Cabotegravir plus rilpivirine (PrCabenuva) in PLWH with viremia

Issue Statement and Background

At the time of the last CDET review of long-acting (LA) injectable cabotegravir and rilpivirine (CAB-RPV, PrCabenuva) in April 2023, there were very limited data to support its use in PLWH with detectable viral load (>40 copies/mL). In accordance with the Canadian Product Monograph [ViiV Healthcare] and international HIV treatment guidelines, the CDET recommended against the of CAB/RPV in the setting of detectable viremia.

In a March 2024 recommendation, the IAS-USA Treatment Guidelines Panel issued the following statement regarding CAB-RPV [Sax]:

"These accumulating data on using CAB-RPV in people with HIV viremia add to a growing body of evidence that long-acting injectable therapy offers an important treatment option for people with HIV who struggle with oral medication adherence. Based on these data, and the high risk of disease progression or death in persons with advanced HIV disease who are not taking ART, the IAS-USA panel now makes the following revision to the Guidelines.

"When supported by intensive follow-up and case management services, injectable cabotegravir and rilpivirine (CAB-RPV) may be considered for people with viremia who meet the criteria below when no other treatment options are effective due to a patient's persistent inability to take oral ART (rating AIIa under the conditions described).
• Unable to take oral ART consistently despite extensive efforts and clinical support
• High risk of HIV disease progression (CD4 cell count <200/μL or history of AIDS-defining complications)
• Virus susceptible to both CAB and RPV"

Key Clinical Question(s)

Is there sufficient evidence to indicate that starting CAB-RPV LA injections in PLWH with detectable viral load (VL) is effective in suppressing VL? If so, in which patients has effectiveness been shown, and under what circumstances would the benefits of CAB-RPV LA injectable therapy potentially outweigh the risks?

Findings

Published medical literature (2022-2024) and CROI 2024 presentations include 337 patients who started CAB-RPV LA injections in the setting of viremia. Follow-up virologic data are available for 278, as summarized in the table on next page.

Table: Summary of available follow-up virologic data for patients who started CAB-RPV LA injections in the setting of viremia (May 2024, n=278)

First Author, reference	Setting	N with viremia and f/u VL results	BL VL in copies/ mL	N with BL VL >100K copies /mL	N with VL <20 or <50 copies /mL at f/u	f/u time	Oral lead-in (OLI)/Inj schedule
Barnett, AIDS 2022	Case report	1	341K	1	1	6 mo	1 mo OLI/Q4wk
Bartalucci, AIDS 2024	Italian multi-centre cohort	2[1]	Med 57.5 (IQR 55, 104)	0?	2	6 mo	33% OLI/ Q8wk
D'Amico, HIV Med 2023	Inter-national CAP[2]	28	Med 60.3K (range 86-10million)	11	16[3] (57%)	Med 10 mo (range 1-47)	66% OLI/ Q4wk
Hsu, Open Forum Infect Dis 2023	OPERA Cohort, 84 US clinics	176[4]	Med 126 (IQR 63, 6310)	0?	132 (75%) with ≥1 f/u VL were <50 at last VL	Med 6.1 mo (IQR 3.5, 10.1)	?OLI/Q4wk?
Brock, CID 2024	1 US clinic	12	Mean 153K (range 2410-566K)	?	12 at 3 mo (all <200 at last f/u)	3 mo (last f/u 1-17 mo)	6 started Q4wk then Q8wk; 6 started Q8wk[5]
Hickey, CROI 2024	Ward 86 clinic, San Francisco	59	22 (37%) 10K-100K; 19 (32%) ≥100K	19	48 (81%)	48 weeks	No OLI/Q4 first 3-6 mo

1. An additional 6 patients had not yet reached the 6-month timepoint
2. Compassionate Access Program (supported by ViiV Healthcare and Janssen)
3. 3 virologic failures had RPV RAMs at baseline
4. Outcomes not reported for an additional 53 patients
5. Loading doses at 0 and 1 month then every other month

The two largest observational cohorts that are included in the summary table, Ward 86 and OPERA, are described in more detail below.

Retrospective results of a demonstration project in a hard-to reach population with ART adherence challenges and high levels of substance use, mental illness, and marginal housing have been published [Gandhi; Christopoulos], and 48-week results were presented at CROI 2024 [Hickey]. As of 31 Jan 2024, 286 PLWH have started CAB-RPV LA at **Ward 86**, a teaching hospital-affiliated, publicly-funded HIV clinic in San Francisco. The clinic protocol starts CAB-RPV LA injections Q4 weeks directly (without oral lead-in) for all patients regardless of their viral suppression status. Optional transition to a Q8 week injection schedule is offered once the participant has achieved VL suppression for 3-6 months. The CROI 2024 poster [Hickey] presented results of 59 PLWH who started CAB-RPV LA injections, without other ART, while having a baseline VL of ≥50 copies/mL, by 5-Dec-2022 (and therefore have ≥56 weeks follow-up). At CAB-RPV baseline, 29/59 (49%) had CD4 count <200/μL and 41/59 (69%) had VL ≥10,000 copies/mL. **By week 48, 48/59 (81%) remained on CAB-RPV LA and had VL <50 copies/mL**; 1 (1%) had VL>50 and <200 copies/mL after intensification with lenacapavir; 5 (8%) had discontinued CAB-RPV and

resumed oral ART (all VL<50); **3 (5%) had virologic failure with emergent resistance**; and 2 (3%) were lost to follow-up (VL>50, off oral ART). Of note, the Ward 86 protocol includes patients who are unable to adhere to oral ART and thus have no other options for treatment, and excludes patients with RPV resistance or >1 INSTI RAM (due to experience with early virologic failure in such patients) [Gandhi, Christopoulos]. The Ward 86 clinic provides comprehensive, low-barrier multidisciplinary care with individualized case management, community-based supports, and small financial incentives for injection visits and blood draws.

The **OPERA Cohort** has published "real-world" results from 84 US clinics. CAB-RPV LA treatment was started in 321 PLWH, 43 of whom had VL ≥50 copies/mL at the time of their first injection and had a median 4.7 months of follow-up [Sension]. Further results from the same cohort were presented at IDSA 2023 [Hsu], including 229 PLWH with VL ≥50 copies/mL at initiation of CAB-RPV LA injections. Median (IQR) baseline CD4 was 579 (350, 759) /μL and VL was 126 (63, 6310) copies/mL. **Of the 176 PLWH with ≥1 follow-up VL result after starting CAB-RPV LA injections, 132 (75%) had VL <50 copies/mL at their latest study visit, with a median follow-up time of 6.1 (3.5, 10.1) months**. **Confirmed virologic failure** (VL ≥200 copies/mL x 2 consecutively) **occurred in 7/176 (4%); resistance test results were not available**.

A recent study (ACTG A5259, Rana, CROI 2024) and a small cohort (MXM community clinic, Mehtani, JAIDS May 2024) are of interest and are described below. Their results were not included in the summary table for the reasons given.

Results of **ACTG A5359**, the only randomized controlled trial to address this issue, were presented as a late-breaker at CROI 2024 [Rana]. This prospective, randomized, open-label trial compared CAB-RPV LA to standard-of-care (SOC) oral ART in PLWH with a history of suboptimal adherence for ≥6 months. A total of 434 eligible participants with no RPV or INSTI resistance were enrolled at 33 sites in the US. Study participants received adherence support and cash incentives for achieving VL ≤200 copies/mL on SOC oral ART for ≤24 weeks, and 294 were then randomized to continue oral ART or start CAB-RPV LA injections Q4 weeks (with or without oral lead-in). At the time of a pre-planned interim analysis, the week 48 cumulative probability of regimen failure (= virologic failure or treatment discontinuation) was 38.5% (47 events/148 randomized participants) in the SOC arm and 24.1% (28 events/145 randomized participants) in the CAB-RPV LA arm. The DSMB recommended stopping the study early and offering CAB-RPV LA to all participants, as all efficacy endpoints favoured the CAB-RPV LA arm. The decision to stop the study early may have hampered the ability to assess the risk of developing resistance over the longer term in each treatment arm.

Of the 294 participants randomized in ACTG A5259, 34 had VL >200 copies/mL on the day of randomization, of whom 10 were randomized to continue oral ART and 24 to switch to CAB-RPV LA (8 with VL >10,000 copies/mL) [Rana]. Separate results were not reported for these 34 participants, and therefore could not be included in the summary table.

The Maria X Martinez (**MXM**) Health Resource Centre is a publicly-funded, low-barrier, community-based clinic in San Francisco serving people who are homeless or unstably housed, a population with a high burden of comorbid substance use and severe mental illness. In November 2021, the MXM clinic started an injectable ARV program; results of the first 2 years of the program were published recently [Mehtani]. As with the Ward 86

program, PLWH at MXM started CAB-RPV LA injections directly Q4 weeks with optional transition to Q8 weeks after 6 months. Of the 18 PLWH who started CAB-RPV LA at MXM, 14 had VL >30 copies/mL at baseline and 4 had known RPV resistance mutations. Two were included in the Ward 86 demonstration project and 4/18 also received lenacapavir. After a mean of 9.7 months (range 1-24 months), 17/18 (94%) PLWH achieved or maintained virologic suppression. Of the 4 patients with baseline RPV resistance, 2 (who received CAB-RPV without lenacapavir) acquired further resistance mutations following treatment interruptions: 1 only to RPV and 1 to both CAB and RPV. Both had achieved "substantial improvements in symptoms and CD4 counts" before CAB-RPV LA was discontinued at 6 months [Mehtani]. These results have not been included in the summary table because of possible duplication with the Ward 86 data, and because separate results are not reported for the 14 PLWH who received CAB-RPV LA without lenacapavir.

Guidance/Recommendations

As of May 2024, evidence is accumulating on the use of CAB-RPV LA injections in PLWH with viremia. However, much of the evidence is preliminary and is limited to observational cohort data including <300 PLWH. In addition, data are very limited (N ~30) regarding the efficacy of this two-drug regimen in PLWH with high viral loads (>100,000 copies/mL).

The CDET therefore has revised its recommendation as follows:

When supported by intensive follow-up and case management services, injectable CAB-RPV without prior oral lead-in may be considered for PLWH with persistently detectable viral load who meet the following criteria: (Grade C)

- Unable to take oral ART consistently despite extensive efforts and clinical support
- High risk of HIV disease progression (CD4 cell count <200/μL or history of AIDS)

Other BC-CfE eligibility criteria for CAB-RPV LA still apply, including:

- ≥12 years of age and weighing ≥35 kg
- not HIV subtype A1/A6
- no resistance to integrase inhibitors or NNRTIs (with the exception of K103 substitution)
- not pregnant or planning pregnancy
- no relevant drug interactions
- caution if BMI ≥30 kg/m^2

References

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Appendix 1: Review Methodology

Type of literature reviewed

Publications in peer-reviewed literature

CROI 2024 presentations (oral or poster)

Databases used

Ovid MEDLINE

PubMed

Search terms

Cabotegravir + rilpivirine + injectable or injections

Inclusion criteria

- Injectable cabotegravir and rilpivirine (CAB-RPV) used for HIV treatment, with no concurrent antiretrovirals
- CAB-RPV started when viral load detectable (at any level)
- Follow-up viral load results available