Using Long-acting Injectable Cabotegravir and Rilpivirine to Improve Adherence with HIV-1 Treatment

C. Thompson[1], K. Collins[2], S. Lambert-Johnson[3]

[1]Department of Community Health & Psychiatry, The University of the West Indies, Mona, Kingston 7, Jamaica, W.I.

[2]Department of Medicine, The University Hospital of the West Indies, Kingston 7, Jamaica, W.I.

[3]Independent Researcher, Tucson, Arizona, USA 85747

Corresponding Author

Dr. Chadane Thompson
Medical Officer
Department of Community Health & Psychiatry
The University of the West Indies, Mona
Kingston 7
Jamaica, W.I.
Email: chadanethompson@gmail.com

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INTRODUCTION

Since its discovery in the 1980's, the human immunodeficiency virus (HIV) has evolved into a global epidemic.[1] Worldwide, an estimated 37.7 million people were infected with HIV as of the end of 2020.[2] Notably, of the people living with HIV (PLWHIV) in 2020, only 73% were on antiretroviral therapy (ART), and only 66% of those accessing treatment had viral suppression.[2] The rates were recorded at 82% and 89% in the Caribbean region, respectively.[2] Though this marks steady progress for the global community, we were still below the 90% target of the Joint United Nations Programme on HIV/ AIDS (UNAIDS) for HIV treatment and viral suppression in 2020. Importantly, the advent of ART has made this once universally fatal condition now treatable. Therefore, ART is recommended for all PLWHIV. Strict ART adherence limits viral transmission, prevents resistance, reduces morbidity, improves quality of life, and prevents progression to acquired immunodeficiency syndrome (AIDS).[3] However, to maintain therapeutic plasma level concentrations of antiretrovirals and achieve these ideal targets, 95% medication adherence is needed—this is difficult for most individuals to sustain.[3-4]

Drug adherence describes the degree to which a patient follows the prescriber's exact recommendations for a particular medication. Successful adherence to ART is multifactorial and depends on considerations such as the patients' sociodemographics, psychological state, stage and duration of illness, and complexity of treatment regimens. In PLWHIV, drug adherence greatly influences the rate of progression to AIDS and subsequent demise. Conveniently, ART is mainly given today as a daily oral prescription. However, compliance to this treatment regimen is still hindered by lifetime pill burden, daily dosing frequency, and the timing of medication administration. Cabenuva has been a recent innovation formulated as a long-acting (LA) injectable antiretroviral combination drug. This 2-drug regimen, comprising cabotegravir (CAB) and rilpivirine (RPV), was approved for use by the US Food and Drug Administration (FDA) in 2021 for virally suppressed PLWHIV-1 who (i) are on a stable regimen, (ii) have no past treatment failure with CAB or RPV and (iii) have no resistance to CAB or RPV.[5] Cabenuva can revolutionize the lives of PLWHIV-1 by

improving ART adherence and optimizing personal and public health outcomes.

DISCUSSION

HIV is a retrovirus with two known infecting strains, HIV-1 and HIV-2. After transfer, commonly through unprotected sexual contact, vertical transmission, or sharing contaminated drug paraphernalia, HIV replicates and destroys CD4+ T cells and leads to a cellular immune deficiency. Consequently, there is an increased susceptibility to opportunistic infections and predisposition to malignancies. Nevertheless, significant strides have been made in HIV treatment since the first antiretroviral drug, Zidovudine, was approved by the US FDA in 1987. Today, there are seven classes of antiretroviral drugs that target HIV using varying mechanisms of action. These drugs are mainly in oral preparation. Antiretroviral therapy (ART) has the endpoint of either preventing fusion of HIV with CD4+ T cells or blocking enzymes needed for HIV replication which ultimately yields viral suppression, ideally to undetectable levels.

The most crucial goal for PLWHIV is to achieve sustained viral suppression, which requires a commitment to daily oral multi-drug treatment for life. However, there are many concerns surrounding these oral ART treatment regimens. Some drawbacks of daily oral ART include high lifetime pill burden, daily dosing frequency, recalling correct timing of doses, the health impact of drug resistance with poor compliance, drug-drug interaction, and fears or social stigma attached to being seen with antiretroviral drugs.[5] In approaching the inadequacies surrounding adherence to oral therapies, alternate but efficacious antiretrovirals can minimize or eliminate these major treatment hurdles for PLWHIV. In an effort to resolve this issue of adherence to oral ART, LA injectables such as Cabenuva were developed.

Cabenuva consists of two (2) drugs, cabotegravir (CAB) plus rilpivirine (RPV). CAB is an HIV integrase strand transfer inhibitor that disrupts a critical step in the viral replication cycle by binding to the integrase active site.[6] This subsequently interferes with the strand transfer step of retroviral integration into deoxyribonucleic acid.[6] On the other hand, RPV is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor of HIV-1 that blocks its replication via non-competitive inhibition of HIV-1 reverse transcriptase.[6] In 2020, two randomized, international, multicenter, parallel-group, open-label clinical trials were published: FLAIR (First Long-Acting Injectable Regimen) and ATLAS (Antiretroviral Therapy as Long-Acting Suppression). In these phase III clinical trials, the first once monthly LA injectable CAB plus RPV were evaluated as alternatives to oral antiretroviral medications in PLWHIV-1.

The FLAIR trial consisted of randomized participants who were HIV-1 positive and ART-naive and it comprised four phases. After the initial screening phase, the participants underwent a 20-week induction phase with a course of oral dolutegravir and two oral nucleoside reverse transcriptase inhibitors. Thereafter, participants with HIV RNA < 50 copies/ml proceeded to the maintenance phase, which first consisted of 4 weeks of oral lead-in CAB and oral RPV to establish drug safety. Finally, participants were maintained on once-monthly intramuscular injections with CAB plus RPV alone. At trial week 48, the percentage of participants who were not virally suppressed was assessed as the primary endpoint. On the other hand, the ATLAS trial included ART-experienced participants with at least six months of viral suppression. After the initial screening phase, randomized participants directly entered the maintenance phase with LA injectable CAB plus RPV after completing the same 4-week oral lead-in as in FLAIR. At trial week 48, ATLAS assessed the same primary end point as FLAIR did. The main adverse reactions included mild-to-moderate injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash.[5] Of note, drug interactions that may decrease CAB and/or RPV plasma concentration include anticonvulsants, antimycobacterials, systemic glucocorticoids, and herbal products like St. John's wort.[5]

These trials demonstrated that the combination of LA injectable CAB plus RPV was non-inferior to daily oral ART in maintaining HIV-1 viral suppression in individuals on a stable regimen and no past treatment failure with or resistance to these drugs.[7-9] Additionally, LA CAB plus RPV were found to be acceptable for eight weekly dosing regimens as outlined by an extension of ATLAS, termed the ATLAS-2M (Antiretroviral Therapy as Long-Acting Suppression every 2 Months) trial. In the ATLAS-2M trial,

the eight weekly LA CAB plus RPV were a safe and preferred therapeutic option over the previous oral therapy by participants, demonstrating high treatment satisfaction and acceptance.[10] In addition, high rates of viral suppression and low failure rates were also reported. Compared with daily lifetime oral ART, LA injectables can therefore make treatment more acceptable, tolerable, and convenient for PLWHIV-1.[10]

Following a single 4-week oral lead in, the monthly or two -monthly administration of LA injectable CAB plus RPV eliminates pills and complex daily dosing schedules that can hinder adherence. This long-acting regimen affords PLWHIV-1 more freedom from a "daily reminder" of their HIV status, and a greater degree of privacy by not having to take antiretroviral medications at home or work.[10] An additional benefit to this includes the potential for more frequent physician-patient contact on a monthly or two-monthly basis, which is often not the case when prescribing oral therapies. Moreover, in this way, additional concerns that may affect antiretroviral adherence can be readily addressed at each visit. Finally, LA injectable CAB plus RPV form a dominant and cost-effective option for PLWHIV-1.[11]

The implementation of long-acting formulations has proven effective in other conditions such as contraception and mental health.[12-13] Similarly, long-acting antiretroviral therapy could provide positive effects and additional treatment choices to PLWHIV. This treatment option can fill the gaps for other HIV therapy options and address behavioral barriers to medication adherence. This high level of medication adherence is crucial to achieving virologic suppression to increase the scope of patients who can achieve 'undetectable equals untransmittable' (U=U) status.[13] Despite the considerable potential of long-acting antiretroviral drugs, some potential challenges exist, including accessibility, affordability, and long-lasting drug concentrations that could lead to the development of drug resistance.[13] Further research into the advances of long-acting injectable HIV therapy can aid in overcoming these challenges and implementing strategies that can have a positive impact on HIV treatment and health care burden.

CONCLUSION

In conclusion, HIV is a significant global public health concern. Use of LA injectable drugs CAB plus RPV (Cabenuva) is an economical, viable and sustainable therapeutic addition to the treatment armamentarium that can significantly improve adherence to ART for PLWHIV-1. This further contributes to an overall improvement in quality of life. As the UNAIDS has proposed 95% treatment goals for 2030, providing access to LA injectable ART in HIV treatment programmes will be instrumental. This breakthrough regarding LA injectable CAB plus RPV is only a preview of the revolutionary innovations that are still to come for HIV treatment.

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