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Injectable Long-Acting Cabotegravir–Rilpivirine Therapy for People Living With HIV/AIDS: Addressing Implementation Barriers From the Start

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Abstract

Injectable cabotegravir and rilpivirine (CAB/RPV), administered bimonthly by a medical provider, is convenient and improves privacy and medication management. One year after approval, myriad implementation barriers threaten the access and sustainability of this life-saving innovation: (1) eligibility issues (viral suppression, drug resistance, and failed oral regimens); (2) injection requires medical provider and transportation to facility; (3) strict medication adherence; (4) life challenges—mental health, homelessness, joblessness; and (5) lack of insurance and high cost. Universal implementation of CAB/RPV calls for social, human, and health organizations to partner and provide HIV continuum of care and prevention services to facilitate CAB/RPV access and maintenance and for transparent health insurance billing practices to abate uncertainty concerning CAB/RPV's classification as a pharmaceutical or medical benefit and related cost implications.

Key words: implementation barriers, CAB/RPV, injectable long-acting antiretroviral therapy, LA ART

In January 2021, the U.S. Food and Drug Administration (FDA) approved the use of cabotegravir–rilpivirine (CAB/RPV), the first injectable long-acting antiretroviral therapy (LA ART), for people living with HIV (PLWH; Bernstein, 2021; NIH, 2021). CAB/RPV seems to improve patients' experience through convenience, privacy, and overall medication management. Nonetheless, researchers and health care providers have identified myriad barriers to the universal implementation of CAB/RPV (Scarsi & Swindells, 2021). Herein, we document current barriers and forecast future barriers to CAB/RPV implementation. We conclude by making policy and practice recommendations for addressing these barriers.

Background on Cabotegravir–Rilpivirine and Long-Acting Antiretroviral Therapy

The FDA has approved 48 medications for the treatment of HIV, within 10 classes of antiretroviral drugs. Most patients, when diagnosed with HIV, begin a three-drug or two-drug regimen, including medication from different drug classes (Saag et al., 2020). Long-Acting Antiretroviral Therapy is the latest innovation in HIV treatment medication. CAB/RPV is administered by a health care provider through two injections, one for each of its main ingredients, CAB and RPV, every 1 or 2 months. Increase in cabotegravir resistance in every 2-month regimen versus the 1-month regimen has been observed, suggesting a careful explanation of risks and benefits when deciding on the 1-month or 2-month regimen for individual patients. Research suggests that PLWH may tolerate and accept potential side effects of injectable LA ART because it reduces the burden of daily oral medication (Simoni et al., 2020). Interviews with CAB/RPV clinical trial participants indicate that the new medication, compared with oral regimens, is more convenient and easier to integrate into one's daily activities. Participants cited the private nature of injectable medications as less likely to draw stigma and/or discrimination toward PLWH taking oral medications. They also discussed reduced worry because injectable medication removes the barrier of having to pack significant quantities of pills for long periods of travel time and/or other similar situations (Mantsios et al., 2020).

Alongside the advantages of an injectable LA ART, health care providers (e.g., nurses, pharmacists, social workers, and physicians), PLWH, and HIV advocates, including the current authors, have predicted numerous barriers to the universal implementation of CAB/RPV. Grounded in our collective experiences as members of a statewide HIV/AIDS coalition, as well as input from

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other coalition members, herein, we describe barriers to CAB/RPV implementation and provide policy and practice recommendations for overcoming them.

Cabotegravir–Rilpivirine Eligibility Criteria

Before starting a patient on a CAB/RPV regimen, health care providers must assess patients for potential resistance (i.e., when the medicine no longer blocks HIV replication) to both CAB and RPV. A genotype of a patient's HIV is collected at a patient's initial HIV diagnosis and screened for resistance to CAB/RPV. CAB/RPV is not an option for all PLWH; for those patients exhibiting resistance, oral HIV treatment may be the only feasible option for achieving viral suppression at this time. The three main criteria for patient eligibility to receive CAB/RPV are (1) a documented undetectable viral load, (2) documented absence of resistance to either CAB or RPV, and (3) no prior antiretroviral treatment failures.

Maintaining Viral Suppression (Undetectable Viral Load)

As a general recommendation, when a patient is diagnosed with HIV, a baseline viral load is taken to determine the level of virus in the bloodstream. Antiretroviral medication is then indicated to reduce viral load, and viral load tests at 4 weeks are recommended as a baseline. Additional viral load samples are checked every 1 to 2 months to monitor adherence to medication and possible resistance to antiretroviral therapy. After a patient achieves an undetectable viral load, viral load tests are recommended once every 6 months to ensure maintenance and adherence to the drug regimen. The timeframe for each test will often vary from patient to patient.

To receive CAB/RPV, an individual must have a suppressed HIV viral load, which demonstrates qualified adherence to oral medication. CAB/RPV has not been studied in patients with a detectable viral load and should not be used by these patient groups. However, the CDC in 2019 estimated that only 56.8% of PLWH were virally suppressed or undetectable (CDC, 2021), suggesting less than half of all PLWH in the United States may qualify for CAB/RPV. Research has identified myriad barriers to medication adherence and to becoming virally suppressed, including low self-efficacy and stressful life events (Corless et al., 2017), disclosure of HIV status (Sweeney & Vanable, 2016), poverty (Kalichman & Grebler), violence (Hatcher et al., 2015), homelessness (Aidala et al., 2016), and isolation (Rozanova et al., 2015). These challenges can contribute to PLWH missing medication doses, using inaccurate doses, and developing resistance to medication (Chen et al., 2017).

Oral Antiretroviral Treatment Failures

Before patients can receive CAB/RPV, health care providers must confirm if their patients have experienced failed HIV medication regimens in the past, meaning that the medication was not capable of maintaining HIV RNA levels below 200 copies/mL, a phenomenon observed in some cohorts of PLWH (Mesic et al., 2012). Ensuring an accurate antiretroviral medication history, including a patient-centered discussion on all past antiretrovirals and reasons for failure or discontinuation is paramount before starting a patient on CAB/RPV.

Cost and Insurance Approval

Commercial insurance companies must approve the use of CAB/RPV before a patient can receive the medication. The wholesale acquisition cost of the initial/loading dose is $5,940, and monthly/maintenance injections are $3,960 (Bernstein, 2021). ViiV Health care oversees the production of CAB/RPV and offers a payment assistance program for individuals on commercial insurance for up to $13,000 (Moncayo et al., 2021; ViiV Health care, 2021). However, cost estimates from payment assistance programs often do not indicate a viable financial safety net for patients to afford out-of-reach expensive medication. Although coverage for CAB/RPV is expanding, some insurance companies are yet to provide a definitive classification for CAB/RPV as a pharmaceutical or health care benefit, which will ultimately dictate the cost involved in the administration of CAB/RPV and which portion of that cost will be billed to insurance companies or patients. Likewise, some government insurance programs, Medicare and Medicaid, are still solidifying reimbursement processes around CAB/RPV. Because private insurance companies often classify drug billing practices to reflect Medicaid and Medicare, uncertainty around billing issues may make CAB/RPV inaccessible to many U.S. patients regardless of the type of insurance they carry.

Cabotegravir–Rilpivirine Oral Lead-In

There is an oral lead-in with a pill version of CAB/RPV that is used for 28 days before the first injection. This strategy is used to determine if a patient will have side effects from CAB/RPV, such as a rash from an allergic reaction. The oral-lead requires patients to take two pills per day. Most other HIV oral regimens require one daily dose and the increase to two pills per day, even for a short timeframe,

may disrupt adherence or create more burden for the patient (Chen et al., 2017).

Administration of Cabotegravir–Rilpivirine

CAB/RPV must be administered by a health care professional at a designated health facility using the "z-track" method, which involves the positioning of an intramuscular injection into the gluteal muscles to reach the appropriate tissue layer. This represents another barrier to CAB/RPV implementation because previous research suggests that access to health care providers skilled in this administration method can be limited due to geographic location and the cost of HIV care (Pellowski, 2013). It is unclear beyond the results of the clinical trial for CAB/RPV how the burden of injections every 2 months will affect patients' medication adherence.

CAB/RPV Adherence Maintenance

For CAB/RPV to produce an optimal effect, patients need to adhere to their CAB/RPV administration appointments. It is suggested that patients pick a day of the month to receive their injections and keep that day on a bimonthly basis. There is a window period of administration of CAB/RPV that is 7 days before and after a scheduled monthly appointment. However, missing a dose may increase the chance of medication resistance (Smith, 2006). Anticipated challenges to appointment adherence include competing life activities, feeling sick (e.g., symptoms of fatigue, nausea, and aches), stigma, depression, mental illness, expensive/unreliable transportation, and forgetfulness (Yehia et al., 2015). If a patient misses an appointment, an oral substitute of CAB/RPV, which is the same as the oral lead-in, might help mitigate this problem. Oral substitutes can be shipped to patients when their provider deems them the best course of action. However, our community collaborators attest that many patients prefer not to have medications left at their door or on their porch for concerns of privacy and theft. This creates a logistical challenge for adherence, and increases the likelihood of resistance, if a patient cannot attend or receive their CAB/RPV injection.

Recommendations

Injectable CAB/RPV may afford convenience and more privacy than oral regimens; however, it does not fully resolve the fact that individual and structural barriers, including HIV stigma, may keep patients from accessing CAB/RPV. The authors are not suggesting that health care providers should or would ignore the science to advocate for or prescribe CAB/RPV when it might be more harmful than beneficial. We are, however, suggesting that health care professionals consider how current initiatives to reduce stigma around HIV can be tailored to this new context. We also need to be cognizant that universal implementation of CAB/RPV hinges on health clinics and community-based organizations being able to overcome disruptions due to the COVID-19 pandemic and to sustain current efforts to help PLWH to access and stay in the HIV care continuum (Pinto & Park, 2020). COVID-19 disruptions included the closure of community sites and the rise of telemedicine, which made it impossible for some patients to receive CAB/RPV injections. As we face uncertain times and possible future pandemics, stakeholders are encouraged to implement home delivery of long-acting drugs, increase staff to manage and reschedule missed appointments, and acquire equipment to appropriately refrigerate CAB/RPV between 2°C and 8°C (De Vito et al., 2022). Research shows that early linkage to HIV health care improves the odds of viral suppression, a major goal of the care continuum. Therefore, continued emphasis on linkage support will likely also improve access to CAB/RPV. This requires policymakers to invest in partnerships and services that will bring and help maintain patients in the HIV care continuum.

Determination of eligibility will require clear and specific communication between health care providers and patients before and after starting a regimen of CAB/RPV. Said communication will need to include discussions about the individual and structural barriers laid out above. We recommend that training about eligibility and barriers to CAB/RPV access be offered for both health care personnel (e.g., nurses) and providers of social and public health services (e.g., social workers). The extant literature suggests that the latter might be well equipped to offer patients correct information and solutions to barriers in ways that are more easily understood and accessible to underserved patients (Mgbere et al., 2015; Pinto et al., 2021). To achieve universal implementation of CAB/RPV, health care facilities will need to collaborate with community-based health programs and organizations providing social and human services (e.g., transportation, counseling, and substance misuse treatments), which altogether might help mitigate barriers.

Patients receiving CAB/RPV will need support in maintaining strong appointment adherence. Hence, health care systems and community-based organizations should tailor existing prevention and care continuum services to facilitate access to injections at a health care facility by a trained professional. Currently, access to oral substitutes for those who might miss an injection appointment

requires approval by a patient's health care provider. In the future, patients will require more options as to where and how to access CAB/RPV. Perhaps, efforts need to be made to stock pharmacies' emergency supplies with oral substitutes to facilitate access. Collaboration between social service and health practitioners will be required to follow-up with patients receiving oral substitutes and relink them to injectable CAB/RPV when appropriate. Here, we wish to stress the crucial role of pharmacists as a bridge between patients and health care providers in the CAB/RPV context.

Based on our collective experience as HIV service providers and advocates, we assert that the policy and practice recommendations we put forth can only be fully implemented when health insurance billing practices related to CAB/RPV are made transparently available to all. Service-providing organizations and insurance companies are encouraged to work synergistically to determine how best to categorize CAB/RPV as a pharmaceutical or health benefit. Government-subsidized health insurance also needs to develop feasible reimbursement practices if we wish to encourage the use of injectable CAB/RPV.

Conclusion

Care and prevention innovations may take decades to reach those who might benefit the most from them. Therefore, early detection of barriers and adoption of feasible solutions may improve the speed of implementation and thus save lives. CAB/RPV, administered bimonthly by a health care provider, has the potential to help millions of people because it provides more convenience, privacy, and medication regimen management. The potential for the universal implementation of CAB/RPV will be improved when social, human, and health organizations work in partnership to offer HIV continuum of care and prevention services that have been shown to facilitate CAB/RPV access and maintenance. Transparent health insurance billing practices are imperative to abate uncertainty concerning CAB/RPV's classification as a pharmaceutical or health benefit and related cost implications.

Disclosures

The authors report no real or perceived vested interests related to this article that could be construed as a conflict of interest.

Author Contributions

All authors on this paper meet the four criteria for authorship as identified by the International Committee of Medical Journal Editors (ICMJE); all authors have contributed to the conception and design of the study, drafted or have been involved in revising this manuscript, reviewed the final version of this manuscript before submission, and agree to be accountable for all aspects of the work.

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