeks)-was administered.[7]

The primary outcome measure was the percentage of subjects with virologic failure, defined as HIV RNA ≥50 copies/mL. After 48 weeks, six subjects (2.1%) in the cabotegravir/rilpivirine group and seven patients in the active comparator (2.5%) group had HIV RNA ≥50 copies/mL (adjusted difference, −0.4 percentage points; 95% confidence interval [CI], −2.8 to 2.1).[7] With no statistically significant difference between the study arms, this result met the criterion of non-inferiority for the primary endpoint.

At 48 weeks, 93.6% of subjects in the cabotegravir/rilpivirine arm and 93.3% of subjects in the active comparator arm achieved HIV RNA <50 copies/mL (adjusted difference 0.4%; 95% CI − 3.7 to 4.5), a key secondary endpoint.[7] Like the primary efficacy outcome, no statistically significant difference between the groups was seen for the key secondary endpoint. Fur-

ther, 257/259 (99%) of responding subjects in the long-acting injectable arm of the study reported a preference for long-acting injectable over oral therapy using the HIV Treatment Satisfaction Questionnaire (HIVTSQ).[7]

Apart from injection site reactions, the most common adverse events in the cabotegravir/rilpivirine arm included nasopharyngitis, headache, upper respiratory tract infections (URI), and diarrhea.[7] Serious adverse events occurred in 18 (6%) of the subjects in the long-acting injectable arm and 12 (4%) of the participants in the oral treatment arm.[7] Pain at the injection site was the most common adverse event in the long-acting group and occurred in 227/278 (82%) of subjects.[7]

ATLAS (NCT02951052) Trial[8]

The ATLAS trial was designed to demonstrate the noninferiority of once-monthly injections of cabotegravir/rilpivirine compared to current ART regimen in the maintenance of viral suppression in treatment-experienced subjects.[8] Included subjects were at least 18 years of age, had been on an uninterrupted, approved ART regimen for at least 6 months prior to screening, and had an HIV RNA level of less than 50 copies/mL.[8] Subjects were excluded if they had evidence of active HBV infection, previous virologic failure, InSTI or NNRTI resistance mutations, or interruption of ART regimen exceeding one month within 6 months prior to screening.[8] The median duration of treatment prior to the start of the trial was 4.3 years.[8] Most ART regimens at entry included two NRTIs plus an NNRTI (50%), an InSTI (33%), or a PI (17%).

At the start of the trial, 618 subjects were randomized (1:1) to either continue their current ART regimen (n=308) or switch to cabotegravir/rilpivirine (n=308). Participants in the cabotegravir/rilpivirine group were started on oral lead-in therapy using the same protocol described above in the FLAIR trial. The primary outcome measure was the percentage of subjects with virologic failure, defined as HIV RNA ≥50 copies/mL.[8] The intention-to-treat analysis found the cabotegravir/rilpivirine had 5 (1.6%) subjects with an HIV RNA level greater than 50 copies/mL compared to 3 (1.0%) subjects in the oral treatment arm (adjusted difference, 0.6 percentage points; 95% CI, −1.2 to 2.5) at 48 weeks.[8] This result showed no statistically significant differences between the groups meeting the prespecified criterion for noninferiority defined in the study protocol. Additionally, at 48 weeks, 285 (92.5%) of subjects in the injectable cabotegravir/rilpivirine long-acting arm and 294 (95.5%) of subjects in the oral treatment arm had HIV RNA less that 50 copies/mL, a key secondary endpoint (adjusted difference, −3.0 percentage points; 95% CI, −6.7 to 0.7, no statistically significant difference).[8]

Further, 266/273 (97%) of responding subjects in the long-acting injectable arm of the study reported a preference for long-acting injectable over oral therapy using the HIVTSQ.[8] Virologic failure occurred in three participants who received long-acting therapy and four participants who received oral therapy. Virologic failure in the injectable arm was attributed to resistance to rilpivirine. Like the FLAIR trial, the most common adverse events in the long-acting therapy arm were injection-site reactions, occurring in 83% of participants.[8]

Adverse Effects and Precautions

The safety data for cabotegravir/rilpivirine was derived from a pooled analysis of results from the FLAIR and ATLAS studies. Adverse events include those associated with oral and injectable formulations of cabotegravir and rilpivirine.[4,7,8,9] Most patients receiving a combination ART regimen experience adverse events throughout the course of treatment. The most common adverse reactions (Grade 1-4) occurred in greater than or equal to 2% of

Table 2 | Primary and Secondary Outcomes from Cabenuva® Trials[7,8]

Trial	Treatment Duration	Outcomes	Intervention	Result (%)	Result (95% CI)
FLAIR (n=566)	48 weeks	Primary HIV RNA ≥50 copies/mL	CAB/RIL[a] (n=283)	2.1	-0.4 (-2.8—2.1)
			SOC[b] (n=283)	2.5	
		Secondary HIV RNA <50 copies/mL	CAB/RIL[a] (n=283)	93.6	0.4 (-3.7—4.5)
			SOC[b] (n=283)	93.3	
ATLAS (n=618)	48 weeks	Primary HIV RNA ≥50 copies/mL	CAB/RIL[a] (n=308)	1.6	-3.0 (-6.7—0.7)
			SOC[c] (n=308)	1.0	
		Secondary HIV RNA <50 copies/mL	CAB/RIL[a] (n=308)	92.5	0.6 (-1.2—2.5)
			SOC[c] (n=308)	95.5	

[a]IM cabotegravir/rilpivirine; [b]standard of care (dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg or dolutegravir 50 mg plus two other NRTIs [if HLA-B*5701 positive]); [c]standard of care (two NNRTI or NRTI + InSTI or NNRTI or boosted PI or boosted atazanavir)

subjects. Injection site reactions occurred in 83% of patients receiving cabotegravir/rilpivirine and 0% of patients receiving oral therapy. [4,7,8,9] Pyrexia (fever, chills, hot-flashes) occurred in 8% of subjects receiving cabotegravir/rilpivirine compared to 0% of subjects in the comparator group. 5% of subjects receiving cabotegravir/rilpivirine experienced fatigue. Further, 4% developed headaches, 3% reported musculoskeletal pain, 3% experienced sleep disorders, 2% reported sleep disorders, dizziness, and rash.[4,7,8,9] Less common adverse events were defined as occurring in less than 2% of patients and included weight gain, psychiatric disorders, and hypersensitivity reactions.[4,7,8,9] A summary of adverse events occurrences is provided in **Table 3.**

Table 3 | Common Cabenuva Adverse Effects[4,7,8,9]

Adverse Effect	Incidence Rate
Injection Site Reaction	83%
Pyrexia	8%
Fatigue	5%
Headache	4%
Musculoskeletal Pain	3%
Nausea	3%
Sleep Disorders	2%
Dizziness	2%
Rash	2%

Dosage and Administration

Following oral lead-in therapy for at least 28 days with cabotegravir 30 mg daily and rilpivirine 25 mg daily, injectable cabotegravir/rilpivirine must be administered by a healthcare professional.[4] Prior to initiation of the injectable series, clinicians should consider the likelihood on patient adherence to the monthly injections and should discuss with patients the importance of compliance with the regimen. A loading dose of cabotegravir 600 mg IM once and rilpivirine 900 mg IM once should be administered on the last day of oral lead-in therapy.[4] Following the loading dose series, maintenance doses of cabotegravir 400 mg IM and rilpivirine 600 mg IM should be administered monthly. The injections should be given at separate gluteal injection sites (at least 2 cm) apart during the same visit.[4]

If an injection is missed, clinicians should reevaluate the patient to ensure it is appropriate to resume therapy.[4] If cabotegravir/rilpivirine is to be continued and it has been less than 2 months since the last injection, maintenance doses of cabotegravir 400 mg IM and rilpivirine 600 mg IM should be administered as soon as possible. If greater than 2 months has passed, doses of cabotegravir 600 mg IM once and rilpivirine 900 mg IM once should be administered as soon as possible and monthly maintenance doses should be resumed on the new schedule.[4] Cabotegravir/rilpivirine is supplied in kits of cabotegravir 400mg/rilpivirine 600mg and cabotegravir 600mg/rilpivirine 900mg in separate vials.

Special populations

Renal & Hepatic Impairment

There is no dosage adjustment for those with creatinine clearance (CrCL) of 30 mL/min or higher.[4] Cabotegravir/rilpivirine may be used in patients with CrCL less than 30 mL/min however such use does warrant more frequent monitoring for adverse events. Additionally, there is no dosage adjustment in patients with mild to moderate hepatic impairment (Childs-Pugh A or B). The effects of severe hepatic impairment (Childs-Pugh C) on cabotegravir/rilpivirine pharmacokinetics have not been studied.[4]

Pregnancy & Lactation

There is insufficient data on the use of cabotegravir/rilpivirine during pregnancy to assess a drug-associated risk of birth defects and miscarriage in humans. Use of dolutegravir, another InSTI, was associated with neural tube defects, but there is insufficient data to determine if the association exists with cabotegravir.[4] Animal studies of cabotegravir showed no drug-related fetal toxicity at doses several fold higher than in humans. Available data indicate that use of rilpivirine during pregnancy is not associated with an increased risk of birth defects when compared to the background rate of birth defects in the United States.[4] Cabotegravir and rilpivirine are detected in systemic circulation for up to 12 months or longer after discontinuing injections. Clinicians should discuss the potential risks and benefits of treatment with patients of childbearing age or who are pregnant. In patients with HIV-1, the CDC recommends against breastfeeding due to risk of transmission to the infant. Breastfeeding while using cabotegravir/rilpivirine is not recommended due to the potential for resistance development (HIV-positive infants), adverse reactions in the infant, and detection of cabotegravir and rilpivirine up to 12 months after administration.

Pediatric & Geriatric Patients

Pediatric subjects were excluded from both the FLAIR and ATLAS trials. The use of cabotegravir/rilpivirine in pediatrics has not been evaluated, and it is not approved by the FDA for use in patients less than 18 years of age.[4] Too few geriatric patients were included in clinical trials to adequately assess the safety and efficacy of cabotegravir/rilpivirine in patients older than 65 years of age. Caution should be used when administering cabotegravir/rilpivirine in geriatric patients due to a greater likelihood of hepatic, renal, and/or cardiac impairment.[4]

Drug Interactions

Since the components of cabotegravir/rilpivirine are metabolized via distinct pathways, drug interactions arise with respect to the distinct components. Cabotegravir is conjugated via glucuronidation by UGT1A1 (major) and UGT1A9 (minor).[4] Induction of the UGT system results in significantly decreased plasma concentrations of cabotegravir, which may lead to virologic failure. Rilpivirine is metabolized via the hepatic CYP3A family. Coadministration of drugs that induce the CYP3A system may cause significant decreases in the plasma rilpivirine concentrations, which may lead to loss of virologic response and possible resistance to rilpivirine or NNRTIs as a class. Coadministration of drugs that inhibit the CYP3A system may result in increased plasma rilpivirine concentrations, which may lead to increased likelihood of adverse events.[4] Administration of rilpivirine is associated with prolongation of

the QTc interval, thus co-administration with drugs also know to prolong the QTc interval may lead to serious arrythmias such as Torsade de Pointes.[4]

Cabotegravir/Rilpivirine is contraindicated in patients with a history of hypersensitivity to cabotegravir, rilpivirine, or any component of the injectable formulation.[4] Additionally, cabotegravir/rilpivirine is contraindicated in patients receiving drugs which cause significant decreases in cabotegravir and/or rilpivirine plasma concentration due to induction of hepatic cytochrome P450 3A or UGT1A1, as co-administration may result in loss of virologic response.[4] A list of drugs that induce metabolism of cabotegravir and/or rilpivirine are included in **Table 4.**

Cost

Cost is a major concern with almost all ART regimens, as many of the medications are not available as generics. Cabotegravir/rilpivirine is associated with significant cost, but it does not vary greatly from other marketed ART regimens. The oral lead-in therapy is provided free-of-charge from the manufacturer. The wholesale acquisition cost of the injectable loading dose of cabotegravir/rilpivirine is $5,940/month, and the wholesale acquisition cost of the injectable maintenance dose is $3,960/month.[10] Since cabotegravir/rilpivirine injections are administered in a clinical setting, health insurers may cover the cost as a medical benefit or pharmacy benefit depending on the plan.

Clinical Implications

The approval of cabotegravir/rilpivirine, the first long-acting injectable combination therapy available for maintenance of viral suppression, further simplifies treatment for vulnerable patient populations. The FLAIR study demonstrated that cabotegravir/rilpivirine was effective in maintaining virologic suppression in treatment-naïve subjects who began a first-line induction regimen. Following induction treatment, the use of an active comparator to determine the relative efficacy of cabotegravir/rilpivirine improves robustness of the positive results seen. This study included a relatively large sample size and was well powered to detect statistically significant differences with regards to the relevant endpoints (97% for the primary endpoint; 90% for key secondary endpoint).[7] Validated clinical endpoints were used as the primary and secondary outcome measures. Another strength of the FLAIR trial was the stratification and analysis of subjects based on characteristics such as initial viral load, body mass index (BMI), and specific resistance mutations. The study found that initial viral load had no significant effect on the results for the primary endpoint. Conversely, subjects with a BMI >30 and the L74I integrase polymorphism (3) experienced virologic failure.[7] Such an insight could guide clinicians in selecting candidates for treatment with cabotegravir/rilpivirine. Though limitations were not listed in the study, the study population was primarily composed of males (78%), whites (74%), and those <35 years of age (51%), which may limit the generalizability of the study to patients who do not fit these criteria.[7] Additionally, the open-label design of the study creates the possibility for certain biases and confounding, which were not addressed in the discussion of results.

The ATLAS study determined that cabotegravir/rilpivirine was noninferior to combination oral therapy for maintenance of viral suppression in treatment-experience patients who were on a variety of combination ART regimens.[8] Similar to the FLAIR study, ATLAS compared cabotegravir/rilpivirine to standard-of-care, oral ART regimens, which improved the robustness of the results. The study included a large sample size and had approximately 97% power to detect statistically significant differences for the primary endpoint, along with approximately 94% power to detect statistically significant differences for the key secondary endpoint.[8] The study authors listed several limitations. Primarily, inclusion of only virally suppressed subjects without prior virologic failure may limit the generalizability of the study. Separately, the study population was generally older than the FLAIR trial with a median age of 42 years compared to 34 years. Males (78%) and whites (74%) were potentially overrepresented in the study, and a plurality of subjects had a CD4+ count ≥500 cells/mcL.[8] These limitations may limit the generalizability of the study to patients outside of these groups.

Adverse effects associated with use of cabotegravir/rilpivirine were mostly mild and predominantly involved injection-site reactions. Patients receiving ART regimens are often well-acquainted with medication-related adverse effects with greater

Table 4 | Effect of Enzyme Inducers on Cabotegravir and Rilpivirine Concentrations[4]

Drug Class	Effect on Concentration	Enzyme(s) Affected
Anticonvulsants (carbamazepine, phenobarbital, phenytoin)	↓ cabotegravir, ↓ rilpivirine	UGT1A1 CYP3A
Rifamycins (rifampin, rifapentine, rifabutin)	↓ cabotegravir, ↓ rilpivirine	UGT1A1 CYP3A
Systemic Glucocorticoids	↓ rilpivirine	CYP3A
St. John's Wart	↓ rilpivirine	CYP3A

than 80% of subjects experiencing adverse events in both the FLAIR and ATLAS studies, regardless of treatment group.[7,8,9] As such, the adverse effect profile of injectable cabotegravir/rilpivirine is unlikely to dissuade patients and providers from using the drug, as a large majority of subjects preferred long-acting injectable therapy to oral therapy despite the high prevalence of adverse effects.[7,8,9]

Cabotegravir/rilpivirine has the ability to greatly improve patient adherence due to simplification of the dosing regimen from daily to monthly. Nonadherence to oral ART regimens is a primary driver of morbidity and mortality in patients living with HIV, and often, nonadherence is not the fault of the patient, but caused by an unfortunate set of circumstances. There is a clinical trial (LATITUDE Study; NCT03635788) actively recruiting subjects, at the time of this manuscript, to assess the efficacy and safety of cabotegravir/rilpivirine in individuals with a history of sub-optimal adherence.[8] The results of this study will likely provide primary evidence to drive clinical decision making for HIV providers across the US and has the potential to greatly streamline treatment for this subpopulation of patients. To be a candidate to receive the drug, a patient must have sustained maintenance viral suppression with a viral RNA load of less than 50 copies/mL and a stable ART regimen.[4] The transition from daily oral therapy to monthly injections will streamline treatment and free patients from the pill burden inherent in many ART regimens significantly improving patient satisfaction. Additionally, administration in a healthcare setting could help to ensure adherence to treatment. The cost of cabotegravir/rilpivirine injections is comparable to oral combination ART regimens and will likely not impose an undue burden on patients due to the availability of PAPs for the medication.[10]

HIV is a disease that carries a heavy stigma, and patients may be embarrassed or ashamed about their disease status and need for daily medication.[1] Clinicians should offer support to patients living with HIV by advocating for their physical and mental health. Cabotegravir/rilpivirine offers a unique opportunity to significantly improve patient satisfaction and adherence, with over 90% of patient preferring the monthly injections to oral therapy in clinical trials.[7,8,9] Since cabotegravir/rilpivirine injections must be administered monthly in a healthcare setting, clinicians will have additional opportunities for follow-up with patients receiving the medication. These additional encounters provide opportunities to discuss emergent issues throughout the course of treatment such as adverse events related to therapy. The United States Department of Health and Human Services (DHHS) Adults and Adolescents Antiretroviral Guidelines Panel updated their guidelines in February 2021 to include a recommendation that cabotegravir/rilpivirine may be used as an optimization strategy for people currently on oral ART regimens if they meet the specified criteria.[11] The inclusion of cabotegravir/rilpivirine injection in the DHHS guidelines works to further define a place in therapy for clinicians seeking to participate in evidence-based practice. Cabotegravir/rilpivirine provides an exciting new development in the treatment of HIV, and long-acting injectables may soon become a mainstay in treatment of chronic HIV-1 infection.

Conclusion

The FDA approval of the long-acting, injectable Cabenuva® (cabotegravir/rilpivirine) in January 2021 is an important development in the treatment of virologically suppressed patients living with HIV-1 infection. The drug combines two independently proven treatments that were only available orally before 2021. It is the first approved long-acting, injectable treatment for HIV and furthers the trend of the simplification of ART regimens. Simplified treatment regimens for HIV are essential in improving patient adherence and satisfaction. The most recently updated HIV treatment guidelines from DHHS recommend use of Cabenuva® (cabotegravir/rilpivirine) in eligible patients, and it should prove to be a useful tool in the treatment of HIV.

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Drug Update:
New Indications and Dosage Forms
August 2021

Twyneo® (tretinoin and benzoyl peroxide) Cream
New formulation: Indicated for treatment of acne vulgaris in adults and children 9 years of age and older

Saphnelo® (anifrolumab-fnia) Injection
New formulation: Type I interferon (IFN) receptor antagonist indicated for the treatment of moderate to severe systemic lupus erythematosus in conjunction with standard therapy

TicoVac® (tick-borne encephalitis vaccine) Injection
New formulation: Inactivated vaccine indicated for immunization to prevent tick-borne encephalitis in patients 1 year of age and older

Skytrofa® (lonapegsomatropin-tcgd) Injection
New formulation: Human growth hormone used once-weekly for the treatment of pediatric growth hormone deficiency

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