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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

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Background. Long-acting injectable antiretroviral therapy (LAI-ART) is approved for treatment-naive or experienced people with human immunodeficiency virus (HIV; PWH) based on trials that only included participants with viral suppression. We performed the first LAI-ART demonstration project to include PWH unable to achieve or maintain viral suppression due to challenges adhering to oral ART.

Methods. Ward 86 is a large HIV clinic in San Francisco that serves publicly insured and underinsured patients. We started patients on LAI-ART via a structured process of provider referral, multidisciplinary review (MD, RN, pharmacist), and monitoring for on-time injections. Inclusion criteria were willingness to receive monthly injections and a reliable contact method.

Results. Between June 2021 and April 2022, 51 patients initiated LAI-ART, with 39 receiving at least 2 follow-up injections by database closure (median age, 46 years; 90% cisgender men, 61% non-White, 41% marginally housed, 54% currently using stimulants). Of 24 patients who initiated injections with viral suppression (median CD4 cell count, 706 cells/mm^3), 100% (95% confidence interval [CI], 86%–100%) maintained viral suppression. Of 15 patients who initiated injections with detectable viremia (median CD4 cell count, 99 cells/mm^3; mean $\log_{10}$ viral load, 4.67; standard deviation, 1.16), 12 (80%; 95% CI, 55%–93%) achieved viral suppression, and the other 3 had a 2-log viral load decline by a median of 22 days.

Conclusions. This small demonstration project of LAI-ART in a diverse group of patients with high levels of substance use and marginal housing demonstrated promising early treatment outcomes, including in those with detectable viremia due to adherence challenges. More data on LAI-ART in hard-to-reach populations are needed.

Keywords. HIV/AIDS; long-acting antiretroviral therapy; injectable cabotegravir and rilpivirine; viral suppression; engagement in care.

Treatment for human immunodeficiency virus (HIV) benefits people with HIV (PWH) [1–4] and eliminates onward transmission [5], both crucial to the visionary goal of Ending the HIV Epidemic (EHE) [6]. Despite advances in the tolerability and efficacy of oral antiretroviral therapy (ART) [7, 8], the Centers for Disease Control and Prevention estimates that only approximately 60% of those with diagnosed HIV achieve sustained viral suppression [9]. Disparities in viral suppression exist by lower income, younger age, Black race, Hispanic ethnicity, mental illness, and substance use [10–12]. Structural and societal drivers of these disparities include lack of access to care [13], inability to meet subsistence needs [14], homelessness and unstable housing [15], HIV-related stigma [16], language barriers [17], medical mistrust [18, 19], and structural racism [20].

In an HIV treatment landscape where the benefits of ART are experienced unevenly due to these challenges, an exciting recent development is the advent of long-acting ART (LA-ART). Due to its extended dosing interval, LA-ART has the potential to mitigate many barriers to daily oral ART adherence, including pill fatigue, pills as a reminder of being people with HIV, fear of inadvertent disclosure from possessing pills, not having a

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place to store pills safely, and inability to sustain a routine around daily pill-taking [21, 22]. In January 2021, the US Federal Drug Administration (FDA) approved a combination of 2 injectable antiretroviral medications, cabotegravir (CAB) and rilpivirine (RPV), given every 4 weeks, and subsequently approved the option of an 8-week dosing interval in February 2022 and removed the requirement for an oral CAB/RPV lead-in in March 2022. Of note, since the clinical trials [23–25] that form the basis for regulatory approval enrolled only virally suppressed participants, the FDA has approved the medication only for those with viral suppression.

As the real-world rollout of long-acting injectable CAB/RPV (CAB/RPV-LA) begins, approaches that enable its use in PWH with challenges adhering to oral ART are of paramount importance, given the potential for individual and public health benefits. While CAB/RPV-LA provides an additional treatment option for those stably suppressed on oral ART as studied in clinical trials, it also offers the opportunity to treat PWH unable to take a daily oral regimen to achieve or maintain viral suppression. We describe a patient-centered CAB/RPV-LA care delivery program in an academic HIV clinic that serves urban PWH with high levels of psychosocial and economic vulnerability and present early clinical outcome data of this demonstration project.

METHODS

Study Setting and Population

Ward 86 is one of the oldest HIV clinics in the United States and the safety-net HIV clinic for the city and county of San Francisco. The clinic serves more than 2400 PWH aged ≥18 years (85% cisgender men, 13% cisgender women, 2% transgender women and men, 21% Black, 27% Hispanic) who have government insurance (ie, Medicaid, Medicare) or are covered through a municipal program for uninsured San Francisco residents. The clinic-wide viral suppression rate is approximately 84% [26], and prior analyses have shown that approximately 10% of patients have chronic viremia [27]. Patients without viral suppression at Ward 86 have high rates of stimulant use, mental illness, and marginal housing [15, 28, 29]. In 2019, the clinic developed a comprehensive multidisciplinary drop-in primary care model called POP-UP to better meet the needs of chronically virally nonsuppressed patients with marginal housing who struggle to engage in traditional HIV care that resulted in an increase in viral suppression from 0% to 55% for those enrolled [30].

Description of the Ward 86 Long-Acting Injectable ART Program

We developed a program to support patients and providers to initiate CAB/RPV-LA and to promote patient adherence to injections. Patients with or without viral suppression are allowed to enter the program. Key considerations for CAB/RPV-LA are willingness to receive 2 gluteal injections at each visit, attend regularly scheduled injection appointments, and resume oral ART if CAB/RPV-LA is interrupted, as well as provide a reliable form of communication (eg, phone, text, MyChart) and an additional method of contact (eg, friend, family member, case manager). Patients with any history of RPV-associated resistance mutations are not considered for CAB/RPV-LA [31]; however, the program allows ≤1 integrase strand transfer inhibitor (INSTI) mutation [23–25, 32]. The program also allows patients with hepatitis B infection to enter if they are willing to continue or initiate hepatitis B–directed treatment. Patients on medications known to decrease drug levels of CAB/RPV-LA [33] are not placed on injections.

Providers at Ward 86 received education on CAB/RPV-LA, the process of referral, and feedback on outcomes of CAB/RPV-LA in the clinic at regular provider meetings. A detailed clinic protocol provides additional guidance on referral considerations. Providers refer patients to the pharmacy team for consideration of CAB/RPV-LA via a structured electronic medical record template. The clinic pharmacist reviews referrals for resistance mutations to INSTIs and nonnucleoside reverse transcriptase inhibitors, drug–drug interactions, and hepatitis B status (to ensure maintenance/initiation of treatment for chronic hepatitis B). Patients recommended for CAB/RPV-LA are then scheduled for a pharmacist visit that includes education and counseling on the efficacy of therapy, potential side effects including local injection site reactions, and the risks of interrupting regular injections. Patients are asked to agree to take fully active oral ART in case of interruption until injections can be resumed. A pharmacy technician oversees the process of insurance authorization and procurement of medications.

Our protocol favors a direct-to-inject (DTI; no oral lead-in) approach as approved by the FDA [34], regardless of viral suppression status. The DTI option removes the barrier of needing to adhere to oral ART for an additional month for those with adherence challenges as well as any obstacles related to taking oral RPV with food or without gastric acid–reducing medications. Patients without viral suppression have individualized plans for injection adherence, including identification of community-based supports, for example, case managers, home and street-based nursing services, community-based injection sites (including harm reduction sites), and receipt of small financial incentives (drawn from the Ryan White Program or city-provided funds for adherence support) for visits or blood draws. All referred and active patients are reviewed in a biweekly multidisciplinary (ie, physician, nursing, pharmacy) case conference, with additional discussion of POP-UP patients in a weekly POP-UP case conference.

After the first injection visit, the pharmacy team conducts a follow-up telephone visit within 7 days to ensure tolerability. Injection appointment reminders and missed appointment follow-up calls/texts are performed by the pharmacy technician

who is bilingual in English and Spanish. For patients who start without viral suppression, an HIV viral load is repeated every 4 weeks until it is below the lower limit of detection for our laboratory's assay (<30 copies/mL), with resistance testing performed at the second injection visit if the viral load remains detectable. Consideration of the FDA-approved 8-week dosing interval requires demonstration of sustained viral suppression for 6 months with every 4-week dosing based on data from the antiretroviral therapy as long acting suppression (ATLAS) 2-M study [25, 35], which found that confirmed virologic failure (CVF) occurred most commonly early in the 8-week arm (7 of 8 participants with CVF failed in the first 24 weeks).

If a patient plans to miss a scheduled injection by more than 7 days, they are counseled to restart oral ART until injections are resumed; they are advised to keep 1 month of their prior oral ART regimen on hand for this purpose. In the event of an unplanned missed injection, the pharmacy technician immediately attempts to contact the patient (if not reachable, their listed contacts). If repeated attempts using different modes of contact, that is, phone, text, or letter, are unsuccessful, clinic staff pursue in-person outreach. If an injection is delayed by 10 days or more, blood work for resistance testing is obtained in addition to viral load testing. Although modeling of CAB/RPV-LA pharmacokinetics suggests that an interval of 60 days is sufficient to continue the maintenance dose (CAB 400 mg/RPV 600 mg) after a missed visit [36, 37], we favor a more conservative approach and allow a shorter interval of 42 days (28 days plus up to 14 days late), after which time the initiation dose (CAB 600 mg/RPV 900 mg) is given.

Data Collection and Analysis

Data were extracted from pharmacy team logs and the medical record. Providers reported housing status and stimulant use (methamphetamines, cocaine) at the time of referral. Descriptive statistics were used to characterize patients who had initiated CAB/RPV-LA by 10 February 2022 and thus were expected to have at least 2 scheduled follow-up injections by the time of database closure (15 April 2022). We present the median and range number of injections received by these patients and viral suppression outcomes, stratified by viral suppression status at the time of CAB/RPV-LA initiation. We calculated 95% confidence intervals (CIs) for proportions using the modified Wilson method [38]. For patients who initiated CAB/RPV-LA without viral suppression, we display viral load measurements over time. All patients described in this analytic sample were on dosing of every 4 weeks and had at least 1 viral load measurement after initiation of CAB/RPV-LA. On-time injections were defined as injections given 28 days ± 7 days from the initial injection. Viral suppression after initiation of injections was defined as viral load <30 copies/mL on the measurement most proximal to database closure. The University of California–San Francisco Institutional Review Board approved the study.

RESULTS

Between 1 February 2021 and 15 April 2022, providers referred 132 patients, of whom 51 were started on injections. Reasons for not starting included referral in process (n = 35), on hold due to patient or provider preference (n = 24), awaiting initial injection (n = 13), ineligible due to RPV-associated resistance mutations (n = 5), subsequently declined (n = 2), and transferred care (n = 2). Of 51 patients who received injections between June 2021 and April 2022, our analytic sample with at least 2 follow-up injections consisted of 39 patients (Table 1). Median age was 46 years (interquartile range, 39–55); there were 3 cisgender women and 1 transgender woman and 24 (61%) had non-White race/ethnicity, 16 (41%) were experiencing unstable housing or homelessness, and 20 (54%) endorsed current stimulant use. Three patients were monolingual Spanish speakers. One patient had an N155H resistance mutation at baseline. Five patients were receiving other long-acting injections (antipsychotics n = 4, naltrexone n = 1).

Of 24 patients who initiated CAB/RPV-LA with viral suppression (median CD4 cell count, 706 cells/mm^3), 19 (79%) DTI with a median of 6 injections (range, 2–8), 100% (95% CI, 86%–100%) maintained viral suppression after starting injections. One patient successfully transferred care to another clinic, and another patient had unplanned travel to his home country and took oral therapy in the interim and was found to have viral suppression when he returned 83 days after his last injection. Of 15 patients who started with detectable viremia, (median CD4 cell count, 99 cells/mm^3; mean $\log_{10}$ viral load, 4.67 with standard deviation 1.16), all DTI with a median of 6 injections (range 3–11,), 12 (80%; 95% CI, 55%–93%) had achieved and maintained viral suppression, including the patient with the baseline N155H mutation. For the 3 patients who had not yet achieved viral suppression, all had a 2-log decline by a median of 22 days (Figure 1). No patient decided to discontinue CAB/RPV-LA due to side effects. In general, injection site reactions were mild to moderate; 1 patient developed cellulitis at the injection site and received oral antibiotics. No cases of hepatitis B viremia were observed with discontinuation of tenofovir/emtricitabine-containing regimens, although we did not systematically measure hepatitis B DNA levels in our cohort.

Thirty-four patients (87%; 95% CI, 73%–94%) had on-time injection attendance, with 1 patient late for 1 injection and 2 patients late for 2 injections each. Two episodes of lateness required reinduction with CAB 600 mg/RPV 900 mg dosing. All of these patients were documented to have viral suppression after the delayed visits. At the time of database closure, 1 additional patient was 7 days late for his injection and had not yet presented to the clinic; this patient had viral suppression at his last injection. Two patients in our cohort who were experiencing homelessness received injections in community locations (a harm reduction mobile van and a community clinic) in collaboration with street-based nursing services.

Table 1. Characteristics of 39 Patients Initiating Long-Acting Injectable Cabotegravir and Rilpivirine With at Least 2 Follow-up Injections

Characteristic	N (%)
Age, median (IQR, range), years	46 (39–55, 31–68)
Gender	
Cis-gender man	35 (89.7)
Cis-gender woman	3 (7.7)
Transgender woman	1 (2.6)
Race/Ethnicity	
Black	8 (20.5)
Hispanic	10 (25.6)
White	15 (38.5)
Multiracial/Other	6 (15.4)
Housing	
Stable	23 (59.0)
Unstable	13 (33.3)
Homeless	3 (7.7)
Insurance	
Medicare	25 (64.1)
Medicaid	13 (33.3)
Healthy San Francisco (uninsured)	1 (2.6)
Current stimulant use	20 (54.1)
Antiretroviral regimen at referral	
TAF/FTC/BIC	15 (38.5)
TAF/FTC/DRV-c	12 (30.8)
ABC/3TC/DTG	4 (10.3)
Other DTG-containing regimen[a]	4 (10.3)
TDF/3TC/DOR	2 (5.1)
ELV-c containing regimen[b]	2 (5.1)
HIV VL ≥30 copies RNA/mL at time of referral	18 (46.2)
HIV VL ≥30 copies RNA/mL proximal to first injection	15 (38.0)
Log_{10} HIV VL of those with ≥30 copies RNA/mL at first injection, mean (standard deviation)	4.67 (1.16)
CD4 cell count/mm^3[c], median (IQR)	
Those with VL ≥30 copies/mL	99 (51–299)
Those with VL <30 copies/mL	732 (364–883)
Attended a primary care visit in each 6-month period of the year prior to first injection	
Those with VL ≥30 copies/mL[d]	14 (93.3)
Those with VL <30 copies/mL	20 (83.3)

Housing status and stimulant use (methamphetamines, cocaine) were reported by providers on the referral form. Unstable housing was defined as single room occupancy/hotel, temporarily staying with friends/family, or treatment/transitional program.

Abbreviations: 3TC, lamivudine; ABC, abacavir; BIC, bictegravir; DOR, doravirine; DRV-c, darunavir/cobicistat; DTG, dolutegravir; ELV-c, elvitegravir/cobicistat; FTC, emtricitabine; HIV, human immunodeficiency virus; IQR, interquartile range; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load.

[a]Includes DRV-c/DTG, 3TC/DTG, 3TC/DOR/DTG, and TAF/FTC/RPV/DTG.

[b]Includes TAF/FTC/ELV-c and TAF/FTC/DRV/ELV-c.

[c]CD4 cell count defined using measurements up to 1 year prior to and up 28 days after the first injection. There were 9 patients without measurements in this time frame due to a history of stable CD4 cell counts >200 cells/mm^3.

[d]One patient had 2 visits in the 6-month period prior to the first injection.

DISCUSSION

Here, we describe the first demonstration project to our knowledge to use CBV/RPV-LA in patients with challenges adhering to oral ART. Our data demonstrate preliminary short-term effectiveness of using every 4-week CAB/RPV-LA in patients with and without viral suppression in a diverse urban clinic that serves publicly insured patients with high levels of marginal housing and stimulant use. Consistent with clinical trial populations, those who initiated injections with viral suppression maintained suppression. A more striking finding is that those who began injections with detectable viremia successfully achieved viral suppression or had a 2-log decline in viral load within 1 month of their first injection. Two of these patients, both of whom were people with HIV for more than 10 years, had never previously been virally suppressed, including the patient with the baseline N155H mutation who has now demonstrated >8 months of viral suppression. The program allowed this patient to enroll because clinical trial participants on every 4-week dosing who developed CVF failed with RPV in addition to INSTI mutations, rather than a single INSTI mutation alone. Achieving viral suppression in those who have never been suppressed spotlights the key role LA-ART can play in benefitting those with challenges adhering to oral ART.

We note that the majority of patients in our cohort were from priority populations in EHE efforts, that is, Black, Hispanic (including monolingual Spanish-speaking PWH), and those currently using stimulants, highlighting the potential of CAB/RPV-LA to reach groups of interest. However, we had no patients aged <30 years and only a small number of women among these early adopters of CAB/RPV-LA, illuminating the need for exploration of awareness and preferences in these groups. Importantly, a small subset of patients in our program were receiving other long-acting injections, that is, antipsychotics, highlighting the promise of leveraging attendance at other injection visits to deliver CAB/RPV-LA in those with psychiatric conditions. Nearly all injections were "on-time," and no patient had viral rebound after a late injection. In-person outreach was deployed twice for patients with unplanned missed injections. The case of the patient who went to his home country emphasizes the importance of a supply of oral ART in the event of an unplanned missed injection. No patients discontinued injections due to injection site reactions. While patients were willing to regularly attend injection appointments, some had difficulty with the recommended laboratory monitoring schedule. Small incentives, for example, $10 grocery store vouchers, are one strategy to encourage blood draws that our program has used with success.

We acknowledge several program features as facilitators of implementation. At the provider level, centralization of insurance authorization, injection initiation, and injection visit monitoring by the pharmacy team have encouraged provider referrals. At the patient level, availability of a DTI strategy removed a significant obstacle for those patients who already had demonstrated challenges to adherence. The importance of minimizing the need for adherence to oral ART prior to initiation of injections is reflected in changes made to the protocol of the ongoing AIDS Clinical Trial Group 5359 long-acting therapy to improve treatment success in daily life (LATITUDE) study in order to increase enrollment of PWH with adherence challenges, shortening the required period on oral ART from 24 to 12 weeks, and allowing

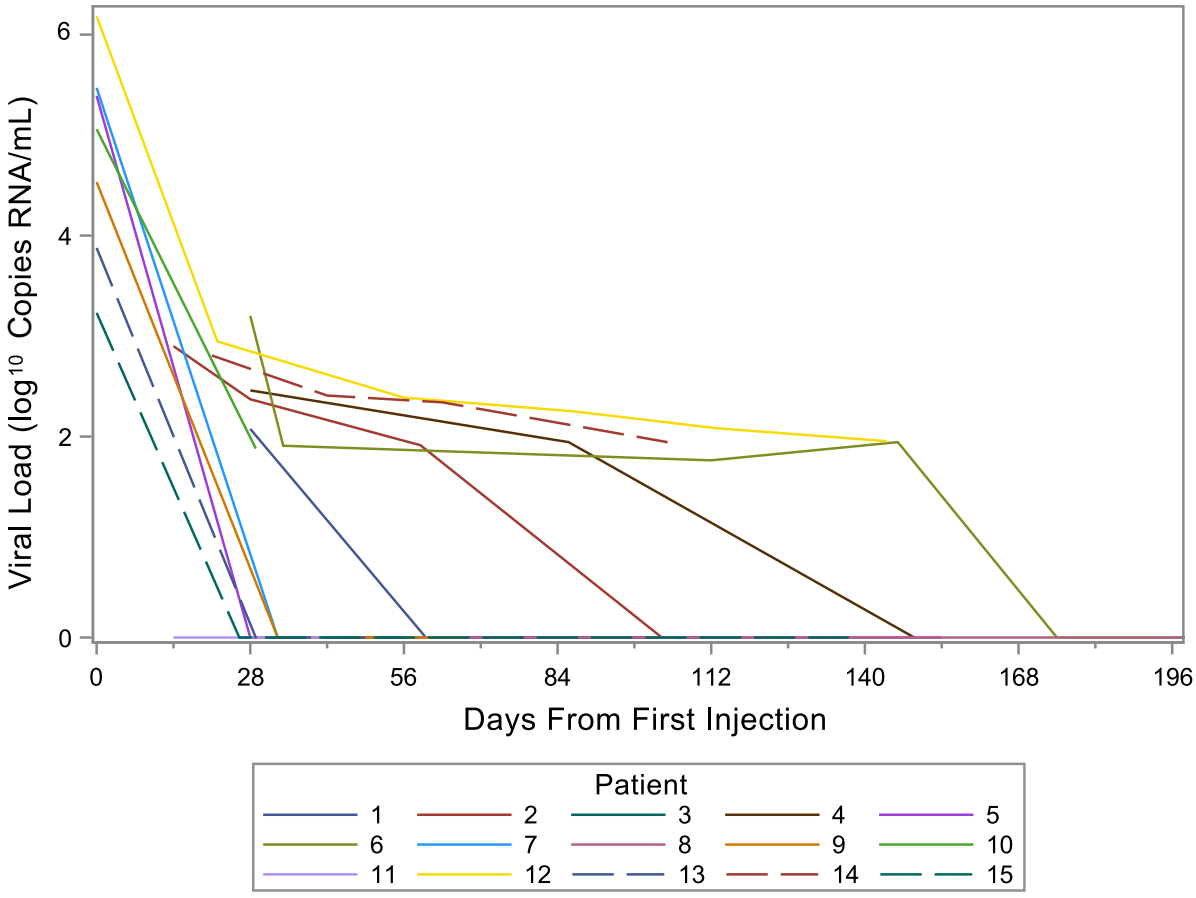

Figure 1. HIV viral loads over time for patients initiating injections with detectable viremia. Data censored for participants 10, 12, and 14 due to database closure. Day 0 HIV load includes viral load measurements within 14 days prior to the first injection. Five patients (2, 3, 4, 8, 11) have more remote viral load measurements (range 26–119) days and thus do not have a day 0 HIV viral load represented. Abbreviation: HIV, human immunodeficiency virus.

a DTI option for those achieving viral suppression. In addition, allowing patients to drop in at Ward 86 on a designated injection day with flexibility on the exact time has supported retention for difficult-to-engage patients. A bilingual pharmacy technician facilitates communication with monolingual Spanish-speaking patients. Finally, partnering with community programs to deliver injections in the field has enabled the offer of injections to some of the highest-risk patients in the clinic POP-UP program, which serves PWH experiencing homelessness or marginal housing who require low-barrier care. For example, 1 POP-UP patient with detectable viremia at baseline received injections and most viral load monitoring at a mobile harm reduction van in partnership with street-based nursing staff from the San Francisco Department of Public Health. Building on these partnerships to increase access to CAB/RPV-LA is essential to reach PWH unable to achieve viral suppression on oral ART due to homelessness, substance use, or severe mental illness.

At the policy level, an important feature of the local context that has facilitated CAB/RPV-LA initiation is that all of the patients in our safety-net clinic had government-based insurance or benefits, which in California saw rapid availability of CAB/RPV-LA on formularies (May 2021 for Medicaid and October 2021 for the AIDS Drug Assistance Program, or, ADAP) with relatively streamlined processes for acquiring the drugs. Prior authorization processes for commercial insurance can be more challenging [39]. Of these government-based programs, only Medicare has had copays, which for most patients were covered by ADAP. The pharmacy technician refers patients whose income is too high to qualify for ADAP to private foundations for copay coverage. CAB/RPV-LA is billed as pharmacy rather than a medical benefit, which facilitates community-based injections rather than requiring administration in a healthcare facility.

Limitations of our study are that we evaluated a small cohort of patients at a single clinical site during the first year of the CAB/RPV-LA rollout. In addition, early adopters of CAB/RPV-LA may be among the most highly motivated PWH to uptake and persist with injections and as such may not be representative of those who initiate CAB/RPV-LA at later points in time. Our findings may not be transferable to rural areas or

jurisdictions with different insurance formulary requirements. Nevertheless, we believe our experience provides important knowledge about the use of CAB/RPV-LA outside of clinical trial settings.

In summary, in this small demonstration project, we found that patients with detectable viremia due to challenges adhering to oral ART can be successfully started on CAB/RPV-LA. Our data show early success in suppressing this group of patients on CAB/RPV-LA and in keeping patients with viral suppression suppressed. A longer period of follow-up and a larger cohort, along with other demonstration projects to examine the use of CAB/RPV-LA in hard-to-reach populations and qualitative assessments of acceptability, are needed.

Notes

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