Clinical and Case Study Article

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Monthly injectable cabotegravir/rilpivirine to manage HIV infection in adults

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ABSTRACT

The FDA recently approved a unique treatment regimen for management of HIV-1 infection in adults. A one-time per month injection of cabotegravir/rilpivirine can replace a current, stable antiretroviral regimen in those with virologic suppression, without history of treatment failure, or known or suspected resistance with cabotegravir or rilpivirine. A one-month oral trial should be initiated before switching to the extended-release injectable formulation. Cabotegravir/rilpivirine showed continued virologic suppression without clinically relevant changes in CD4+ cell counts. Clinicians should understand this new HIV regimen, its indications and suitability for select patients, administration and dosing, interactions, and most reported adverse events.

Keywords: AIDS; cabotegravir/rilpivirine; HIV; Infectious disease; pharmacology; primary care.

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Current data regarding HIV infection in the United States

The HIV epidemic in the United States is an ongoing problem. At the conclusion of the latest Centers for Disease Control and Prevention (CDC) reporting period (2019), an estimated 1,189,700 people aged 13 years and older were living with HIV in the United States, with 13% of these persons being undiagnosed (CDC, 2021a). In addition, 36,801 new HIV diagnoses occurred in the United States and its dependent areas (CDC, 2021b). Blacks/African Americans made up most of these new cases (15,340; CDC, 2021c), with male-to-male sexual contact remaining the highest risk for transmission (24,084; CDC, 2021d). Florida recorded most new infections in the United States (4,378), with California (4,354), Texas (4,302), Georgia (2,439), New York (2,330), North Carolina (1,365), Illinois (1,252), New Jersey (1,057), Pennsylvania (989), and Ohio (980) contributing to the top 10 states for new infections (CDC, 2021e). There were 15,815 deaths in adults and adolescents with diagnosed HIV in 2019; however, these deaths could be from any cause (CDC, 2021f).

Screening, initial laboratory diagnosis, and initial antiretroviral treatment of HIV infection

Screening for HIV in primary care settings continues to be essential (Goldschmidt & Chu, 2021). Current guidelines suggest screening all patients aged 15–65 years at least once and then retesting annually based on risk factors (Goldschmidt & Chu, 2021; Watson, 2021 [**Table 1**]). All pregnant women should be screened (including those who present in labor or delivery with unknown status; Goldschmidt & Chu, 2021). Others who should be screened include those being evaluated for preexposure or postexposure prophylaxis, those who are suspected of presenting with acute HIV infection (seen with a constellation of fever, chills, night sweats, fatigue, myalgia, lymphadenopathy, headache, odynophagia, and/or diarrhea) with exposure within the last two months, and those suspected of having chronic, untreated HIV infection (seen with a constellation of fever, lymphadenopathy, malaise/fatigue, weight loss, and symptoms of opportunistic infections; Goldschmidt & Chu, 2021).

Any positive antibody screening test (e.g., ELISA, home-based, point-of-care, or rapid tests) should be confirmed by a laboratory-based Western blot (University of California at San Francisco, 2021). CD4+ cell counts, quantitative plasma HIV RNA level (often referred to as viral load), and HIV drug resistance laboratory evaluations

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Table 1. Risk Factors Necessitating Annual Screening for HIV

Patient History of[a]:
Multiple sex partners
Unprotected sex with someone who is or could be living with HIV or whose sexual history is unknown
Injection drug use
History of (or need for screening for) tuberculosis, hepatitis, sexually transmitted diseases (syphilis, gonorrhea, chlamydia, or herpes)
Sex in exchange for drugs or money

[a]Subjective reporting of sex with any partner who has a history of these risk factors also indicates need for annual HIV screening.

should be obtained in patients with a confirmed HIV diagnosis (Goldschmidt & Chu, 2021). A comprehensive overview of the necessary laboratory evaluations and suggested frequency of assessment in the chronic management of HIV infection can be found in the work of Goldschmdt and Chu (2021). Although 50% of persons living with HIV are untreated or insufficiently treated with antiretroviral therapy (ART), current recommendations indicate immediate initiation of ART at time of diagnosis (Goldschmidt & Chu, 2021; Saag et. al, 2020; United States Department of Health and Human Services, 2021). HIV RNA suppression (HIV-1 RNA <50 copies/mL; Glaxosmithkline, 2021) to undetectable levels should be achieved within 8–24 weeks using a three- or two-drug regimen (Goldschmidt & Chu, 2021; **Table 2**).

HIV management: a clinical case study approach

Conrad (he, him), a 32-year-old, single, African American, gay man, presents to your clinic for follow-up on his laboratories and refill his antiretroviral therapy (ART) for HIV. (The name and clinical history of the patient portrayed in this clinical case are fictitious and were created by the authors for educational purposes. No identification with actual persons [living or deceased] is intended or should be inferred.) He received a reactive rapid HIV-1 test result at a community event and his confirmatory sample confirmed HIV-1 infection 2 years ago. He was asymptomatic and was immediately linked to care. He received bictegravir 50 mg + tenofovir alafenamide 25 mg + emtricitabine 200 mg, achieving sustained viral suppression (HIV-1 RNA <50 copies/mL) within the first 3 months of starting ART. His CD4+ count has remained stable as well and today's value is 925 cells/mL. Although he has been compliant with his oral treatment, he read in his local newspaper about the option for injectable HIV treatment and he wants to discuss his eligibility and potential transition to this ART alternative.

Cabotegravir/rilpivirine pharmacology

Cabotegravir is an HIV-1 integrase strand transfer inhibitor, and rilpivirine is an HIV-1 nonnucleoside transcriptase inhibitor (Glaxosmithkline, 2021). Integrase strand transfer inhibitors work by blocking the HIV enzyme integrase, which is vital to insertion of viral DNA into the DNA of the host CD4+ cell (National Institutes of Health [NIH], 2021a). Nonnucleoside transcriptase inhibitors bind to, and block, the HIV enzyme reverse transcriptase, which is used to convert HIV RNA to DNA, preventing HIV from replicating (NIH, 2021b). Cabotegravir/rilpivirine is metabolized in the liver and excreted in the urine and feces (Glaxosmithkline, 2021). No clinically significant differences in the pharmacokinetics of cabotegravir are expected in patients with mild, moderate, or severe renal disease; it has not been evaluated when used in end-stage renal disease (ESRD) patients not on dialysis or those with severe hepatic impairment (Glaxosmithkline, 2021).

However, pharmacokinetics are not altered in mild-to-moderate (Child-Pugh A or B) hepatic impairment (Glaxosmithkline, 2021). Mild renal impairment is not expected to alter the pharmacokinetics of rilpivirine, but there are

Table 2. Three- and 2-drug antiretroviral treatment regimens for HIV

Drug Combination Agents and Dosing	Frequency
Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg	Once every day
Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg	Once every day
Dolutegravir 50 mg	Once every day
Plus one of the following:	
Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg	Once every day
Emtricitabine 200 mg/tenofovir alafenamide 25 mg	Once every day
Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg	Once every day
Dolutegravir 50 mg/lamivudine 300 mg	Once every day
Raltegravir 400 mg	Twice every day
Plus one of the following:	
Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg	Once every day
Emtricitabine 200 mg/tenofovir alafenamide 25 mg	Once every day
Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg	Once every day

Table 3. Missed dose regimen

Missed Injection Interval	Response Treatment Regimen
Planned missed injections	
>7 Days	Cabotegravir 30 mg oral daily and rilpivirine 25 mg oral daily for up to two consecutive months
Unplanned missed injections	
<2 Months	Resumption of cabotegravir 400 mg (2 ml) and rilpivirine 600 mg (2 ml) intramuscular injection monthly
>2 Months	Cabotegravir 600 mg (3 ml) and rilpivirine 900 mg (3 ml) intramuscular; then in 30 days, resumption of cabotegravir 400 mg (2 ml) and rilpivirine 600 mg (2 ml) IM monthly

no data on pharmacokinetic effects of the drug in patients with moderate or severe renal impairment, ESRD, or severe hepatic disease. Parallel to cabotegravir, pharmacokinetics of rilpivirine is not altered in mild-to-moderate (Child-Pugh A or B) hepatic impairment. Data regarding pharmacokinetic effects of cabotegravir and rilpivirine were based on analysis of oral administration of the agents; data have yet to be derived from investigation of the injectable formulation (Glaxosmithkline, 2021).

Patient selection, dosing, and administration of cabotegravir/rilpivirine

When patients reach full viral suppression (HIV-1 RNA <50 copies/mL) on a stable ART regimen without history of ART failure, switching to treatment with once-monthly cabotegravir/rilpivirine injections is an available treatment option (Glaxosmithkline, 2021). However, this regimen should be avoided in individuals with known or suspected resistance or hypersensitivity reactions to either cabotegravir or rilpivirine (Glaxosmithkline, 2021). In addition, patients should be well-educated that the regimen requires two intramuscular (IM) injections into the gluteal region(s) once per month.

Before initiating treatment with the monthly injectable cabotegravir/rilpivirine regimen, patients must be given a one-month (minimum of 28 days) lead-in trial of oral cabotegravir 30 mg daily and oral rilpivirine 25 mg daily to determine tolerability (Glaxosmithkline, 2021). It is recommended that these agents be taken together with a meal (Glaxosmithkline, 2021). If well tolerated, on the last day of the oral lead-in trial, patients should be given cabotegravir 600 mg (3 ml) and rilpivirine 900 mg (3 ml) by two separate gluteal IM injections (bilateral gluteal sites or 2 cm apart if unilateral; Glaxosmithkline, 2021). From month 3 onwards, cabotegravir 400 mg (2 ml) and rilpivirine 600 mg (2 ml) should be IM injected using the same technique (Glaxosmithkline, 2021).

If missed doses of injectable cabotegravir/rilpivirine are planned for >7 days, cabotegravir 30 mg daily and rilpivirine 25 mg daily can both be taken orally for up to two consecutive months (Glaxosmithkline, 2021). If the time since last injection is ≤2 months, cabotegravir 400 mg (2 ml) and rilpivirine 600 mg (2 ml) IM should be administered (Glaxosmithkline, 2021). If the time since last injection is >2 months, cabotegravir 600 mg (3 ml) and rilpivirine 900 mg (3 ml) IM should be administered followed by resumption of cabotegravir 400 mg (2 ml) and rilpivirine 600 mg (2 ml) IM in 30 days (**Table 3**; Glaxosmithkline, 2021).

Interactions and adverse events associated with cabotegravir/rilpivirine

Coadministration of drugs that induce uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1 and/or cytochrome P450 (CYP3A) enzymes may reduce plasma concentrations of cabotegravir and/or rilpivirine (Glaxosmithkline, 2021). This may cause a loss in virologic response. Common drug classes that induce these enzymes include some anticonvulsants, antimycobacterials, systemic glucocorticoids, and herbal products (**Table 4**; Glaxosmithkline, 2021).

Tosade de Pointes is a dysrhythmia associated with QTc prolongation (which can degenerate into ventricular fibrillation; Cohagen & Brandis, 2021). Macrolide antibiotics are known to increase the risk of Torsade de Pointes when used with cabotegravir/rilpivirine, azithromycin less so (Glaxosmithkline, 2021). Adverse events most associated with use of cabotegravir/rilpivirine injection include injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash (**Table 4**).

Hepatotoxicity has been reported in patients taking cabotegravir or rilpivirine; and those with preexisting liver disease or marked elevation in transaminases before treatment initiation may be at higher risk (Glaxosmithkline, 2021). Consequently, evaluation of transaminase levels before treatment initiation and periodic monitoring during treatment is advised. In clinical trials, 4% of participants receiving IM cabotegravir/rilpivirine

Table 4. Most common adverse events associated with injectable cabotegravir/rilpivirine and examples of drugs that induce (UGT)1A1 or CYP450 (CYP) 3A4 (Glaxosmithkline, 2021)

Adverse Event[a]	Percentage of Occurrence[b]
Injection site reactions	83%
Pyrexia	8%
Fatigue	5%
Headache	4%
Musculoskeletal pain	3%
Nausea	3%
Sleep disorders	2%
Dizziness	2%
Rash	2%

Drugs that Induce (UGT)1A1 or CYP450 (CYP) 3A4[c]	Examples[d]
Anticonvulsants	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
Antimycobacterials	Rifabutin, rifampicin, rifapentine
Systemic glucocorticoid	Dexamethasone > single-dose treatment
Herbal product (*Hypericum perforatum*)	St. John's wort

[a]See section 6 for additional information and comprehensive descriptions of adverse events associated with cabotegravir/rilpivirine.
[b]Based on data reported in cabotegravir/rilpivirine injection clinical trials.
[c]Concomitant use of cabotegravir/rilpivirine with drugs that induce (UGT)1A1 or CYP450 (CYP) 3A4 can result in lower cabotegravir/rilpivirine plasma levels and loss of virologic response.
[d]See section 7 for additional information and comprehensive descriptions of drug–drug interactions associated with cabotegravir/rilpivirine.

discontinued the regimen because of adverse events compared with 2% of those receiving placebo (Glaxosmithkline, 2021).

Provider's approach to Conrad's visit

Conrad is eligible for injectable ART, given his viral suppression and stable CD4+ count. The first step should be to test tolerability by switching him to a 30-day regimen of oral cabotegravir 30 mg + oral rilpivirine 25 mg once a day. Conrad should look for fever, fatigue, headaches, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash. On one hand, tolerability may be compromised if any of these adverse drug reactions appear and if the severity is of concern, and the provider should discuss with Conrad about returning to the previous ART regimen.

On the other hand, if the oral treatment is tolerated, Conrad can receive cabotegravir 600 mg (3 ml) and rilpivirine 900 mg (3 ml) via two separate gluteal IM injections, with a follow-up visit in 1 month. During that visit, viral load and CD4+ count should be assessed and, if stable, the injectable ART regimen can be repeated then and monthly thereafter. Conrad must also be aware that he has a 7-day window to receive the next injection and should contact his provider if he will miss this window to establish an ART catch-up strategy, either orally or by modified injectable regimens.

Conclusion

Use of long-acting injectable antiretroviral therapy (LA ART) is an emerging strategy in managing HIV-1 infection in adults. Many benefits have been associated with use of LA ART, including reduced concern about challenges to adherence associated with oral ART medications (e.g., difficulties in scheduling follow-up visits), less frequent dosing, lessening of HIV-associated stigma, and promotion of logistic and psychosocial autonomy (Dandachi et al., 2021; Mantsios et. al, 2020). In addition, change from a stable daily oral regimen to an injectable LA ART regimen should not affect clinical efficacy (Dandachi et al., 2021; Mantsios et. al, 2020; Swindells, 2022). Evaluation of a phase 3 study evaluating injectable LA ART showed that 98% of participants maintained viral

suppression (<50 HIV RNA copies/mL) after switching from a daily oral to monthly injectable LA ART (Swindells, 2022).

These data strongly suggest that one-time-per-month injection of cabotegravir/rilpivirine can be used as a substitute treatment for adults living with HIV on a current, stable antiretroviral regimen who have reached virologic suppression, without history of treatment failure, hypersensitivity, or known or suspected resistance with cabotegravir or rilpivirine (United States Food and Drug Administration, 2021; Glaxosmithkline, 2021). To ensure tolerance, a 1-month oral trial of these agents should be completed before switching to the extended-release injectable formulation.

The once-monthly injectable cabotegravir/rilpivirine regimen is associated with continued virologic suppression without clinically relevant changes in CD4+ cell counts (FDA, 2021; Glaxosmithkline, 2021). Providers should avoid concomitant prescribing of medications which induce (UGT)1A1 or CYP450 (CYP) 3A4 as these agents may decrease plasma concentrations of cabotegravir/rilpivirine (Glaxosmithkline, 2021). The regimen should also be used cautiously in combination with drugs with risk of Torsade de Pointes, including macrolide antibiotics (Glaxosmithkline, 2021).

Frequently reported adverse events included injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disturbance, dizziness, and rash. But only a small number of patients (4%) in clinical trials discontinued use of monthly injectable cabotegravir/rilpivirine because of adverse events compared with 2% of patients taking placebo. Pricing for the injectable regimen of cabotegravir/rilpivirine varies depending on patients' health insurance and payment means. Nurse practitioners (NPs) and other clinicians should be knowledgeable on how to access ViiVConnect (2021), which can assist in linking patients to access to cabotegravir/rilpivirine.

HIV remains a serious epidemic in the United States; screening for HIV remains a priority directive for primary care providers, including NPs. Because many primary care providers are taking a more active role in the monitoring and management of HIV infection (Romanelli, 2009), it is vital they have an awareness of emerging trends in HIV treatment. This must also include novel approaches to reaching the ultimate treatment objective of HIV RNA suppression to undetectable levels.

This article provided a thorough review of a newly FDA-approved complete treatment regimen for clinical management of HIV-1 infection in adults. A case study approach was used. The goal of this work was to educate NPs and other providers on how this HIV regimen differs from traditional HIV infection management approaches, its indications and suitability for select patient populations, its administration and dosing, interactions, and most reported adverse events.

C.W. Blackwell performed all the literature review and analyses and wrote the initial draft of the manuscript. H. Lopez Castillo reviewed the initial draft and added additional essential content. Both authors developed the project and revised the manuscript for final submission.

The authors report no conflicts of interest.

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