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MAJOR ARTICLE

Case Series of People With HIV on the Long-Acting Combination of Lenacapavir and Cabotegravir: Call for a Trial

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Background. Injectable cabotegravir (CAB)/rilpivirine (RPV) is the only combination long-acting (LA) antiretroviral regimen approved for HIV. RPV may not be effective among individuals with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance, which has >10% prevalence in many countries. Lenacapavir (LEN) is an LA capsid inhibitor given every 6 months, but has not been studied in combination with other LA agents.

Methods. We assembled a case series from 4 US academic medical centers where patients with adherence challenges were prescribed LEN subcutaneously every 26 weeks/CAB (+/− RPV) intramuscularly every 4 or 8 weeks. Descriptive statistics, including viral load (VL) outcomes, were summarized.

Results. All patients (n = 34: 76% male; 24% cis/trans female; 41% Black; 38% Latino/a; median age [range], 47 [28–75] years; 29% and 71% on CAB every 4 or 8 weeks) reported challenges adhering to oral ART. The reasons for using LEN/CAB with or without RPV were documented or suspected NNRTI mutations (n = 21, 59%), integrase mutations (n = 5, 15%), high VL (n = 6, 18%), or continued viremia on CAB/RPV alone (n = 4, 12%). Injection site reactions on LA LEN were reported in 44% (32% grade I, 12% grade 2). All patients but 2 (32/34; 94%) were suppressed (VL <75 copies/mL) after starting LEN at a median (range) of 8 (4–16) weeks, with 16/34 (47%) suppressed at baseline.

Conclusions. In this case series of 34 patients on LEN/CAB, high rates of virologic suppression (94%) were observed. Reasons for using LEN/CAB included adherence challenges and underlying resistance, mostly to NNRTIs. These data support a clinical trial of LEN/CAB among persons with NNRTI resistance.

Keywords. cabotegravir; HIV; lenacapavir; long-acting antiretroviral therapy; NNRTI resistance.

Although there are highly effective options for once-daily oral antiretroviral therapy (ART) for people with HIV (PWH), adherence challenges to oral regimens persist. The Medical Monitoring Project from the Centers for Disease Control and Prevention (CDC) estimates the rate of sustained virologic suppression among PWH on ART in the United States to be 59% [1]. In a cohort study across 31 countries from 2010 to 2019, only 65% of adults achieved virologic suppression (VS) 3 years after starting oral ART [2]. Adherence challenges range across individual and structural barriers, such as stigma, marginal housing, substance use, mental illness, food insecurity, insurance issues, and transportation issues or stockouts, reasons that are likely to vary by country resources and patient population [3, 4]. As long-acting agents for contraception [5], substance use [6], and mental health [7] have been used successfully with the aim of increasing medication adherence, long-acting ART could similarly be helpful for PWH who report challenges with adherence to oral ART.

The only long-acting ART regimen approved in the United States and Europe is a combination of intramuscular (IM) cabotegravir (CAB), an integrase strand transferase inhibitor (INSTI), and IM rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor (NNRTI). The registrational clinical trials for long-acting (LA) CAB/RPV were conducted among participants with preceding VS on oral ART, resulting in LA CAB/RPV being approved exclusively for this population by the Food and Drug Administration (FDA). However, HIV practitioners have prescribed LA CAB/RPV off-label to patients

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with adherence challenges unable to take oral ART as their only treatment option. A demonstration project offering LA CAB/RPV to PWH in San Francisco with viremia (n = 57) who had multiple concomitant structural challenges to daily pill-taking achieved rates of VS that were similar to those in the clinical trials [8]. A small case series of PWH in Mississippi with preceding viremia (n = 12) demonstrated achievement of VS in all patients on the LA ART regimen [9]. A retrospective chart review of data from OPERA cohort participants (who represent ~14% of PWH in the United States) who received LA CAB/RPV off-label when HIV viral loads were ≥50 copies/mL (n = 176) showed that 82% achieved HIV RNA levels <50 copies/mL (with 94% reaching HIV RNA levels <200 copies/mL) [10]. A recently completed study in the AIDS Clinical Trials Group (A5359) — which showed that long-acting CAB/RPV was superior to oral ART in achieving or maintaining virologic suppression in those with adherence challenges — is likely to lead to greater use of this LA combination for those with difficulties adhering to oral ART [11]. The IAS-USA guidelines recently endorsed long-acting ART in those with viremia and adherence challenges as a result of all of these studies [12]

Notably, due to the prolonged use of efavirenz-based regimens as first-line therapy worldwide and the subsequent relatively high prevalence of NNRTI resistance, LA CAB/RPV is not being yet being deployed worldwide [13]. In the February 2024 WHO HIV drug resistance surveillance report, the overall estimated prevalence of pretreatment resistance to RPV ranged from 0% to 16.6% across the world [13]. Preexisting RPV-associated mutations (RAMs) were the strongest independent predictor of virologic failure in the LA CAB/RPV registrational trials [14], with the emergence of INSTI resistance as a possible consequence of virologic failure on this LA ART combination. High levels of RPV resistance may therefore preclude the use of LA CAB/RPV in some regions of the world. Moreover, the availability of virologic resistance testing is limited in many regions of the world, making prescreening for RPV resistance before using LA CAB/RPV logistically difficult. If options for LA ART continue to be restricted to individuals in high-income countries, the LA ART rollout will likely resemble the initial rollout of oral ART, with profound initial disparities in access for PWH in low- and middle-income countries (LMICs) [15].

For patients who cannot take oral ART due to a variety of challenges that impact adherence, even intensive adherence support and wraparound services may be insufficient to achieve and sustain viral suppression. Indeed, a recent modeling study comparing ART strategies among virally nonsuppressed patients with adherence barriers found that—with INSTI-based oral ART plus intensive adherence support—projected VS at 3 years would be merely 38% [16]. This VS rate is far short of the UNAIDS 95:95:95 targets, which call for 86% population-level viral suppression among all persons with HIV worldwide by 2025 [17]. For patients with NNRTI resistance and for whom oral ART remains a challenge, additional LA ART options are needed.

A third injectable ART agent, lenacapavir (LEN), administered via subcutaneous (sq) injection every 26 weeks, was recently approved for the treatment of multidrug-resistant (MDR) HIV. LEN is a first-in-class capsid inhibitor that has been studied in patients with MDR HIV (CAPELLA study) [18] and in phase 2b studies in treatment-naïve participants (CALIBRATE) [19], both in combination with oral background agents. Given that only 3 LA ART medications are currently approved, the only currently available long-acting ART option that would be potentially effective for individuals with NNRTI resistance is a combination of LA CAB and LA LEN. LA LEN has yet to be studied in combination with LA CAB for the treatment of patients with adherence challenges to oral ART and NNRTI resistance. However, providers (MDs and PharmDs) in the United States have begun to obtain LA LEN through insurance programs and combine it with LA CAB (+/− RPV) for select patients with adherence challenges if clinically indicated.

We assembled a cases series of 34 patients from across 4 US-based academic medical centers who had been on LA LEN and LA CAB combination therapy, with or without accompanying LA RPV. We report on reasons provided for the use of this combination and early virologic outcomes to inform a larger trial of LA LEN/CAB in patients who could benefit from this regimen.

METHODS

Participants in Case Series

Four clinics where providers were using a combination of LA CAB/RPV or LA LEN with LA CAB for selected patients with adherence challenges were identified: The Owen Clinic at the University of California, San Diego (UCSD), serves 3100 PWH; the Ward 86 HIV Clinic at the University of California, San Francisco (UCSF), treats >2600 PWH; MetroHealth's HIV Clinic in Cleveland, Ohio, has 1700 active patients with HIV in the practice; and the UPenn HIV Clinic serves 2500 PWH across 2 sites in Philadelphia. Providers at each of these clinics have been using LA LEN in combination with LA CAB for select patients since the approval of LA LEN in December 2022 by the Food and Drug Administration (FDA). We assembled a case series of patients prescribed LA LEN and LA CAB from these 4 clinics from February to October 2023.

Every patient in this case series had oral ART options available to them, which would be active against the virus despite mutations, but each individual reported challenges taking oral ART as prescribed and preference for injectable treatment. Each of these individuals were thereby offered an injectable

regimen by their clinicians. We required patients to have had at least 1 viral load measurement after starting LEN to be included in the case series, along with information on baseline demographic variables collected in the medical record. Providers did not select this regimen for patients who had viral resistance mutations that conferred resistance to CAB [20].

Variables Collected and Ethical Approval

The following data points were abstracted from the medical record and reported for this case series for each patient on LA LEN/CAB: sex, gender, age, race, ethnicity, current housing status, substance use, viral load (VL) before starting LEN/CAB, duration between CAB doses (every 4 or 8 weeks given as 400 and 600 mg, respectively), whether injectable RPV was also given, viral mutations in the NNRTI or INSTI class (with details on which mutations), time on the regimen, and LEN injection site reaction information. The primary outcome of this analysis was the proportion of patients who achieved VS (HIV RNA <75 copies/mL) after initiation of LEN/CAB. We also report time to VS.

Patient Consent

The MD/PharmD authors of this report are all directly involved in the care of the patients included in this case series, and therefore reviewed the medical records of the patients for the purposes of clinical care and for this case series. The design of the work has been approved by the local ethical committees at the 4 academic medical centers (MetroHealth, UCSF, UCSD, UPenn). Each clinic had permission from its local institutional review board (IRB) to report retrospective patients from their clinics without patient identifiers for the purpose of clinical quality improvement. This case series does not include any patient identifying information.

RESULTS

A total of 34 patients who were started on LA LEN and LA CAB (with or without LA RPV) at UCSF, UCSD, MetroHealth/CWRU, and UPenn were included in this case series. Data were collected from February to October 2023. All patients were administered intramuscular CAB as a "direct-to-inject" agent without an oral lead-in, and all patients received two 600-mg loading doses of LEN (on 2 consecutive days) with the subcutaneous injection. Table 1 shows the characteristics of the 34 patients: 76% male gender; 24% cis/trans female; 42% Black; 36% Latino/a; median age (range) 47 (28–75) years. Nearly three-fourths (24/34; 70.6%) received LA CAB (600 mg) every 8 weeks, with the remainder (10/34; 29.4%) receiving LA CAB (400 mg) every 4 weeks. While barriers to taking daily oral regimens varied, 55% reported housing insecurity, substance use, or both.

The patients are grouped in Table 1 by the reason for being offered LA LEN and LA CAB. The reasons for either adding LA LEN to LA CAB/RPV (67%) or using LA LEN/CAB without LA RPV (33%) were as follows: documented/suspected NNRTI mutations (n = 21, 59%); minor INSTI mutations (n = 5, 15%), in which case LEN + CAB/RPV was used; high VL when switching or starting LA ART (n = 6, 18%); or continued viremia on CAB/RPV alone (n = 5, 15%), leading to the addition of LEN. One patient was started on LA LEN + LA CAB/RPV due to a high body mass index, and another experienced intolerance to LA RPV, with the development of a flu-like reaction. Injection site reactions on LA LEN were reported in 44% (32% grade 1, 12% grade 2). Two of the patients discontinued LA LEN due to injection site reactions.

Overall, 16 (47%) were virologically suppressed at baseline before starting a regimen including LA LEN. All patients but 2 (32/34, 94%) achieved virologic suppression (VL <75 copies/mL) after starting LA LEN + LA CAB +/− LA RPV at a median (range) of 8 (4–16) weeks. All 21 patients with documented or suspected NNRTI mutations (11 with VS at baseline; 10 without VS at baseline) maintained or achieved VS.

DISCUSSION

We present the first case series of patients on a novel combination of long-acting ART with subcutaneous lenacapavir and intramuscular cabotegravir among patients with HIV. Among these US-based patients, all of whom experienced challenges to taking oral ART (the main reason for the prescription of LA ART), we found that the most common reason for use of this particular off-label combination was the presence of NNRTI mutations. Overall, viral suppression doubled from 47% at baseline to 94% following initiation of the combination of LA LEN and LA CAB. Patients with documented or suspected NNRTI mutations all achieved VS on LA LEN and LA CAB [21].

Although a case series alone cannot lead to changes in treatment guidelines, the demonstration that the combination of LA LEN and LA CAB seems to have preliminary effectiveness (with a doubling in VS rate to >90% in this small cohort) can provide proof of concept to support a trial of this regimen. Of note, the rates of virologic failure and resistance were lower in the ATLAS study (CAB given every 4 weeks) [22] than the ATLAS 2M study (CAB given every 8 weeks) [23]. When CAB is provided in combination with LEN for patients with adherence challenges, an initial frequency of administering the CAB every 4 weeks, rather than every 8 weeks, may be prudent pending further study. However, in terms of implementation, providing CAB every 8 weeks may be easier with another medication—LEN given every 6 months. We did not have difficulties obtaining the LEN for use in our patients with HIV as it is newly approved for patients with resistant HIV and our patients generally had viral resistance (mainly to

Table 1. Details of Patients on LA LEN/CAB in Case Series (n = 34)

Reason for LEN	Patient Number	Age/Sex/Gender/Race-Ethnicity/Substance Use and/or Housing Insecurity/BMI (kg/m^2)/Viral Subtype	VL Before LEN/CAB, Copies/mL	NNRTI or Minor INSTI Mutations for Patients 28–32	Regimen Before LEN/CAB	Weeks Between CAB Doses/RPV Included/ISR[a]	VS <75 After LEN/CAB Start/Time to VS
NNRTI mutations- virologically suppressed when started LEN	1	55/M/M/Latino/yes/29.1	UD	A98G, K103N, V179E, G190A	DRV/c/FTC/TAF	4 wk/no/no	Yes/NA
	2	32/M/M/Latino/no/33.8	UD	K103N, G190A	DRV/c/FTC/TAF + DTG	8 wk/yes/no	Yes/NA
	3	28/M/M/Latino/no	UD	K103R, V179D	DRV/c + DTG	4 wk/yes/grade 1	Yes/NA
	4	47/F/F/Latina/no/28.1	UD	L100I, K103N	DRV/c + DTG	8 wk/no/no	Yes/NA
	5	75/F/F/Black/no/23.1/B	UD	L100I, K103N, V179I, Y181C	DTG + 3TC + DRV/r	8 wk/no/no	Yes/NA
	6	41/M/M/Black/yes/23.57/B	UD	V108I, V179D	EVG/c/FTC/TAF + DRV	8 wk/no/grade 1	Yes/NA
	7	55/M/M/White/no/21.7/B	UD	V90I, E138G	BIC/TAF/FTC	8 wk/yes/no	Yes/NA
	8	29/F/F/Black/no/30.9/AG	UD	Y181C	DTG/ABC/3TC	8 wk/yes/grade 1	Yes/NA
NNRTI mutations—viremic when started LEN	9	58/F/F/Latina/yes/29.2/B	329	K101K/Q, K103R, V179I	BIC/TAF/FTC + DOR	4 wk/yes/grade 2	Yes/4 wk
	10	48/M/F/Black/yes/26.7/B	815	V90I, V106I, Y181C, H221Y	DTG + TAF/FTC	4 wk/no/grade 1	Yes/12 wk
	11	41/M/M/Black/no/46.22/B	5280	Y181C, Y188L K103V	DRV/c/FTC/TAF + DTG	8 wk/yes/grade 1	Yes/4 wk
	12	54/M/M/Black/yes/22.1/B	9760	L100I, K103N, Y181Y/C, H221H/Y	EVG/c/FTC/TAF + DRV	8 wk/yes/grade 1	Yes/16 wk
	13	50/M/M/Latino/yes/23/B	36 342	L100I, V179I, Y181I	DRV/c/FTC/TAF	4 wk/no/grade 2	Yes/4 wk
	14	51/M/M/White/yes/28.2/B	239 000	L100I, K103N	DRV/c/FTC/TAF + DTG	4 wk/no/grade 1	Yes/4 wk
	15	59/M/M/Latino/no/19.9/B	1 271 051	V106I, G190S, V179T, F227L	DRV/c/FTC/TAF + DTG	4 wk/no/no	Yes/8 wk
Suspected archived NNRTI mutations	16	31/M/M/Black/no/25.18/B	7740	None	BIC/TAF/FTC + DRV/c	8 wk/yes/no	Yes/8 wk
	17	54/M/M/Black/yes/21.8/B	229 000	None	DRV/r/TAF/FTC	8 wk/yes/no	Yes/16 wk
High VL within 3 mo before starting LA ART (+/– NNRTI mutations)	18	57/M/M/Black/yes/22.0	UD	K103N, V108I, P225H	LA CAB/RPV	8 wk/yes/no	Yes/NA
	19	43/M/M/Black/no/24.9/B	UD	K103N, V108I, P225H	DRV/c/FTC/TAF + DTG	8 wk/yes/no	Yes/NA
	20	42/M/M/White/yes/19.4/B	UD	None	LA CAB/RPV	8 wk/no/grade 2	Yes/NA
	21	28/M/M/Latino/no/30.5	UD	None	LA CAB/RPV	8 wk/no/no	Yes/NA
	22	60/M/M/White/yes/28.2/B	190	None	BIC/TAF/FTC	8 wk/yes/no	Yes/12 wk
	23	39/M/M/Latino/yes/21.2/B	194 000	None	BIC/TAF/FTC	8 wk/yes/no	Yes/5 wk
Low-level viremia on CAB/RPV	24	39/M/M/Latino/no/36.0/B	UD	K103R	LA CAB/RPV	8 wk/yes/no	Yes/NA
(+/– NNRTI mutations)	25	35/M/M/Black/yes/34.7/B	95	None	LA CAB/RPV	8 wk/yes/no	Yes/3 wk
…	26	38/M/M/Latino/yes/23/B	145	None	LA CAB/RPV	4 wk/yes/grade 2	No/no VS
…	27	42/M/M/White/yes/26.5/B	165	K103N, V106I	LA CAB/RPV	8 wk/yes/no	Yes/16 wk
INSTI mutations	28	34/M/M/Latino/yes/22/B	UD	V90I, T66T/I	BIC/TAF/FTC	4 wk/yes/grade 1	Yes/NA

Table 1. Continued

Reason for LEN	Patient Number	Age/Sex/Gender/Race-Ethnicity/Substance Use and/or Housing Insecurity/BMI (kg/m^2)/Viral Subtype	VL Before LEN/CAB, Copies/mL	NNRTI or Minor INSTI Mutations for Patients 28–32	Regimen Before LEN/CAB	Weeks Between CAB Doses/RPV Included/ISR[a]	VS <75 After LEN/CAB Start/Time to VS
	29	52/M/M/White/yes/22.2/B	105	E92Q	DTG/RPV + DRV/c	8 wk/yes/no	Yes/16 wk
	30	44/F/F/Black/no/25.5/B	228	T97A	BIC/TAF/FTC	8 wk/yes/no	No/no VS
	31	40/F/F/Latina/no/24.8/B	290	E92Q	DRV/c/FTC/TAF + DOR	8 wk/yes/grade 1	Yes/9 wk
	32	72/M/M/Black/yes/17.7/B	50 900	T97A	BIC/TAF/FTC + DRV/c	8 wk/yes/no	Yes/5 wk
Other	33[b]	47/F/F/Black/no/41.2/B	UD	None	BIC/TAF/FTC	8 wk/yes/grade 1	Yes/NA
	34[c]	57/M/M/White/yes/22.7/B	UD	None	LA CAB/RPV	4 wk/no/grade 1	Yes/NA

Abbreviations: 3TC, lamivudine; BIC, bictegravir; BMI, body mass index; CAB, cabotegravir; DOR, doravirine; DRV/c, darunavir/cobicistat; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; INSTI, integrase strand transferase inhibitor; ISR, injection site reaction; LA, long-acting; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; RPV, rilpivirine; TAF, tenofovir alafenamide; UD, undetectable; VS, virologic suppression.

[a]K103(X) mutations not counted as RPV-associated mutations.

[b]High BMI >40 kg/m^2.

[c]Intolerance to LA RPV.

NNRTIs). However, for implementation, each clinic did need to set up a tracking system, a call reminder system for patients, and a way to administer injections rapidly without long waiting times.

The field of LA ART is relatively young and remains restricted to the only approved treatment combination of LA CAB/RPV. Although this regimen shows promise as a switch regimen for patients on oral ART with virologic suppression and data on its use among patients with viremia with ongoing adherence challenges are accumulating [8–10], LA CAB/RPV cannot be used in patients with underlying resistance mutations to RPV. In the global context, these restrictions are concerning given that a combination of efavirenz/tenofovir disoproxil fumarate (TDF)/lamivudine (or emtricitabine [XTC]) was the recommended first-line therapy for >15 years in both high-income and LMICs (until the World Health Organization switched to a recommendation of DTG/TDF/XTC as first-line therapy in 2019) [24]. With the widespread use of efavirenz worldwide until recently, and the relatively low genetic barrier to resistance for efavirenz, mutations to NNRTIs are more prevalent than mutations to any other class of ART medications. The prevalence of NNRTI mutations in many countries in Sub-Saharan Africa can range from 10% to >20%, with an estimated rate of RPV resistance of up to 16.6% by the latest WHO surveillance report [13].

In the late 1990s and early 2000s, oral ART was widely accessible mainly in high-income countries, while access to oral ART in LMICs was poor. This disparity in access to ART contributed to divergent HIV outcomes between high-income countries and the rest of the world and remains a historical blight on the global response to HIV. As new LA agents are being developed, we call for a trial of LA LEN and LA CAB for those with NNRTI resistance. The fact that these compounds are each owned by a different company may initially present a barrier to a larger study. However, these companies have each expressed a commitment to widening access and decreasing health inequities in working toward ending the HIV pandemic. The combination of oral dolutegravir (DTG) and lamivudine (3TC) was first studied in a small cohort (PADDLE) of 20 participants [25] before later phase studies eventually led to its approval. The companies that make LEN and CAB have now expressed interest in a small PADDLE-like study of LEN/CAB initially among participants with NNRTI resistance to be conducted in the AIDS Clinical Trials Group (ACTG), now renamed Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections. The benefit of unique designs for trials of LA ART is currently being debated [26], with single-arm trials being considered for patients with challenges taking oral ART, given that the rate of virologic suppression in this patient population is unacceptably low [16].

The presentation of this case series serves as a call for a trial of this novel LA ART combination among individuals with

adherence barriers to oral ART and NNRTI resistance. Trials of LA ART are necessary, with meaningful collaboration across industry, academia, HIV providers, and patient advocates, to ensure that the significant population of people with HIV and NNRTI mutations are not left behind. This case series serves as one example of a call from HIV providers across the United States for a trial of LA LEN and LA CAB among PWH.

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References

1. Centers for Disease Control and Prevention (CDC). Behavioral and clinical characteristics of persons with diagnosed HIV infection—Medical Monitoring Project, United States, 2020 cycle (June 2020–May 2021). **2022**. Available at: https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Accessed October 21, 2023.
2. Han WM, Law MG, Egger M, et al. Global estimates of viral suppression in children and adolescents and adults on antiretroviral therapy adjusted for missing viral load measurements: a multiregional, retrospective cohort study in 31 countries. Lancet HIV **2021;** 8:e766–75.
3. Pugh LE, Roberts JS, Viswasam N, et al. Systematic review of interventions aimed at improving HIV adherence to care in low- and middle-income countries in Sub-Saharan Africa. J Infect Public Health **2022;** 15:1053–60.
4. Locher C, Messerli M, Gaab J, Gerger H. Long-term effects of psychological interventions to improve adherence to antiretroviral treatment in HIV-infected persons: a systematic review and meta-analysis. AIDS Patient Care STDS **2019;** 33: 131–44.
5. Teal S, Edelman A. Contraception selection, effectiveness, and adverse effects: a review. JAMA **2021;** 326:2507–18.
6. Hegde A, Singh SM, Sarkar S. Long-acting preparations in substance abuse management: a review and update. Indian J Psychol Med **2013;** 35:10–8.
7. Taub S, Krivoy A, Whiskey E, Shergill SS. New approaches to antipsychotic medication adherence—safety, tolerability and acceptability. Expert Opin Drug Saf **2022;** 21:517–24.
8. Gandhi M, Hickey M, Imbert E, et al. Demonstration project of long-acting antiretroviral therapy in a diverse population of people with HIV. Ann Intern Med **2023;** 176:969–74.
9. Brock JB, Herrington P, Hickman M, et al. Long-acting injectable cabotegravir/rilpivirine effective in a small patient cohort with virologic failure on oral antiretroviral therapy. Clin Infect Dis. **2024**; 78(1):122–124. doi:10.1093/cid/ciad511
10. Hsu RK, Sension M, Fusco JS, et al. Real-world use of long-acting cabotegravir + rilpivirine in people with HIV with detectable viral loads at initiation: findings from the OPERA cohort. Paper presented at: IDWeek 2023; October 11–15, **2023**; Boston, MA.
11. Rana LI, Zheng L, Bao Y, et al. Long-acting injectable CAB/RPV is superior to oral ART in PWH with adherence challenges: ACTG A5359. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 3–6, **2024**; Denver, CO.
12. Sax P. Updated treatment recommendation on use of cabotegravir and rilpivirine for people with HIV from the IAS-USA guidelines panel. JAMA **2024**; doi:10.1001/jama.2024.2985. Available at: https://www.jwatch.org/na56618/2023/09/25/observations-id-and-beyond-long-acting-cabotegravir. Accessed October 21, 2023.
13. World Health Organization. HIV drug resistance – brief report 2024. February 29, **2024**. Available at: https://www.who.int/publications/i/item/9789240086319. Accessed March 15, 2024.
14. Orkin C, Schapiro JM, Perno CF, et al. Expanded multivariable models to assist patient selection for long-acting cabotegravir + rilpivirine treatment: clinical utility of a combination of patient, drug concentration, and viral factors associated with virologic failure. Clin Infect Dis. **In press**.
15. Bekker LG, Alleyne G, Baral S, et al. Advancing global health and strengthening the HIV response in the era of the sustainable development goals: the International AIDS Society-Lancet Commission. Lancet **2018**; 392:312–58.
16. Chen W, Gandhi M, Sax PE, 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:XXX–XX.
17. Denning P, DiNenno E. Communities in crisis: is there a generalized HIV epidemic in impoverished urban areas of the United States? Center for Disease Control and Prevention. **2019**. Available at: https://www.cdc.gov/hiv/group/poverty.html. Accessed January 22, 2024.
18. Ogbuagu O, Segal-Maurer S, Ratanasuwan W, et al. Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial. Lancet HIV **2023;** 10:e497–505.
19. Gupta SK, Berhe M, Crofoot G, et al. Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial. Lancet HIV **2023;** 10:e15–23.
20. Marzinke MA, Fogel JM, Wang Z, et al. Extended analysis of HIV infection in cisgender men and transgender women who have sex with men receiving injectable cabotegravir for HIV prevention: HPTN 083. Antimicrob Agents Chemother **2023;** 67:e0005323.
21. Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet **2019;** 393:143–55.
22. Swindells S, Lutz T, Van Zyl L, et al. Week 96 extension results of a phase 3 study evaluating long-acting cabotegravir with rilpivirine for HIV-1 treatment. AIDS **2022;** 36:185–94.
23. Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with human immunodeficiency virus 1 type 1 infection: 152-week results from ATLAS-2 M, a randomized, open-label, phase 3b, noninferiority study. Clin Infect Dis **2023;** 76:1646–54.
24. World Health Organization. WHO recommends dolutegravir as preferred HIV treatment option in all populations. *WHO News*. July 22, **2019**. vAvailable at: https://www.who.int/news/item/22-07-2019-who-recommends-dolutegravir-as-preferred-hiv-treatment-option-in-all-populations. Accessed October 21, 2023.
25. Cahn P, Rolon MJ, Figueroa MI, Gun A, Patterson P, Sued O. Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naive patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir LamivudinE) study. J Int AIDS Soc **2017;** 20:21678.
26. Gandhi M, Nachega J, Miller V, Wilkin T. Benefits and limitations of different study designs for long-acting antiretroviral therapy among people living with HIV with viremia. J Int AIDS Soc **2023;** 26(Suppl 2):e26093.