

# Projected Benefits of Long-Acting Antiretroviral Therapy in Nonsuppressed People With Human Immunodeficiency Virus Experiencing Adherence Barriers

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**Background.** In a demonstration project, long-acting, injectable cabotegravir-rilpivirine (CAB-RPV) achieved viral suppression in a high proportion of people with HIV (PWH) who were virologically nonsuppressed with adherence barriers. We projected the long-term impact of CAB-RPV for nonsuppressed PWH experiencing adherence barriers.

**Methods.** Using the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model, we compared 3 strategies: (1) standard of care oral integrase inhibitor-based ART (*INSTI*); (2) *INSTI*-based ART with supportive social services ("wraparound services" [WS]) (*INSTI/WS*); and (3) CAB-RPV with WS (*CAB-RPV/WS*). Model outcomes included viral suppression (%) and engagement in care (%) at 3 years, and life expectancy (life-years [LYs]). Base case cohort characteristics included mean age of 47y (standard deviation [SD], 10y), 90% male at birth, and baseline mean CD4 count 150/μL (SD, 75/μL). Viral suppression at 3 months was 13% (*INSTI*), 28% (*INSTI/WS*), and 60% (*CAB-RPV/WS*). Mean loss to follow-up was 28/100 person-years (PY) (SD, 2/100 PY) without WS and 16/100 PY (SD, 1/100 PY) with WS.

**Results.** Projected viral suppression at 3 years would vary widely: 16% (*INSTI*), 38% (*INSTI/WS*), and 44% (*CAB-RPV/WS*). Life expectancy would be 7.4 LY (*INSTI*), 9.0 LY (*INSTI/WS*), and 9.4 LY (*CAB-RPV/WS*). Projected benefits over oral ART would be greater for PWH initiating *CAB-RPV/WS* at lower CD4 counts. Across plausible key parameter ranges, *CAB-RPV/WS* would improve viral suppression and life expectancy compared with oral *INSTI* strategies.

**Conclusions.** These model-based results support that long-acting injectable CAB-RPV with extensive support services for nonsuppressed PWH experiencing adherence barriers is likely to increase viral suppression and improve survival. A prospective study to provide further evidence is needed.

**Keywords.** adherence; HIV; long-acting antiretrovirals; resistance; simulation modeling.

## Introduction

Most people with human immunodeficiency virus (HIV) (PWH) achieve durable viral suppression using currently available oral antiretroviral therapy (ART) regimens [1, 2]. Challenges remain, however, with ART adherence and engagement in care for some PWH due to structural, behavioral, and social barriers [3, 4].

Given the multifaceted nature of adherence barriers, programs that provide intensive psychosocial assistance, care coordination, and outreach can improve engagement in care and ART adherence for some, but others continue to experience persistent viremia due to the severity of challenges such as housing instability, serious mental illness, and substance use disorders [3–7]. A long-acting ART (LA-ART) strategy designed for infrequent, observed dosing would eliminate the need for strict daily adherence to oral ART [8, 9], substantially lowering the barriers to ART adherence.

Recent randomized trials showed that an injectable formulation of cabotegravir (CAB), an integrase strand transfer inhibitor (*INSTI*), with rilpivirine (RPV), a nonnucleoside reverse transcriptase inhibitor (NNRTI), dosed intramuscularly every 4 or 8 weeks was noninferior to oral ART among PWH already virologically suppressed on oral ART and with no history of treatment failure or resistance [10, 11]. Based on the results of these trials, the United States (US) Food and Drug Administration

Received 12 June 2023; editorial decision 09 July 2023; accepted 19 July 2023; published online 22 July 2023

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<https://doi.org/10.1093/ofid/ofad390>

(FDA) approved CAB-RPV in 2021 for both ART-naive and ART-experienced PWH in the US who have sustained virologic suppression [12, 13].

No clinical trials have evaluated CAB-RPV in PWH with viremia, and current treatment guidelines in the US advise against using this regimen in nonsuppressed PWH [13, 14]. A demonstration project in San Francisco, however, reported 96.4% (55/57) viral suppression with CAB-RPV coupled with extensive social and clinical supports in 57 nonsuppressed PWH experiencing barriers to adherence (median follow-up, 26 weeks) [15]. With limited data on the effectiveness of CAB-RPV in nonsuppressed PWH, simulation modeling allows for an examination of the impact of uncertainty in available data, as well as projecting long-term outcomes beyond the time horizon of empirical studies. Our objective was to use an HIV simulation model to project the long-term clinical outcomes of CAB-RPV in nonsuppressed PWH experiencing barriers to adherence to oral antiretrovirals.

## METHODS

### Analytic Overview

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model, a validated microsimulation model of HIV disease and treatment [16–18], to investigate the clinical impact of three treatment strategies for nonsuppressed PWH experiencing adherence barriers: (1) current US standard of care with INSTI-based oral ART, consistent with US Department of Health and Human Services guidelines [13] (*INSTI*); (2) INSTI coupled with additional social services including community-based supports (eg, case managers, nursing services), hereafter referred to as wraparound services, or “WS” (*INSTI/WS*); and (3) long-acting injectable CAB-RPV with the same wraparound services (*CAB-RPV/WS*). This approach allowed us to examine the independent potential benefits of LA-ART and wraparound services.

### Management of Observed Viremia

A major concern about prescribing CAB-RPV to nonsuppressed PWH is the development of acquired drug resistance to two critical classes of ART: INSTIs and NNRTIs [19]. To bias the analysis against CAB-RPV, we assumed that people who develop viremia while using injectable CAB-RPV could develop INSTI and NNRTI resistance and would need to switch to a protease inhibitor (PI)-based oral ART regimen. If PWH are detected to have viremia while prescribed an oral INSTI-based or PI-based regimen, we assume that they restart the same regimen, given the infrequent development of acquired resistance and the availability of genotypic resistance testing in the US to inform ART selection [20, 21].

### Model Structure

CEPAC is an individual-level microsimulation model of HIV disease and treatment that projects long-term clinical outcomes

**Table 1. Selected Base Case Input Parameters in an Analysis of Long-Acting Cabotegravir-Rilpivirine With Wraparound Services Compared With Oral Integrase Inhibitor–Based Antiretroviral Therapy With or Without Wraparound Services for Nonsuppressed People With HIV Experiencing Adherence Barriers**

Parameter	Value	Source	
Cohort characteristics			
Age, y, mean (SD)	47 (10)	Derived from [15]	
Sex at birth, male/female %	90/10		
CD4 count, cells/ $\mu$ L, mean (SD)	150 (75)		
Adherence distribution on oral INSTI-based ART			
	Without WS	With WS	Derived from [7]
Mean, %	65	67	
Proportion with MPR 50%–66%	63	32	
Proportion with MPR 66%–70%	35	57	
Proportion with MPR 70%–95%	2	10	
HIV RNA suppression at 3 mo after ART initiation			
<i>INSTI, INSTI/WS</i>	13%	28%	[7, 21–25]
<i>CAB-RPV/WS</i>	NA	60%	[15]
Subsequent rates of viremia, per 100 PY			
<i>INSTI, INSTI/WS</i>	7.37	7.19	[7, 21–25]
<i>CAB-RPV/WS</i>	NA	3.29	[26]
Engagement in care			
Loss to follow-up rate, per 100 PY, mean (SD)	28 (2)	16 (1)	Derived from [7, 27]
Return to care rate, per 100 PY	18	18	[28]
RMR of non-HIV-related mortality vs the general population	9	9	[29]

Abbreviations: ART, antiretroviral therapy; CAB-RPV/WS, long-acting injectable cabotegravir-rilpivirine with wraparound services; HIV, human immunodeficiency virus; INSTI, oral integrase inhibitor–based antiretroviral therapy; INSTI/WS, oral integrase inhibitor–based antiretroviral therapy with wraparound services; MPR, medication possession ratio; NA, not applicable; PY, person-years; RMR, relative mortality ratio; SD, standard deviation; WS, wraparound services.

and survival [16–18]. Simulated PWH enter the model with age, sex at birth, CD4 count, HIV RNA level, and adherence to care drawn from user-specified distributions (Supplementary Methods). For simulated PWH taking oral ART, PWH with lower adherence have a lower probability of achieving initial suppression and are more likely to develop subsequent viremia. For LA-ART, the probability of initial suppression and subsequent viremia do not depend on the adherence of simulated people because the long-acting formulation eliminates the need for adherence to daily pills. All simulated PWH with lower adherence are also at increased risk of disengaging from care, which results in discontinuing oral or LA-ART. In the absence of any ART, PWH experience a monthly decline in CD4 cell count, an increase in HIV RNA level, and increased HIV-related morbidity and mortality [16–18]. Wraparound services promote better virologic suppression through strengthening engagement in care. Additional details about the CEPAC model are available online: <https://mpec.massgeneral.org/cepac-model/>.

### Model Outcomes

For each strategy, model outcomes included viral suppression, engagement in care, and survival at 3 years, as well as life expectancy.

**Table 2. Projected Clinical Impact of Long-Acting Cabotegravir-Rilpivirine With Wraparound Services Compared With Oral Integrase Inhibitor–Based Antiretroviral Therapy With or Without Wraparound Services for Nonsuppressed People With HIV Experiencing Adherence Barriers**

Strategies	At 3 Years			Life Expectancy, y
	Viral Suppression, % <sup>a</sup>	Engagement in Care, % <sup>a</sup>	Survival, % <sup>a</sup>	
CD4 count = 150 (SD, 75) cells/μL (base case)				
<i>INSTI</i>	16	45	73	7.4
<i>INSTI/WS</i>	38	57	77	9.0
<i>CAB-RPV/WS</i>	44	58	79	9.4
One-way sensitivity analyses for cohorts of PWH with different baseline CD4 counts				
CD4 count = 50 (SD, 25) cells/μL				
<i>INSTI</i>	16	40	62	6.3
<i>INSTI/WS</i>	37	54	71	8.3
<i>CAB-RPV/WS</i>	43	56	74	8.7
CD4 count = 350 (SD, 75) cells/μL				
<i>INSTI</i>	16	46	81	9.0
<i>INSTI/WS</i>	38	59	83	10.2
<i>CAB-RPV/WS</i>	44	59	83	10.4
CD4 count = 500 (SD, 75) cells/μL				
<i>INSTI</i>	16	46	83	9.7
<i>INSTI/WS</i>	38	59	84	10.7
<i>CAB-RPV/WS</i>	44	59	84	10.8

Abbreviations: CAB-RPV/WS, long-acting injectable cabotegravir-rilpivirine with wraparound services; INSTI, oral integrase inhibitor–based antiretroviral therapy; INSTI/WS, oral integrase inhibitor–based antiretroviral therapy with wraparound services; PWH, people with human immunodeficiency virus; SD, standard deviation.

<sup>a</sup>These percentages were calculated by dividing the number of simulated PWH who would be virologically suppressed, engaged in care, or alive at 3 years by the total number of simulated PWH at model start.

For the *CAB-RPV/WS* strategy, we also projected the number of people who develop viremia while treated with CAB-RPV. We use the comparison between *CAB-RPV/WS* with *INSTI* to examine the maximum potential benefit of using CAB-RPV with added supportive services for nonsuppressed PWH. The comparison between *CAB-RPV/WS* with *INSTI/WS* allows the evaluation of additional benefit, if any, of using CAB-RPV in place of oral *INSTI* with the same wraparound services in place.

### Input Parameters

#### Cohort Characteristics

We simulated a cohort with demographic and clinical characteristics similar to those in the demonstration project in San Francisco among nonsuppressed PWH experiencing barriers to adherence [15]. Mean initial age is 47 years, 90% of the cohort is male sex at birth, and mean initial CD4 count is 150/μL (standard deviation [SD], 75/μL) (Table 1). No simulated PWH have *INSTI* or NNRTI resistance mutations at model start.

#### Adherence, Virologic Suppression, and Engagement in Care

We derived probabilities of achieving initial virologic suppression at 3 months and rates of subsequent viremia among PWH with high adherence from randomized controlled trials of oral and injectable ART (Supplementary Methods) [21–25, 30]. To account for lower adherence among a population facing barriers to adherence, we calibrated the model to achieve initial virologic suppression reported from a population before and after wraparound services were available: 13% at 3 months with *INSTI* versus 28%

when wraparound services are provided (*INSTI/WS*) (Supplementary Methods) [7]. Similarly, we derived the rates of subsequent viremia among people achieving initial suppression on *INSTI*: 7.37/100 person-years (PY) (*INSTI*) and 7.19/100 PY (*INSTI/WS*). We selected the lowest reported estimate of virologic suppression at 3 months with *CAB-RPV/WS* (60%), which is substantially lower than that reported in the demonstration project (96.4%) [15], making the analysis conservative with respect to the potential benefits of CAB-RPV. The rate of subsequent viremia on CAB-RPV was 3.29/100 PY for people who received an on-time injection [26]. We estimated mean loss to follow-up (LTFU) rates to be: 28/100 PY (SD, 2/100 PY) without wraparound services and 16/100 PY (SD, 1/100 PY) with wraparound services [7].

#### Non-HIV-Related Mortality

In CEPAC, mortality is stratified by HIV-related causes (eg, opportunistic infections) and non-HIV-related causes (ie, age-stratified and sex-specific mortality). In this modeling analysis, non-HIV-related mortality is adjusted for disadvantageous social determinants of health that are more common among this nonsuppressed population with persistent adherence barriers due to injection drug use, serious mental illness, and unstable housing (Supplementary Table A1) [31, 32].

#### Sensitivity Analysis

To investigate the impact of uncertainty in parameter estimates on model projections, we performed one-way sensitivity analyses by varying key parameters individually across plausible

ranges while holding all other parameters at their baseline values. We examined a range of (1) cohort characteristics (eg, CD4 distribution at model start and percentage of male at birth); (2) ART effectiveness (eg, initial virologic suppression at 3 months, hereafter referred to as efficacy, and subsequent rates of viremia on oral INSTI-based ART; CAB-RPV; and PI-based ART after viremia on CAB-RPV); (3) LTFU rates (eg, during wraparound services, which captures the impact of wraparound services in strengthening engagement in care, and while on CAB-RPV, which captures changes in engagement in care for people taking CAB-RPV and is distinct from the impact of wraparound services); and (4) non-HIV-related mortality (which captures differences in various HIV risk groups among nonsuppressed PWH). Key uncertain parameters including the efficacy of CAB-RPV, the efficacy of PI-based oral ART after viremia on CAB-RPV, and LTFU rates on CAB-RPV were varied widely so that we could examine the impact on model-projected outcomes, if CAB-RPV performs less well than oral ART.

In two multiway sensitivity analyses, we examined the interplay among the most influential parameters from one-way sensitivity analyses. We first compared CAB-RPV/WS with INSTI and examined the efficacy of CAB-RPV, LTFU rates with wraparound services, and the impact of non-HIV-related mortality. Then, we compared CAB-RPV/WS with INSTI/WS and assessed the efficacy of CAB-RPV, the efficacy of PI-based ART after viremia on CAB-RPV, and LTFU rates while on CAB-RPV.

## RESULTS

### Base Case

For a cohort of nonsuppressed PWH experiencing adherence barriers with mean baseline CD4 count of 150/ $\mu$ L (SD, 75/ $\mu$ L), the projected viral suppression at 3 years would be 16% (INSTI), 38% (INSTI/WS), and 44% (CAB-RPV/WS) (Table 2). Engagement in care at 3 years would range from 45% (INSTI) to 57% (INSTI/WS) to 58% (CAB-RPV/WS). The projected survival at 3 years would be 73% (INSTI), 77% (INSTI/WS), and 79% (CAB-RPV/WS), with life expectancy of 7.4 years (INSTI), 9.0 years (INSTI/WS), and 9.4 years (CAB-RPV/WS). Among all PWH who initiated CAB-RPV, 28% would have confirmed viremia on CAB-RPV by 3 years; PWH in care but not suppressed would be transitioned to a PI-based regimen due to potential development of INSTI and/or NNRTI resistance, with 18% of the cohort suppressed when treated with a PI-based regimen. Supplementary Figure A1 displays the projected changes in viral suppression, engagement in care, and survival over time for all three base case strategies.

### Sensitivity Analysis

#### One-Way Sensitivity Analyses

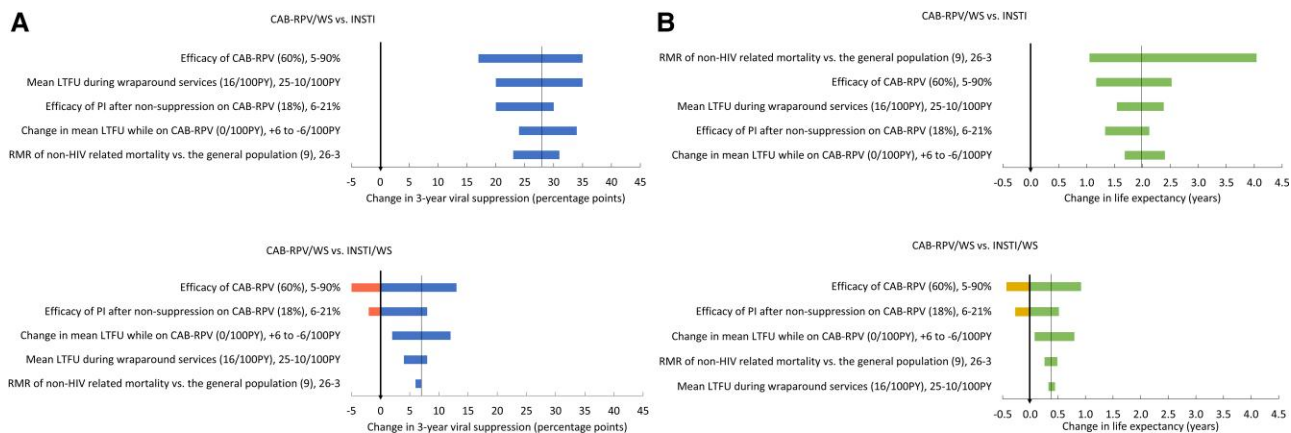
Improvements in short-term outcomes would be greatest among people with lower CD4 counts for CAB-RPV/WS compared with INSTI or INSTI/WS strategies, given their high risk

of AIDS-related complications (Table 2). For a cohort with mean baseline CD4 count 50/ $\mu$ L, 3-year survival with CAB-RPV/WS would increase by 12 percentage points compared with INSTI and by 3 percentage points compared with INSTI/WS. In a cohort with higher CD4 count (mean, 500/ $\mu$ L), 3-year survival would increase by only 1 percentage point with CAB-RPV/WS compared with INSTI and would be the same with INSTI/WS.

Similarly, the life expectancy benefit for CAB-RPV/WS compared with INSTI or INSTI/WS would be greatest among PWH with lower CD4 counts. Among a cohort with mean baseline CD4 count 50/ $\mu$ L treated with CAB-RPV/WS, projected life expectancy would increase by 2.4 years compared with INSTI and 0.4 years compared with INSTI/WS. Life expectancy gains with CAB-RPV/WS would be smaller in magnitude for a cohort with mean baseline CD4 count 500/ $\mu$ L: 1.1 year compared with INSTI and 0.1 year compared with INSTI/WS.

When compared with INSTI, CAB-RPV/WS would result in substantial gains in 3-year viral suppression (17–35 percentage points) and 1.17–4.04 additional years of life gained (YLG) across all parameter ranges considered, even when the parameter estimates were biased against CAB-RPV (Figure 1A and 1B, top panels). The most influential parameters were LTFU rates with wraparound services, the efficacy of CAB-RPV, and non-HIV-related mortality rates. If the efficacy of CAB-RPV at 3 months was 90% (base case: 60%), CAB-RPV/WS would increase 3-year viral suppression by 35 percentage points and lead to 2.5 YLG compared with INSTI; if CAB-RPV efficacy were lower than INSTI efficacy, then CAB-RPV/WS would still increase 3-year viral suppression compared with INSTI because of the benefits of wraparound services. When non-HIV-related mortality varied between 3-fold and 26-fold (base case: 9-fold) greater than in the general population (corresponding to 95% to 85% survival at 1 year with INSTI [29, 33], capturing a wide range of HIV risk groups among nonsuppressed PWH, CAB-RPV/WS would still result in 1.1–4.0 additional YLG compared with INSTI.

When comparing both strategies with wraparound services (CAB-RPV/WS vs INSTI/WS), the most influential parameters were the efficacy of CAB-RPV, the efficacy of PI-based regimens after viremia with CAB-RPV, and LTFU rates while on CAB-RPV (Figures 1A and 1B, bottom panels). When the efficacy of CAB-RPV at 3 months is extremely low, 5% (base case: 60%), CAB-RPV/WS would lead to 3-year viral suppression that is 5 percentage points less than with INSTI/WS, which would result in 0.5 years of life lost; at higher estimates of CAB-RPV efficacy (90%), CAB-RPV/WS would lead to 3-year viral suppression that is 13 percentage points greater than with INSTI/WS, resulting in 0.9 YLG. When the efficacy of the PI-based regimen at 3 months is varied between 6% and 21% (base case: 18%), CAB-RPV/WS would result in change in 3-year viral suppression that ranged from –2 to 8 percentage points and 0.3 years of life



**Figure 1.** One-way sensitivity analyses for strategies that use long-acting cabotegravir-rilpivirine with wraparound services (*CAB-RPV/WS*) compared with integrase inhibitor-based antiretroviral therapy (ART) without wraparound services (*INSTI*) or INSTI-based ART with wraparound services (*INSTI/WS*) for the outcome of change in 3-year viral suppression (*A*) and life expectancy (*B*). The tornado diagrams in each panel display the impact of varying individual parameters on the change in 3-year viral suppression (*A*) and life expectancy (*B*) comparing *CAB-RPV/WS* with *INSTI* (top) and *INSTI/WS* (bottom). Each horizontal bar displays the range of outcomes that result from varying a single parameter. The base case value is in parentheses, followed by the range varied; the left-hand value would result in a decrease in the benefit of *CAB-RPV/WS*, and the right-hand value would result in an increase in the benefit of *CAB-RPV/WS* compared with *INSTI* (top) or *INSTI/WS* (bottom). A longer bar reflects a greater change in outcome as the parameter was varied. The thin vertical lines mark the outcomes from base case estimates: 3-year viral suppression (*A*, top: 28 percentage points gain with *CAB-RPV/WS* compared with *INSTI*; bottom: 7 percentage points gain with *CAB-RPV/WS* compared with *INSTI/WS*) and life expectancy (*B*, top: 2.0 years of life gained [YLG] with *CAB-RPV/WS* compared with *INSTI*; bottom: 0.4 YLG with *CAB-RPV/WS* compared with *INSTI/WS*). The thick vertical lines show where outcomes would be the same with the strategies. The bars that extend to the right of thick vertical lines (*A*, blue; *B*, green) show where *CAB-RPV/WS* would result in improved outcomes; bars that extend to the left of thick vertical lines (*A*, pink; *B*, yellow) show where *INSTI* (top) or *INSTI/WS* (bottom) would be preferred. Abbreviations: CAB-RPV/WS, long-acting injectable cabotegravir-rilpivirine with wraparound services; HIV, human immunodeficiency virus; INSTI, oral integrase inhibitor-based antiretroviral therapy; INSTI/WS, oral integrase inhibitor-based antiretroviral therapy with wraparound services; LTFU, loss to follow-up; PI, oral protease inhibitor-based antiretroviral therapy; PY, person-years; RMR, relative mortality ratio.

lost to 0.5 YLG compared with *INSTI/WS*. When the LTFU rate while on CAB-RPV was increased or decreased by 6/100 PY from the base case (16/100 PY), *CAB-RPV/WS* would result in 3-year viral suppression between 2 and 12 percentage points greater than with *INSTI/WS* and 0.1 to 0.8 YLG. All other parameters, including subsequent rates of viremia on CAB-RPV, LTFU rates during wraparound services, and percentage of male at birth were not found to be influential. Appendix Figure A2 shows the one-way sensitivity analyses results for the outcome of change in 3-year engagement in care for comparisons between *INSTI*, *INSTI/WS*, and *CAB-RPV/WS*.

### Multiway Sensitivity Analyses

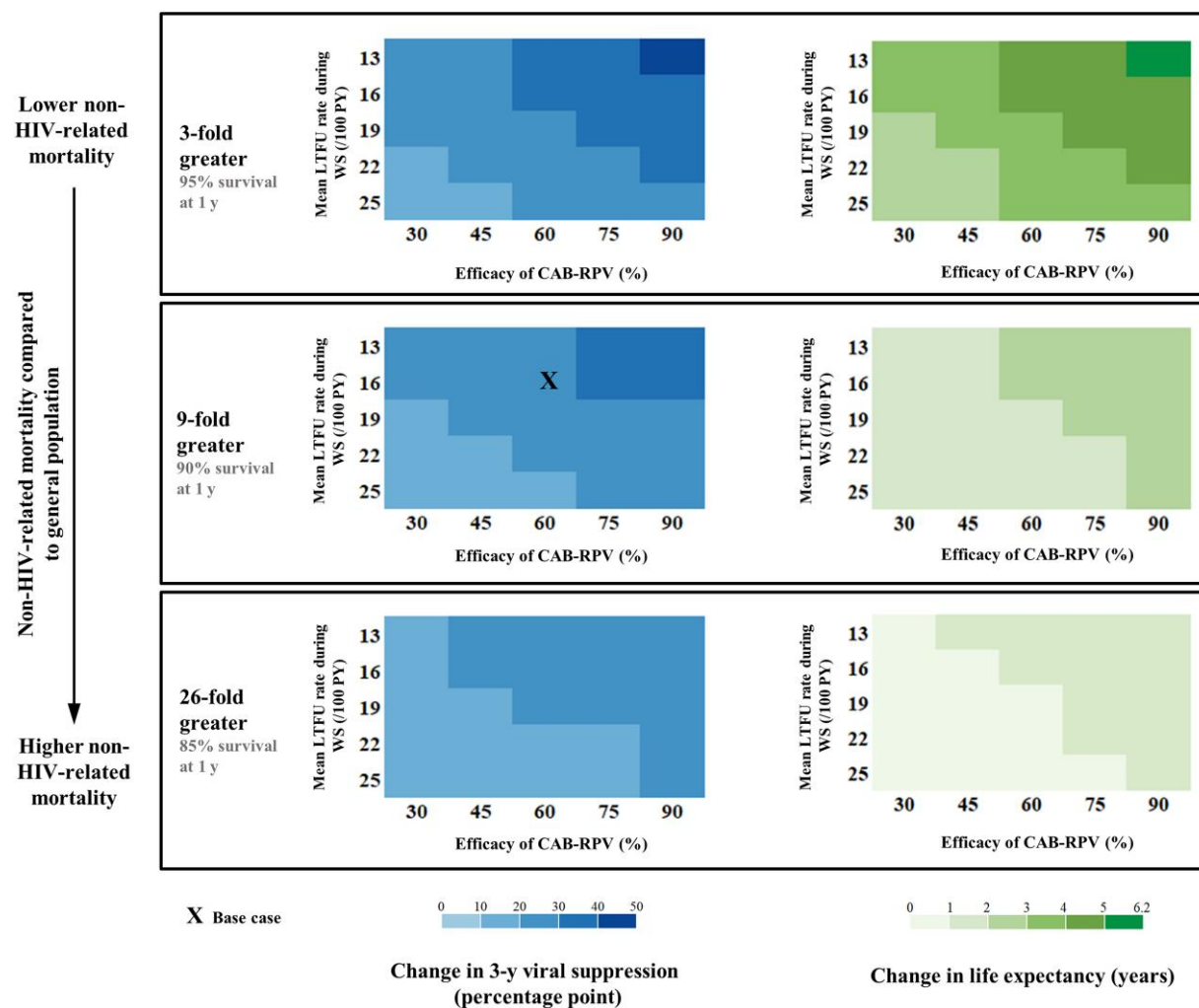
In multiway sensitivity analyses, comparing *CAB-RPV/WS* with *INSTI*, we varied LTFU rates with wraparound services, the efficacy of CAB-RPV, and non-HIV-related mortality (Figure 2). Across wide ranges, *CAB-RPV/WS* would improve 3-year viral suppression (base case: 28 percentage points [range, 12–44 percentage points]) and life expectancy (base case, 2.0 years [range, 0.6–5.5 years]) compared with *INSTI*. Benefits would be greatest in a population with lower non-HIV-related mortality.

Compared with *INSTI/WS*, *CAB-RPV/WS* would improve 3-year viral suppression and life expectancy except at extremely low CAB-RPV efficacy (Figure 3, left of each shaded rectangle) or low efficacy of PI-based regimen (Figure 3, bottom of each shaded

rectangle). When the mean LTFU rate on CAB-RPV was higher or the same as on oral ART, *CAB-RPV/WS* would still improve 3-year viral suppression and life expectancy compared with *INSTI/WS*, as long as CAB-RPV efficacy was greater than 75% or 60%, respectively (Figure 3, middle and bottom shaded rectangles), even at extremely low PI efficacy of 6%. When considering that LTFU rates could improve during treatment with CAB-RPV (Figure 3, top shaded rectangle), *CAB-RPV/WS* would improve 3-year viral suppression and life expectancy compared with *INSTI/WS*, even at CAB-RPV efficacy as low as 45%, as long as PI-based regimen efficacy was 12% or greater after viremia on CAB-RPV. Appendix Figures A3 and A4 show the multiway sensitivity analyses results for the outcome of change in 3-year engagement in care for comparisons between *INSTI*, *INSTI/WS*, and *CAB-RPV/WS*.

### DISCUSSION

While most people with HIV in the US achieve and maintain virologic suppression on oral ART regimens, a substantial minority have ongoing viremia given barriers to adherence to oral therapy. In the absence of suppressive therapy, this population remains at substantial risk of HIV disease progression and death [34, 35]. Compared with standard-of-care oral INSTI-based therapy, we found that initiation of long-acting, injectable CAB-RPV with added outreach and social supports



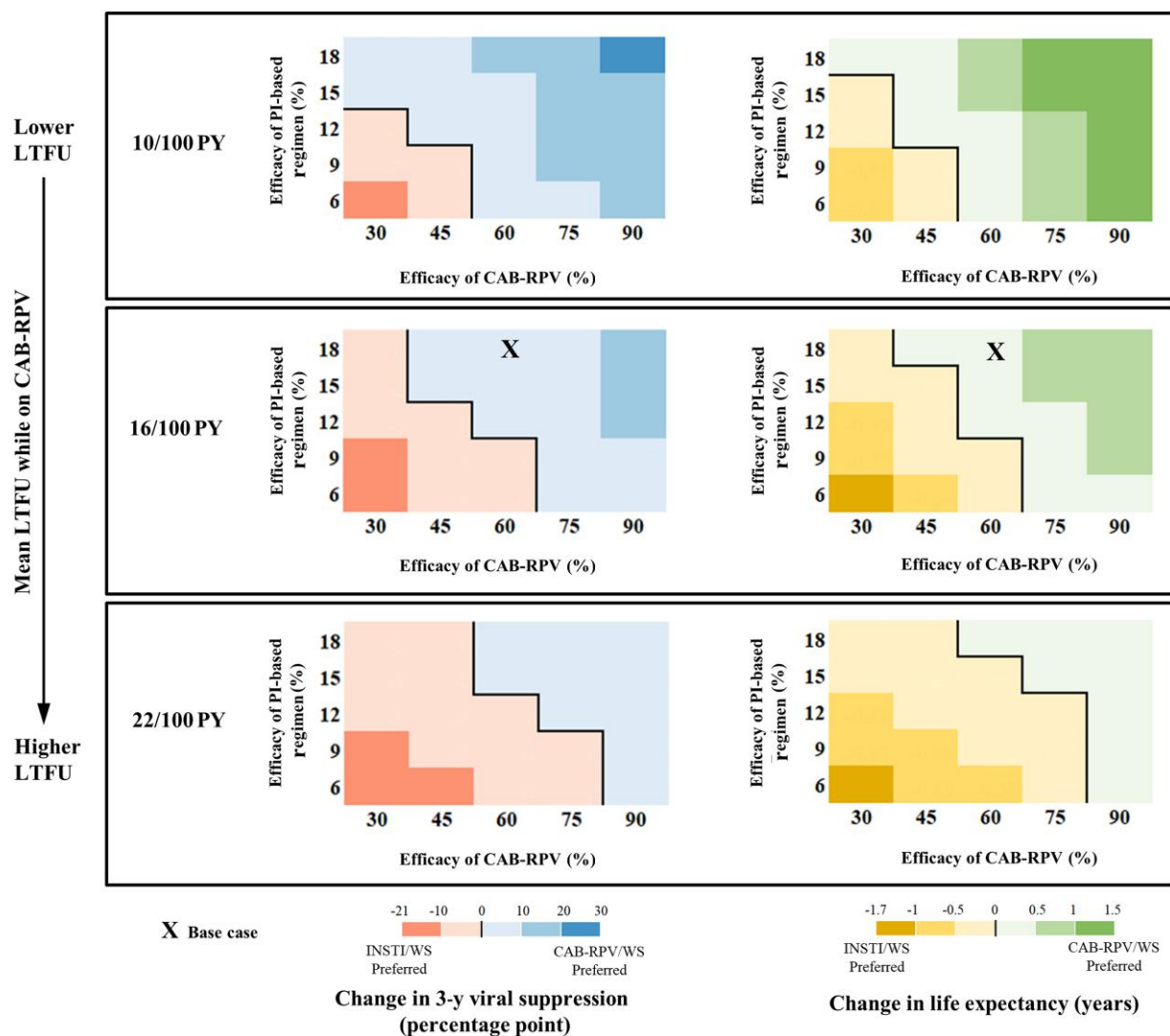
**Figure 2.** Multiway sensitivity analyses comparing the strategies that use long-acting cabotegravir-rilpivirine with wraparound services (*CAB-RPV/WS*) and integrase inhibitor–based antiretroviral therapy without wraparound services (*INSTI*). Comparing *CAB-RPV/WS* with *INSTI*, we examined virologic suppression at 3 years (left) and life expectancy (right) when varying 3 parameters: non-HIV-related mortality (rows), mean loss to follow-up rate during wraparound services (y-axis), and efficacy of CAB-RPV at 3 months (x-axis). The base case is marked with an X. In all scenarios, *CAB-RPV/WS* would result in improved virologic suppression at 3 years (blue) and improved life expectancy (green) compared with *INSTI*. Abbreviations: CAB-RPV, long-acting injectable cabotegravir-rilpivirine; HIV, human immunodeficiency virus; INSTI, oral integrase inhibitor–based antiretroviral therapy; LTFU, loss to follow-up; PY, person-years; WS, wraparound services.

for this group of people would substantially improve viral suppression, engagement in care, and survival over 3 years and beyond. Benefits would be greatest in people with lower CD4 counts at CAB-RPV initiation, reflecting their very high risk of HIV disease progression.

Across wide ranges, a strategy of CAB-RPV with added social services would improve projected viral suppression at 3 years (12–44 percentage points gain) and would lead to substantial gains in life expectancy (0.6–5.5 years) compared with INSTI-based oral ART without wraparound services, even when the efficacy of CAB-RPV was lower than that of INSTI-based oral ART, given the projected benefits of wraparound services. Survival benefits would further increase in a population with lower non-HIV-related mortality, when

additional supportive services focused on substance use disorder or poverty are incorporated [36, 37], or with additional time on suppressive ART [38]. This model-based analysis provides further evidence regarding the benefits of effective and sustainable case management, psychosocial, and nursing support for any strategy focused on improving outcomes for non-suppressed people with HIV experiencing barriers to adherence. Adapting such intensive support to the needs of specific populations remains a key component of the US End the HIV Epidemic strategy [39]; ensuring sustainable funding for these essential services is critical.

Even with social supports in place, however, a strategy of injectable CAP-RPV in place of oral ART would likely result in further improved viral suppression and survival, if CAB-RPV



**Figure 3.** Multiway sensitivity analyses comparing the strategies that use long-acting cabotegravir-rilpivirine with wraparound services (*CAB-RPV/WS*) and integrase inhibitor-based antiretroviral therapy with wraparound services (*INSTI/WS*). Comparing *CAB-RPV/WS* with *INSTI/WS*, we examined virologic suppression at 3 years (left) and life expectancy (right) when varying 3 parameters: the mean loss to follow-up rate while on CAB-RPV (rows), efficacy at 3 months of protease inhibitor-based oral regimen after viremia on CAB-RPV (y-axis), and efficacy of CAB-RPV at 3 months (x-axis). The base case is marked with an X. The black line inside each panel distinguishes scenarios in which *CAB-RPV/WS* (blue) or *INSTI/WS* (pink) would result in improved virologic suppression at 3 years. On the right side, the black line inside each panel distinguishes scenarios in which *CAB-RPV/WS* (green) or *INSTI/WS* (yellow) would result in improved life expectancy. Abbreviations: CAB-RPV, long-acting injectable cabotegravir-rilpivirine; CAB-RPV/WS, long-acting injectable cabotegravir-rilpivirine with wraparound services; INSTI/WS, oral integrase inhibitor-based antiretroviral therapy with wraparound services; LTFU, loss to follow-up; PI, oral protease inhibitor-based antiretroviral therapy; PY, person-years; WS, wraparound services.

retains effectiveness long-term in this population. Indeed, worse outcomes with CAB-RPV compared with oral ART would be projected only at implausibly low estimates of initial virologic suppression with CAB-RPV or if LTFU rates were higher among people prescribed CAB-RPV compared with oral ART regimens. In fact, LTFU may be lower with injectable CAB-RPV than with oral ART.

Despite the success of CAB-RPV in the San Francisco demonstration project, an important concern remains the selection of multiclass drug resistance for people experiencing viremia after CAB-RPV. Of particular importance is the selection of

INSTI resistance because this drug class is part of all recommended first-line ART regimens [13, 14]. Underscoring this concern is that 1%–2% of people in the licensing trials of CAB-RPV developed resistance despite having virologic suppression at baseline and adhering to the recommended dosing schedule [10, 11, 26, 40]. Given the favorable characteristics of the study population in these trials, viremia with acquired drug resistance is likely to be higher among nonsuppressed PWH experiencing barriers to adherence and other psychosocial challenges, especially because inconsistent adherence to the scheduled injections could lead to a prolonged duration of

subinhibitory drug concentrations [8]. Follow-up data from the initial demonstration project in San Francisco demonstrated that 2 of 57 (3.5%) participants developed early virologic failure with resistance [15]. However, when we incorporated substantially higher rates of breakthrough viremia and acquired drug resistance in this modeling analysis, we still found the CAB-RPV/WS strategy to be better at achieving viral suppression than oral ART, leading to improved survival.

Management of people with INSTI and NNRTI resistance after CAB-RPV failure would likely require PI-based ART, which is less effective and more poorly tolerated than INSTI-based ART [23, 24]. However, if substantially higher viral suppression could be achieved with CAB-RPV compared with oral ART, prescribing long-acting, injectable ART to people experiencing adherence challenges would likely outweigh the negative consequences of needing to use a PI-based regimen for the small number of PWH with integrase resistance acquired during CAB-RPV use.

There are several limitations to this study. First, the effectiveness of CAB-RPV compared with oral ART among people with viremia is uncertain and could vary in different populations and settings. We, therefore, selected the lowest reported value in the base case for CAB-RPV efficacy among people with viremia (3-month viral suppression of 60%) [41], which is substantially lower than the 96.4% reported from the demonstration project at 1 year [15]. In sensitivity analyses, we found that a strategy of CAB-RPV/WS would improve clinical outcomes, even at much lower rates of viral suppression. Second, we assumed that viral suppression with CAB-RPV would depend primarily on engagement in care because infrequent dosing would eliminate the need for daily medication adherence. This approach does not capture the complexities of differential patterns of missed injections (eg, length of treatment interruptions, time with sufficient drug concentration) or the association between these patterns and virologic suppression with CAB-RPV [42, 43]. We therefore examined a broad range for LTFU rates on CAB-RPV, including the scenario where LTFU was more frequent on CAB-RPV than on oral ART. Third, we did not try to estimate the likelihood of a more effective injectable agent becoming an available treatment option in the future. Due to the high 3-year mortality in PWH with persistent viremia and advanced immunosuppression, waiting for the potential availability of a more effective regimen is unlikely to be an effective strategy. Fourth, we did not capture either the benefits of reducing transmission to others, or the potential harms of transmitted drug resistance. Finally, we did not conduct a probabilistic sensitivity analysis because the findings from extensive deterministic sensitivity analyses suggest that there would be minimal decision uncertainty [44].

In conclusion, in this model-based analysis, we found that long-acting injectable CAB-RPV coupled with extensive support services in nonsuppressed PWH experiencing adherence

barriers in the US would result in substantial improvements in viral suppression and survival. For people engaged in care but not taking oral ART, this approach could have a major and immediate impact in improving clinical outcomes, especially for people with advanced HIV disease. A prospective study of this important strategy conducted in diverse clinical sites and involving a larger number of participants is needed.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

**Author contributions.** Study design: W. C., K. A. F., and E. P. H. Data analysis: W. C. and E. P. H. Interpretation of results: W. C., M. G., T. W., J. E., P. E. S., K. A. F., and E. P. H. Drafting the manuscript: W. C. and E. P. H. Critical revision of the manuscript and final approval of submitted version: All authors.

**Acknowledgments.** We acknowledge Mr Kyu Young Kevin Chi for his assistance with the analysis and manuscript, and Ms Lotanna Dike for her project management.

**Patient consent.** This study did not include factors necessitating patient consent or institutional review board approval. Research projects utilizing the CEPAC model are approved by the Mass General Brigham Human Research Committee (protocol 2014P002708).

**Disclaimer.** The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

**Financial support.** This work was supported by the AIDS Clinical Trial Group (UM1AI068636 to K. A. F.), which is co-funded by the National Institute on Drug Abuse, National Institute of Neurological Disorders and Stroke, and the National Institute of Allergy and Infectious Diseases (NIAID). The research received additional support from the NIAID (grant number R01AI042006 to K. A. F.) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (grant numbers R01HD079214 to A. L. C. and R01 HD111355-01 to A. M. N.) of the NIH, and the Steve and Deborah Gorlin Massachusetts General Hospital (MGH) Research Scholars Award (to K. A. F.), the MGH Jerome and Celia Reich Endowed Scholar Award (to E. P. H.), the MGH Research Scholars Award in Population and Health Care Research (to A. L. C.), and the MGH Department of Medicine Transformative Scholars Award (to A. M. N.) of the MGH Executive Committee on Research. Research reported in this publication was supported by the NIAID/NIH (award numbers UM1 AI068634, UM1 AI068636, and UM1 AI106701).

**Potential conflicts of interest.** T. W. has served as an ad hoc consultant to Merck and has received grant support (paid to Weill Cornell) from Merck. J. E. is a consultant to Merck, ViiV Healthcare, and Gilead Sciences; his institution receives research support for studies on which he is an investigator. P. E. S. is a consultant to Merck, ViiV Healthcare, and Gilead Sciences; his institution receives research support from Gilead and ViiV Healthcare for studies on which he is an investigator. E. P. H. reports serving as a member of the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. All other authors report no potential conflicts.

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