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Impact of increased uptake of long-acting injectable antiretroviral therapy on HIV incidence and viral suppression in the United States under 2021 FDA guidelines

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Abstract

Objectives: To determine the impact of increased long-acting injectable antiretroviral therapy (Cabotegravir-rilpivirine [CAB/RPV]) use among persons with diagnosed HIV (PWDH) with viral suppression (VLS), per 2021 US Food and Drug Administration (FDA) guidelines, on HIV incidence and levels of VLS in the US.

Methods: We used the HOPE compartmental model to simulate CAB/RPV use during 2023–2035. We first simulated a baseline scenario (no CAB/RPV), in which 69% of PWDH had VLS. We then introduced CAB/RPV in 2023 under two scenarios: (1) where CAB/RPV improved the duration of VLS post-cessation of ART use compared to oral ART; (2) where CAB/RPV additionally improved adherence. We compared cumulative 2023–35 incidence and percentage of PWDH with VLS at year-end 2035 to baseline.

Results: When CAB/RPV increased the duration of VLS only, cumulative incidence was reduced up to 9%, and VLS increased up to 4%. When CAB/RPV also improved ART adherence, incidence was reduced up to 19.5%, and VLS increased up to 9%.

Conclusions: CAB/RPV, even if only used among PWDH with VLS, may reduce HIV incidence and increase VLS, due to longer-lasting VLS post-cessation of usage. If CAB/RPV also improves ART adherence, incidence is further reduced. Improved clinical efficacy of CAB/RPV may translate to improved population-level outcomes, even in limited use cases.

Keywords

Long-acting injectable antiretroviral therapy; antiretroviral therapy (ART); viral suppression (VLS); mathematical modeling; cabotegravir-rilpivirine (CAB/RPV)

Introduction

Long-acting injectable antiretroviral therapy (LA-ART) has the potential to further improve both HIV treatment and prevention outcomes. While standard oral ART regimens are highly effective in treating HIV and are a powerful tool for prevention, adherence to a daily oral ART regimen presents both logistical and psychosocial challenges, including perceived stigma, the need to regularly refill prescriptions, and a high probability of missing doses.^[1–4] Since the FDA approval of an LA-ART regimen, cabotegravir-rilpivirine (CAB/RPV), in 2021, the question of whether shifting from a daily oral ART regimen to injections every one to two months may improve HIV treatment outcomes has been heavily investigated. Studies have shown large percentages of persons with diagnosed HIV (PWDH) reporting that they would prefer CAB/RPV to oral ART, citing perceived freedom from the demands of daily oral ART and the associated stigma, convenience, privacy, increased certainty of efficacy, and perceived reduced transmission risk.^[2, 5–8]

In addition to problems with adherence, daily oral ART regimens are also limited by the rapid loss of viral load suppression (VLS) upon cessation of use. Recent studies have confirmed VLS is lost after 2–3 weeks of treatment interruption with currently recommended oral ART regimens,^[9, 10] the same challenge faced since the earliest versions of oral ART more than twenty years ago.^[11] CAB/RPV offers the potential for substantial improvement in achieving a more durable VLS. While the FDA approved dosing frequency of CAB/RPV is every one or two months to maintain adequate drug levels to prevent resistance and maintain effectiveness, pharmacokinetic modeling studies have demonstrated that the IC-90 (the drug concentration inhibiting 90% of HIV replication) among CAB/RPV users is retained for up to nine months after last injection.^[12–14]

The 2021 FDA guidelines recommend CAB/RPV prescription to PWDH who already have viral suppression under an oral ART regimen, who comprised 65.1% of PWDH in the US as of 2022.^[15–18] Furthermore, in the event of an interrupted CAB/RPV regimen and loss of VLS, the 2021 FDA guidelines recommend that VLS first be established through an oral ART regimen prior to re-initiating CAB/RPV.^[15–17] To the authors' knowledge, no modeling study has specifically addressed the potential impact of CAB/RPV on VLS and/or HIV incidence when administered to PWDH who have VLS, in accordance with the 2021 FDA guidelines. Even within these restrictions, we expect that CAB/RPV should have an impact on HIV incidence and overall levels of VLS.

Cessation of oral ART use and subsequent loss of VLS are not uncommon among PWDH with VLS.^[19–21] As PWDH who have VLS carry effectively no transmission risk,^[22] any improvements to the duration of VLS or adherence to ART are likely to reduce HIV incidence. Given the advantages of CAB/RPV compared to oral ART in the *duration* of VLS, as well as potential improvements in adherence, we expect these benefits with

increased uptake of CAB/RPV among PWDH who have VLS. However, the magnitude of these effects on HIV incidence is not clear. Large effects would provide strong rationale for HIV prevention programs and care providers to encourage patients receiving oral ART with VLS to switch to CAB/RPV.

In this paper, we performed a modeling analysis of CAB/RPV in the United States, considering usage only among PWDH with VLS. For our analysis, we employed the HOPE model, a national-level compartmental model of HIV transmission and disease progression,^[23] which included CAB/RPV use among PWDH already virally suppressed from oral ART. We then examined the potential impact of CAB/RPV on future HIV incidence and VLS by modeling a range of scenarios in which we varied both CAB/RPV uptake, as well as the effects of CAB/RPV use on treatment adherence. We compared the change in levels of VLS and HIV incidence over the period 2023-35 to a baseline scenario with no CAB/RPV use.

Methods

We employed version 10.06 of the HOPE model, a dynamic, national-level compartmental model of HIV in the United States, for our analyses. HOPE simulates HIV transmission through both sexual contact and injection drug use, disease progression, and movement along continuum-of-care stages, incorporating population stratification by transmission group and assigned sex at birth (heterosexual male, heterosexual female, men who have sex with men, and persons who inject drugs), age (13-17, 18-24, 25-34, 35-44, 45-54, 55-64, 65+), number of HIV transmission risk factors, circumcision status, and race/ethnicity (Black/African-American, Hispanic/Latino, and Other). HIV disease stage is defined by CD4 count, and the continuum-of-care for persons living with HIV (PWH) includes five stages: undiagnosed, diagnosed but not engaged in care, engaged in care but not on ART, on ART but not VLS, and VLS.^[23] Transmission probabilities are assumed to vary based on both continuum and disease stage. Transmission risk is highest among PWH unaware of their infection, while PWH with VLS have virtually no risk of sexual transmission. Similarly, transmission is more likely among persons in the acute and late stages of HIV.

The model parameters, including those governing HIV transmission, progression through disease stages and movement within the HIV continuum of care, were determined through a combination of literature values and calibration. When reliable data for specific inputs were known from the scientific literature, we set the corresponding model input value accordingly. However, values for model inputs for which reliable data did not exist, or were only approximate, were determined by a calibration process. This process consisted of testing the model given several thousand sets of values for these inputs sampled over defined ranges, and selecting sets of values that produced model outputs in good agreement with select surveillance targets.

For the present analysis, the surveillance targets used for calibration included incidence, prevalence, mortality, continuum-of-care, and other important data in the years 2019 (for surveillance targets) and 2021 and 2023 (for levels of PrEP usage). We performed the calibration procedure eleven times, producing eleven distinct model configurations. Our baseline model configuration was selected from this set. We validated the baseline model

by comparing model outcomes to surveillance data, including estimated HIV incidence, new HIV diagnoses, percentages of PWDH aware of status, numbers of persons on PrEP, and percentages of PWDH who had VLS during the years 2020–22. The supplementary technical appendix contains further details on HOPE model, including a general overview (section 2), model structure and dynamics (sections 3–4, section 7), model calibration (section 9), parameter values (sections 5–8), validation/comparison with surveillance data (section 9), and sensitivity/uncertainty analyses (section 9).

For the baseline model scenario, we initialized the model in 2010 and ran the simulation until 2035 using the set of model parameter values identified from the parameterization and calibration process described above and presented in Tables 3.1, 4.1–4.6, 5.1–5.9, 6.1–6.14, and 9.1–9.2 of the appendix. We adjusted model parameters during the years 2020–22 to account for the effects of the COVID-19 pandemic (appendix section 5.4.1). Model inputs were restored to pre-pandemic values from the beginning of 2023 onward, and outcomes were collected over an analytic period of 2023–35.

To incorporate the effects of CAB/RPV, we adjusted model inputs during the analytic period. The incorporation of CAB/RPV was the only change made during the analytic period. All other aspects of HIV prevention and care (for example, HIV testing and linkage to care) remained at pre-2023 rates throughout.

Because, under 2021 FDA guidelines, CAB/RPV is only indicated for PWDH with VLS currently on oral ART (64.8% of modeled PWDH at the beginning of the analytic period), we modeled the effect of CAB/RPV by reducing the rate of loss of VLS. Suboptimal ART adherence is by far the largest cause of virologic rebound and ultimately, virologic failure.^[24–26] Therefore, the rate at which VLS is lost is primarily driven by two effects (please see section 5.4.3 of the appendix for a more mathematically rigorous version of this discussion):

1. *Probability of non-adherence*: annual probability of a PWDH with VLS stopping ART in a year
2. *Probability of a non-adherent PWDH losing VLS*: Probability of a PWDH with VLS who has stopped ART losing VLS within a year.

From basic probability, the product of the two probabilities above gives the overall probability of a PWDH losing VLS in a year. Clinical evidence shows that PWDH with VLS on oral ART who cease usage have a 0.5 probability of losing VLS within 22 days.^[10] Assuming an exponential distribution, this implies a probability of 1.0 of losing VLS within one year (please see section 5.4.3 of the appendix for a more detailed derivation). Hence, for oral ART, the second probability above is equal to one. This implies that the probability of a PWDH losing VLS in a year, for oral ART, is the equal to probability of stopping ART. We note that the assumption of an exponential distribution does not introduce any additional assumptions into the model; exponential distributions are implicitly assumed for all rates due to the ordinary differential equation structure of the model.^[27, 28] This assumption is standard in compartmental modeling.

However, pharmacokinetic modeling studies show that CAB/RPV users who cease usage have a 0.75 probability of losing VLS within a year.^[12–14] Due to uncertainty, we consider two CAB/RPV modeling scenarios:

1. *Conservative scenario:* In this scenario, we assume that the only difference between oral ART and CAB/RPV is that PWDH who stop CAB/RPV have a 0.75 probability (rather than 1.0) of losing VLS within a year. In this case, we assume that the loss-of-VLS rate is 0.75 times the rate of oral ART.
2. *Optimistic scenario:* In this scenario, we also assume that CAB/RPV reduces the probability of non-adherence by 0.33. Accordingly, we set the loss-of-VLS rate to 0.5 times that of oral ART, obtained by multiplying the conservative scenario (0.75 times the oral ART rate) by 0.67. This value was conservatively chosen, informed the ABOVE Study, which showed a ~45% reduction in non-adherence among CAB/RPV users.^[29]

Note that the baseline loss-of-VLS probability for oral ART in HOPE was specified for each subpopulation defined by the population race/ethnicity, age, and transmission group, with the values determined through calibration. Therefore, the loss-of-VLS parameter for CAB/RPV reflects the same underlying variation by subpopulation characteristics reported for oral ART. Relevant parameter values are provided in Table 5.5 of the appendix. To evaluate the effects of CAB/RPV, we first performed a baseline simulation in which we assumed no CAB/RPV usage over the analytic period 2023–35. This assumption of no CAB/RPV use was informed by December 2023 data from the HIV outpatient study (HOPS), which showed that the portion of PWDH on CAB/RPV was quite small (2.4%); we assume this was smaller at the beginning of the year. Then, for both CAB/RPV scenarios, we ran several simulations, varying the percentage of PWDH on oral ART and virally suppressed who switched to CAB/RPV over 2023–35: 10%, 30%, 50%, 70% and 90%. For each scenario and level of CAB/RPV usage, we compared both the percentage of PWDH with VLS at the end of 2035 and the cumulative HIV incidence during 2023–35 with those outcomes in the baseline scenario.

To evaluate the robustness of our results and account for uncertainty, we conducted an uncertainty analysis by running both baseline and 90% CAB/RPV scenarios for each of the ten additional, distinct sets of input values defining the additional model configurations identified during the calibration procedure, as previously discussed. These simulations were used to derive possible ranges for our key outcomes during the model calibration and validation (Section 9 of the technical appendix).

Results

In Table 1, we provide the simulation results including the cumulative HIV infections during the years 2023–35, and the percentage of infections averted compared to the baseline scenario (which assumes no use of CAB/RPV over the analytic period), for each model scenario and level of CAB/RPV usage. Without CAB/RPV, we estimated a total of 424,000 HIV infections from 2023–35.

Increasing CAB/RPV use among PWDH who were on oral ART and virally suppressed (that is, switching from oral ART to CAB/RPV) resulted in reductions in simulated HIV incidence. For 10% CAB/RPV use, cumulative infections decreased by 1% in the conservative scenario and 2% in the optimistic scenario. Increasing CAB/RPV usage to 50% resulted in 5% and 10.5% reductions in cumulative incidence for the conservative and optimistic scenarios, respectively. Finally, 90% CAB/RPV usage resulted in 9% and 19.5% reductions in cumulative HIV incidence for the conservative and optimistic scenarios, respectively. We plotted the annual HIV incidence for each simulated scenario during the intervention years in Figure 1.

In the simulation, 69% of PWDH were virally suppressed at the end of 2035 in the baseline scenario (Table 2, Figure 2). The overall percentages of PWDH who were virally suppressed at the end of 2035 at 10%, 20%, 30%, 50%, 70%, and 90% CAB/RPV use were 69.5%, 70%, 71%, and 72%, respectively. In the corresponding optimistic scenarios, these percentages were 70%, 71.5%, 73.5%, 75.5%, and 78%. Increased CAB/RPV use among PWDH with VLS increased overall levels of VLS among PWDH by up to 4% in the conservative scenario and by up to 9% in the optimistic scenario.

Levels of VLS by each racial/ethnic (R/E) group, in the baseline scenario at year-end 2035, were 64% for Black/African-American (B/AA) PWDH, 68% for Hispanic/Latino (H/L) PWDH and 75.5% for PWDH of all other R/E groups (O). Across the conservative scenarios, VLS at year-end 2035 ranged from 64.5% to 68.5% among B/AA PWDH, 68.5% to 72% among H/L PWDH, and 77.5% to 79% among O PWDH. For the optimistic scenarios, these respective ranges were 65%-74%, 69%-77%, and 76%-83%. The observed increases in VLS varied by R/E group. In the conservative scenario, increased CAB/RPV uptake increased viral suppression percentage by up to 4.5% for B/AA PWDH, 4% for H/L PWDH, and 3.5% for PWDH of other racial/ethnic groups. For the optimistic scenario, the respective increases were 10%, 8%, and 7.5% percentage points.

To evaluate the robustness of our results, we simulated the baseline and 90% CAB/RPV optimistic scenarios using ten alternate sets of input values and model configurations. Across the alternate model configurations, total new infections over the intervention period ranged from 341,000-424,000 in the baseline scenario and 235,000-360,000 in the 90% CAB/RPV optimistic scenario. The corresponding percent decreases in cumulative incidence between these scenarios ranged from 17.5% to 26% across the calibration sets. Viral suppression at year-end 2035 ranged from 65%-70.5% and 75.5%-79.5% across the alternate model configurations in the baseline and 90% CAB/RPV optimistic scenarios, respectively. The overall difference in viral suppression at year-end 2035 between the baseline and 90% CAB/RPV optimistic scenario among PWDH was similar across the ten alternate model configurations, ranging from 9%-10.5%.

Discussion

Our simulations showed that CAB/RPV reduces HIV incidence and increases levels of viral suppression, even when uptake is restricted to PWDH who already have VLS under an oral ART regimen. In a conservative scenario, in which CAB/RPV was assumed to improve the

duration of viral suppression upon ART cessation compared to oral ART, but not change ART adherence, incidence was reduced by as much as 9%. In addition, VLS among PWDH increased from 69% in the baseline scenario to as much as 73% at year-end 2035 in this conservative scenario. These results suggest that the increased duration of VLS, post-ART cessation, on its own, may have substantial impacts on key HIV measures.

This impact was greater in the optimistic scenario when we assumed that CAB/RPV provided additional improvements in ART adherence compared to oral ART regimens. At lower levels of CAB/RPV usage (10% and 30%), the simulation showed that approximately twice as many infections were prevented compared to the conservative scenario. The difference between the conservative and optimistic scenarios increased as the percentage of PWDH with VLS on CAB/RPV increased. At 90% levels of CAB/RPV use, more than twice as many infections were prevented in the optimistic scenario compared with the conservative scenario, which was nearly 20% fewer infections than in the baseline scenario. We also observed similar trends in levels of VLS among PWDH. In summary, our simulation results showed that the improved durability of viral suppression offered by CAB/RPV, as well as advantages in ART adherence, can lead to substantial reductions in HIV incidence. Our uncertainty analysis suggested that these findings are robust, as decreases in HIV incidence and increases in VLS were consistent across the simulations from the 10 alternate model configurations.

It is also likely that expanding the use of CAB/RPV more broadly beyond PWDH with VLS will increase its impact. Recent clinical studies have shown that CAB/RPV is effective in increasing VLS among PWDH who have difficulty achieving and maintaining VLS using oral ART regimens, likely due to difficulty in ART adherence.^[6, 30, 31] Additional evidence suggests that CAB/RPV is non-inferior to oral ART in achieving VLS among ART-naïve PWDH.^[32] CAB/RPV thus offers significant potential as a tool to increase levels of VLS among populations not considered within the current study.

Results shown in the current modeling analysis, therefore, represent a lower bound for the potential impact of CAB/RPV when expanding the use of CAB/RPV beyond the 2021 FDA guidelines. If usage is increased among persons who have not achieved durable VLS, or who have not yet initiated ART, the impact will be larger. To better quantify the possible impact of CAB/RPV when expanding the use beyond the limits of the FDA guidelines, additional modeling analyses considering a broader uptake are necessary.

Given present racial/ethnic disparities in levels of VLS, concerns that uptake of CAB/RPV among PWDH with VLS may exacerbate these disparities are well-founded, as has been observed with past innovations in ART.^[33] However, our analysis showed no such increases in racial/ethnic disparities in VLS. In each of the modeled scenarios, as CAB/RPV uptake increased, racial/ethnic disparities in levels of VLS decreased slightly. Nonetheless, significant disparities remained, even in the most optimistic scenario; thus, for CAB/RPV to be a helpful tool for eliminating racial/ethnic disparities in VLS levels, expansion of uptake beyond PWDH with VLS will be necessary.

In this study, we did not model scenarios in which we slowly increase over time the percentage of PWDH with VLS who use CAB/RPV. That framework would be appropriate for a study designed to evaluate specific CAB/RPV implementation programs. However, this study had a different focus, which was to directly understand the overall effect of CAB/RPV when used under 2021 FDA guidelines. This study addresses the question: if a given percentage of PWDH with VLS are using CAB/RPV, what is the resulting response on HIV incidence? In general, the response in incidence to changes in levels of viral suppression is not immediate but requires time to properly assess. Hence, an approach in which we slowly increase the level of CAB/RPV over time complicates how we can interpret the resultant changes in incidence and levels of VLS.

The current study also did not consider important cost and logistical issues associated with increased CAB/RPV, which may be significant.^[34] The modeling analysis in Ross et al.^[35] found that LA-ART (though not CAB/RPV specifically) was cost-effective; however, those authors assumed that CAB/RPV increases levels of VLS among PWDH who have not already achieved durable viral suppression. Although our analyses showed incidence reductions due to increased CAB/RPV among PWDH with VLS, we did not address whether these reductions are sufficient to make increased CAB/RPV usage following the 2021 FDA guidelines cost-effective.

Our analysis is not directly comparable to the other extant modeling literature on this topic. Parker et al.^[36] performed a modeling analysis of increased LA-ART uptake in Canada, in which LA-ART was primarily distinguished from oral ART by improved adherence among non-ART adherent (and hence not virally suppressed) PWDH. Culhane et al.^[37] performed a modeling analysis of LA-ART in Kenya, in which CAB/RPV was assumed to improve ART adherence among PWDH who had not yet achieved VLS. Neither study specifically examined the effects of LA-ART uptake among PWDH who have VLS in high-income countries, and both studies considered LA-ART generically, rather than CAB/RPV specifically. A recent study modeling study from Chen et al. found that CAB/RPV, together with other supportive social services, may be an effective tool to increase levels of VLS among PWDH without VLS who are experiencing adherence barriers.^[38] This study differs from the present as it does not examine the impact of CAB/RPV when administered to PWDH who have VLS; furthermore, the analysis focused on levels of VLS in a specific cohort, and did not assess the broader, population-level impact of CAB/RPV in terms of HIV infections prevented.

Lastly, this analysis did not address the question of what, if any, effect CAB/RPV has had on HIV incidence and diagnosis in 2022, prior to the start of the analytic period in this paper. While this is an important question, we note that, as CAB/RPV uptake is still limited, the magnitude of any such effect is likely to be small.^[29] Additionally, new HIV diagnoses were higher in the US in 2022 compared to the years immediately preceding the COVID-19 pandemic.^[18] This is primarily due to additional HIV diagnoses being detected in 2022 that were missed due to the COVID-19 pandemic in 2020-21, and not necessarily indicative of any changes in HIV incidence trends.^[18, 39, 40] However, these distortions make detecting very small effects of pre-existing CAB/RPV use on diagnosis or incidence to date very challenging.

CAB/RPV offers significant advantages compared to oral ART regimens. In addition to increased durable VLS, injectable regimens likely result in greater ART adherence. Our simulations showed that increased usage of CAB/RPV reduced HIV incidence and increased levels of VLS, even if such usage was limited to PWDH who were already virally suppressed. Leveraging CAB/RPV to ensure its maximal impact will require expanding its use beyond the 2021 FDA guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Source of Funding:

All support for this project was provided by the Centers for Disease Control and Prevention. The authors declare no conflicts of interest.

Disclaimer:

The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

References

1. Boffito M, Jackson A, Owen A, Becker S. New approaches to antiretroviral drug delivery: challenges and opportunities associated with the use of long-acting injectable agents. *Drugs* 2014; 74(1):7–13. [PubMed: 24327298]
2. Slama L, Porcher R, Linard F, Chakvetadze C, Cros A, Carillon S, et al. Injectable long acting antiretroviral for HIV treatment and prevention: perspectives of potential users. *BMC Infect Dis* 2023; 23(1):98. [PubMed: 36803606]
3. Carillon S, Gallardo L, Linard F, Chakvetadze C, Viard JP, Cros A, et al. Perspectives of injectable long acting antiretroviral therapies for HIV treatment or prevention: understanding potential users' ambivalences. *AIDS Care* 2020; 32(sup2):155–161.
4. Gakhar H, Kamali A, Holodniy M. Health-related quality of life assessment after antiretroviral therapy: a review of the literature. *Drugs* 2013; 73(7):651–672. [PubMed: 23591907]
5. Saag MS, Gandhi RT, Hoy JF, Landovitz RJ, Thompson MA, Sax PE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society-USA Panel. *JAMA* 2020; 324(16):1651–1669. [PubMed: 33052386]
6. Collins LF, Corbin-Johnson D, Asrat M, Morton ZP, Dance K, Condra A, et al. Early Experience Implementing Long-Acting Injectable Cabotegravir/Rilpivirine for Human Immunodeficiency Virus-1 Treatment at a Ryan White-Funded Clinic in the US South. *Open Forum Infect Dis* 2022; 9(9):ofac455. [PubMed: 36147599]
7. Murray M, Antela A, Mills A, Huang J, Jäger H, Bernal E, et al. Patient-Reported Outcomes in ATLAS and FLAIR Participants on Long-Acting Regimens of Cabotegravir and Rilpivirine Over 48 Weeks. *Aids and Behavior* 2020; 24(12):3533–3544. [PubMed: 32447500]
8. Akinwunmi B, Buchenberger D, Scherzer J, Bode M, Rizzini P, Vecchio F, et al. Factors associated with interest in a long-acting HIV regimen: perspectives of people living with HIV and healthcare providers in four European countries. *Sexually Transmitted Infections* 2021; 97(8):566–573. [PubMed: 33632889]
9. Sneller MC, Huiting ED, Clarridge KE, Seamon C, Blazkova J, Justement JS, et al. Kinetics of Plasma HIV Rebound in the Era of Modern Antiretroviral Therapy. *J Infect Dis* 2020; 222(10):1655–1659. [PubMed: 32443148]

10. Li JZ, Aga E, Bosch RJ, Pilkinton M, Kroon E, MacLaren L, et al. Time to Viral Rebound After Interruption of Modern Antiretroviral Therapies. *Clin Infect Dis* 2022; 74(5):865–870. [PubMed: 34117753]
11. Chun TW, Davey RT Jr., Engel D, Lane HC, Fauci AS Re-emergence of HIV after stopping therapy. *Nature* 1999; 401(6756):874–875. [PubMed: 10553903]
12. Han K, Baker M, Lovern M, Paul P, Xiong Y, Patel P, et al. Population pharmacokinetics of cabotegravir following administration of oral tablet and long-acting intramuscular injection in adult HIV-1-infected and uninfected subjects. *Br J Clin Pharmacol* 2022; 88(10):4607–4622. [PubMed: 35695476]
13. Han KL, Gevorkyan H, Shaik JS, Crauwels H, Leemereise C, Bontempo G, et al. Pharmacokinetics and tolerability of cabotegravir and rilpivirine long-acting intramuscular injections to the (lateral thigh) muscles of healthy adult participants. *Antimicrob Agents Ch* 2024; 68(1).
14. Bettonte S, Berton M, Battagay M, Stader F, Marzolini C. Development of a physiologically-based pharmacokinetic model to simulate the pharmacokinetics of intramuscular antiretroviral drugs. *Cpt-Pharmacomet Syst* 2024; 13(5):781–794.
15. Cabenuva (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use. In: United States Food and Drug Administration; 2021.
16. McGowan JP, Fine SM, M. VR. Use of Injectable CAB/RPV LA as Replacement ART in Virally Suppressed Adults. In. Baltimore, MD (USA): Johns Hopkins University; 2023.
17. ViiV Healthcare announces US FDA approval of cabenuva (cabotegravir, rilpivirine) for use every two months, expanding the label of the first and only complete long-acting HIV treatment. In: ViiV Healthcare; 2022.
18. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 territories and freely associated states, 2022. In: HIV Surveillance Supplemental Report: Centers for Disease Control and Prevention; 2024.
19. Samji H, Taha TE, Moore D, Burchell AN, Cescon A, Cooper C, et al. Predictors of unstructured antiretroviral treatment interruption and resumption among HIV-positive individuals in Canada. *HIV Med* 2015; 16(2):76–87. [PubMed: 25174373]
20. O'Connor J, Smith C, Lampe FC, Johnson MA, Chadwick DR, Nelson M, et al. Durability of viral suppression with first-line antiretroviral therapy in patients with HIV in the UK: an observational cohort study. *Lancet HIV* 2017; 4(7):e295–e302. [PubMed: 28479492]
21. Craw JA, Beer L, Tie Y, Jaenicke T, Shouse RL, Prejean J. Viral Rebound Among Persons With Diagnosed HIV Who Achieved Viral Suppression, United States. *J Acquir Immune Defic Syndr* 2020; 84(2):133–140. [PubMed: 32084054]
22. Eisinger RW, Dieffenbach CW, Fauci AS. HIV Viral Load and Transmissibility of HIV Infection Undetectable Equals Untransmittable. *Jama-J Am Med Assoc* 2019; 321(5):451–452.
23. Viguerie A, Jacobson EU, Hicks KA, Bates L, Carrico J, Honeycutt A, et al. Assessing the impact of COVID-19 on HIV Outcomes in the United States: A modeling study. *Sex Transm Dis* 2024.
24. SeyedAlinaghi S, Afsahi AM, Moradi A, Parmoon Z, Habibi P, Mirzapour P, et al. Current ART, determinants for virologic failure and implications for HIV drug resistance: an umbrella review. *AIDS Res Ther* 2023; 20(1):74. [PubMed: 37884997]
25. Yuan D, Li M, Zhou Y, Shi L, Lu J, Fu G, et al. Influencing factors and adverse outcomes of virologic rebound states in anti-retroviral-treated individuals with HIV infection. *J Virus Erad* 2023; 9(1):100320. [PubMed: 37008574]
26. McCluskey SM, Siedner MJ, Marconi VC. Management of Virologic Failure and HIV Drug Resistance. *Infect Dis Clin North Am* 2019; 33(3):707–742. [PubMed: 31255384]
27. Breda D, Diekmann O, de Graaf WF, Pugliese A, Vermiglio R. On the formulation of epidemic models (an appraisal of Kermack and McKendrick). *J Biol Dyn* 2012; 6 Suppl 2:103–117. [PubMed: 22897721]
28. Guglielmi N, Iacomini E, Viguerie A. Identification of time delays in COVID-19 data. *Epidemiologic Methods* 2023; 12(1).
29. Garris C, Desai R, Chang R, Clear L, Chen Z, Liu D, et al. 1024. Real-world Adherence and Persistence with Long-Acting Cabotegravir Plus Rilpivirine (CAB+RPV LA) Compared to Oral

- Antiretroviral Therapy (ART) Among People with HIV (PWH) in the US: The ABOVE Study. *Open Forum Infectious Diseases* 2023; 10(Supplement_2).
30. Gandhi M, Hickey M, Imbert E, Grochowski J, Mayorga-Munoz F, Szumowski JD, et al. Demonstration Project of Long-Acting Antiretroviral Therapy in a Diverse Population of People With HIV. *Ann Intern Med* 2023; 176(7):969–974. [PubMed: 37399555]
31. Hocqueloux LM G, Bafong-Ketchemen S, Bois J, Guinard J, Prazuck TS,A, Avettand-Fenoel V. Fully Injectable Antiretroviral Multitherapy to Overcome Decades of Virological Failure in Three Women With HIV-1 and Non-Adherent to Oral Drugs. *International Journal of Antimicrobial Agents* 2024; 64(3):107254. [PubMed: 38925226]
32. Christopoulos KA, Grochowski J, Mayorga-Munoz F, Hickey MD, Imbert E, Szumowski JD, et al. First Demonstration Project of Long-Acting Injectable Antiretroviral Therapy for Persons With and Without Detectable Human Immunodeficiency Virus (HIV) Viremia in an Urban HIV Clinic. *Clin Infect Dis* 2023; 76(3):e645–e651. [PubMed: 35913500]
33. Zalla LC, Cole SR, Eron JJ, Adimora AA, Vines AI, Althoff KN, et al. Association of Race and Ethnicity With Initial Prescription of Antiretroviral Therapy Among People With HIV in the US. *Jama-J Am Med Assoc* 2023; 329(1):52–62.
34. McCrimmon T, Collins LF, Perez-Brumer A, Bazzi AR, Shaffer VA, Kerrigan D, et al. Long-Acting Injectable Antiretrovirals for HIV Treatment: A Multi-Site Qualitative Study of Clinic-Level Barriers to Implementation in the United States. *Aids Patient Care St* 2024; 38(2):61–69.
35. Ross EL, Weinstein MC, Schackman BR, Sax PE, Paltiel AD, Walensky RP, et al. The clinical role and cost-effectiveness of long-acting antiretroviral therapy. *Clin Infect Dis* 2015; 60(7):1102–1110. [PubMed: 25583979]
36. Parker B, Ward T, Hayward O, Jacob I, Arthurs E, Becker D, et al. Cost-effectiveness of the long-acting regimen cabotegravir plus rilpivirine for the treatment of HIV-1 and its potential impact on adherence and viral transmission: A modelling study. *PLoS One* 2021; 16(2):e0245955. [PubMed: 33529201]
37. Culhane J, Sharma M, Wilson K, Roberts DA, Mugo C, Wamalwa D, et al. Modeling the health impact and cost threshold of long-acting ART for adolescents and young adults in Kenya. *EClinicalMedicine* 2020; 25:100453. [PubMed: 32954235]
38. Chen W, Gandhi M, Sax PE, Neilan AM, Garland WH, Wilkin T, et al. Projected Benefits of Long-Acting Antiretroviral Therapy in Nonsuppressed People With Human Immunodeficiency Virus Experiencing Adherence Barriers. *Open Forum Infect Dis* 2023; 10(8):ofad390. [PubMed: 37601728]
39. Viguerie A, Song R, Satcher Johnson AJ, Lyles CM, Hernandez A, Farnham PG. Isolating the Effect of COVID-19-Related Disruptions on HIV Diagnoses in the United States in 2020. *JAIDS* 2023; 92(4):293–299. [PubMed: 36515707]
40. Viguerie A, Song R, Johnson AS, Lyles CM, Hernandez A, Farnham PG. COVID-related excess missed HIV diagnoses in the United States in 2021: follow-up to 2020. *AIDS* 2024.

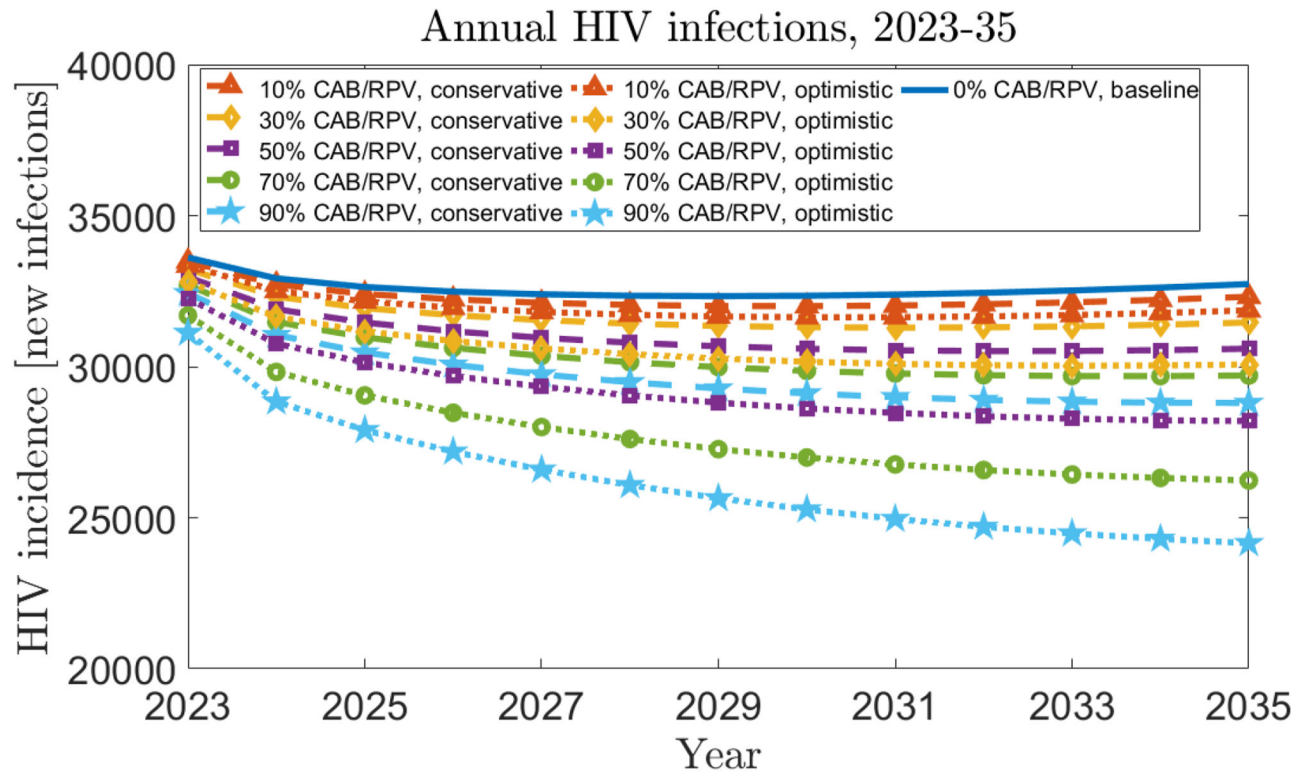


Figure 1: HIV incidence for varying levels of CAB/RPV use in each scenario†.

Note: for reasons of visibility the y-axis scale does not begin at zero.

ART = antiretroviral therapy, B/AA = Black/African-American, CAB/RPV = Cabotegravir-rilpivirine, H/L = Hispanic/Latino, O = other racial/ethnic groups besides B/AA and H/L, PWDH = people with diagnosed HIV, VLS = viral load suppression.

†The *conservative* scenario refers to the scenario in which CAB/RPV increases the length of VLS upon cessation of use; the *optimistic* scenario refers to the scenario in which CAB/RPV is assumed additionally to improve overall ART adherence.

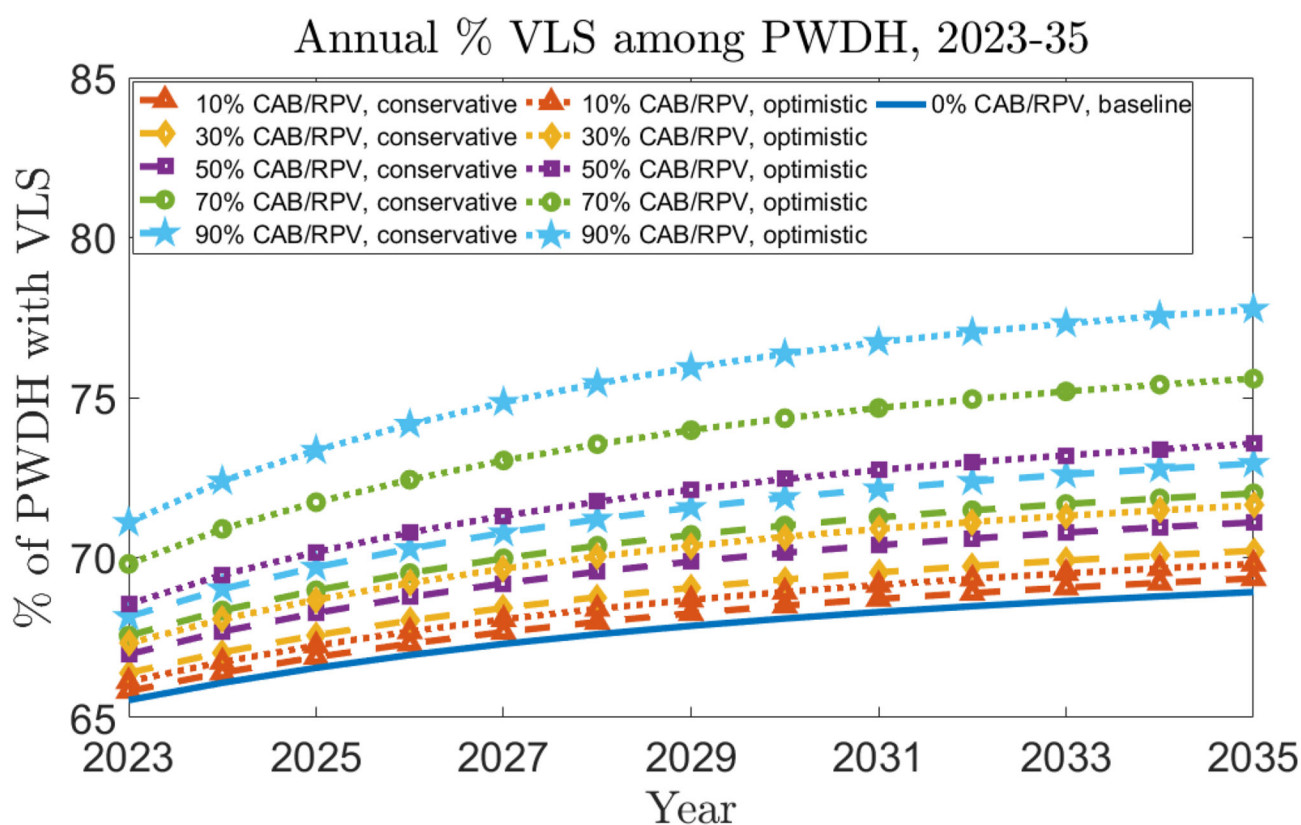


Figure 2: Levels of VLS for varying levels of CAB/RPV usage in each scenario. †

Note: for reasons of visibility the y-axis scale does not begin at zero.

ART = antiretroviral therapy, PWDH = persons with diagnosed HIV, VLS = viral load suppression.

†The *conservative* scenario refers to the scenario in which CAB/RPV increases the length of VLS upon cessation of use; the *optimistic* scenario refers to the scenario in which CAB/RPV is assumed additionally to improve overall ART adherence.

Table 1:

Cumulative HIV infections, 2023-35, for each scenario and level of CAB/RPV usage.

Scenario	Baseline: No CAB/RPV	10% CAB/RPV*	30% CAB/RPV*	50% CAB/RPV*	70% CAB/RPV*	90% CAB/RPV*
Conservative [†]	424,000	420,000 (1.0%)	411,500 (3.0%)	403,000 (5.0%)	395,000 (7.0%)	386,000 (9.0%)
Optimistic [†]	424,000	415,500 (2.0%)	399,000 (6.0%)	380,000 (10.5%)	361,000 (15.0%)	341,000 (19.5%)

Numbers in parentheses are the percentage of new infections averted compared to the baseline scenario.

CAB/RPV = Cabotegravir-rilpivirine, VLS = viral load suppression.

* The percentage refers to the percentage of PWDH with VLS assumed to be on CAB/RPV

[†] The *conservative* scenario refers to the scenario in which CAB/RPV increases the length of VLS upon cessation of use; the *optimistic* scenario refers to the scenario in which CAB/RPV is assumed to also improve overall ART adherence.

Table 2:
Percentage of PWDH HIV who were VLS, year-end 2035.

Scenario	R/E	Baseline: No CAB/RPV	10% CAB/RPV*	30% CAB/RPV*	50% CAB/RPV*	70% CAB/RPV*	90% CAB/RPV*
Conservative †	All	69.0%	69.5% (0.5%)	70.0% (1.0%)	71.0% (2.0%)	72.0% (3.0%)	73.0% (4.0%)
Optimistic †	All	69.0%	70.0% (1.0%)	71.5% (2.5%)	73.5% (4.5%)	75.5% (6.7%)	78.0% (9.0%)
Conservative †	B/AA	64.0%	64.5% (0.5%)	65.5% (1.5%)	66.5% (2.5%)	67.5% (3.5%)	68.5% (4.5%)
Optimistic †	B/AA	64.0%	65.0% (1.0%)	67.0% (3.0%)	69.0% (5.0%)	71.5% (7.5%)	74.0% (10.0%)
Conservative †	H/L	68.0%	68.5% (0.5%)	69.5% (1.5%)	70.0% (2.0%)	71.0% (3.0%)	72.0% (4.0%)
Optimistic †	H/L	68.0%	69.0% (1.0%)	71.0% (3.0%)	72.5% (4.5%)	74.5% (6.5%)	77.0% (9.0%)
Conservative †	O	75.5%	76.0% (0.5%)	76.5% (1.0%)	77.0% (1.5%)	78.0% (2.5%)	79.0% (3.5%)
Optimistic †	O	75.5%	76.0% (0.5%)	78.0% (2.5%)	79.5% (4.0%)	81.0% (5.5%)	83.0% (7.5%)

Numbers in parentheses are the absolute difference in percentage compared to the baseline scenario.

ART = antiretroviral therapy, B/AA = Black/African-American, CAB/RPV = Cabotegravir-rilpivirine, H/L = Hispanic/Latino, O = other racial/ethnic groups besides B/AA and H/L, PWDH = people with diagnosed HIV, VLS = viral load suppression.

* The percentage refers to the percentage of PWDH with VLS assumed to be on CAB/RPV

† The *conservative* scenario refers to the scenario in which CAB/RPV increases the length of VLS upon cessation of use; the *optimistic* scenario refers to the scenario in which CAB/RPV is assumed to also improve overall ART adherence.