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REVIEW ARTICLE

Optimizing the Use of Cabotegravir Plus Rilpivirine Long-acting Therapy in HIV Care: Evidence, Implementation, and Unanswered Questions

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Cabotegravir plus rilpivirine long-acting (CAB + RPV-LA) injectable therapy marks a major milestone in HIV care, offering an efficacious, well-tolerated alternative to daily oral antiretroviral treatment. This article reviews data from pivotal trials and observational studies of CAB + RPV-LA, addressing emerging questions and highlighting key research priorities. We examine factors influencing virological outcomes, including issues related to HIV subtype, archived drug resistance, body mass index, and pharmacokinetics, and discuss challenges related to hepatitis B virus immunity and infection, pregnancy, and adherence. We outline strategies to address barriers to implementation, advocating for a tailored approach to maximize the potential of CAB + RPV-LA in improving outcomes across diverse populations with HIV.

Keywords. HBV; long-acting; pharmacokinetics; resistance; subtype.

Cabotegravir plus rilpivirine long-acting (CAB + RPV-LA) injectable therapy offers an effective and well-tolerated alternative to daily oral treatment [1–3]. it is currently licensed for stably treated adults with virological suppression (HIV RNA <50 copies/mL), no history of virological failure with nonnucleoside reverse transcriptase inhibitors (NNRTIs) or integrase strand-transfer inhibitors (INSTIs), and no NNRTI or INSTI resistance. Guidelines differ regarding the definition of stable antiretroviral therapy (ART), commonly suggesting a period of at least 3–6 months [4–7].

The original registrational trials demonstrated the safety and efficacy of CAB + RPV-LA dosed intramuscularly every 4 weeks (Q4W) for up to 96 weeks (Antiretroviral Therapy as Lond Acting Suppression [ATLAS])), Q4W for up to 124 weeks (First Long-Acting Injectable Regimen [FLAIR]), and Q4W or every 8 weeks (Q8W) for up to 152 weeks (ATLAS-2M) [1–3]. The trials recorded a total of 23 instances of confirmed virological failure ([CVF] confirmed HIV RNA ≥200 copies/mL) among 1651 individuals (1.4%) [8]. Multivariable analysis of these events highlighted several factors associated with CVF: historical RPV resistance-associated mutations (RAMs), HIV-1 subtype A6/A1, an elevated body mass index (BMI), and lower model-predicted CAB and/or RPV trough concentrations (C_{trough}), with cumulative effects of combining ≥2 factors (Figure 1) [8 (including Supplementary data)]. Illustrating the impact of baseline predictive factors in the registrational trials, the Switch Onto Long-Acting Regimen (SOLAR) trial recorded fewer CVFs (3/454, 0.7%) among participants receiving CAB + RPV-LA Q8W over 48 weeks [9]. Individuals with CVF generally lacked archived RPV RAMs and had subtypes other than A6/A1. One had a BMI ≥30 kg/m^2, but CAB/RPV

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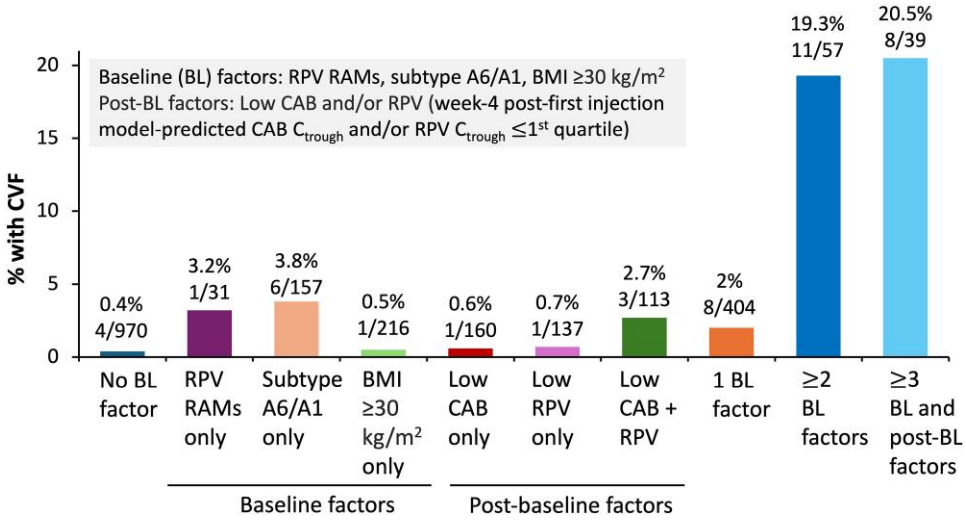

Figure 1. Cases of confirmed virological failure among FLAIR, ATLAS, and ATLAS-2M trial participants according to the presence of baseline and post-baseline factors. The figure was compiled from data published by Orkin et al in reference 8, including the Supplementary material. Abbreviations: BL, baseline; BMI, body mass index; CAB, cabotegravir; C_{trough}, trough plasma concentration; CVF, confirmed virologic failure; RAM, resistance-associated mutation; RPV, rilpivirine.

concentrations at the time of virological rebound were considered appropriate.

To support clinicians in navigating this novel treatment paradigm, we synthesize data from pivotal trials and observational studies of CAB + RPV-LA, examining factors that influence virological outcomes and outlining research priorities. Additionally, we discuss key implementation challenges, including hepatitis B virus (HBV), pregnancy, and incomplete adherence, proposing practical strategies to optimize use across diverse populations.

FACTORS INFLUENCING VIROLOGICAL OUTCOMES

HIV Subtype

Among 1431 participants with complete subtype data in the CAB + RPV-LA registrational trials, subtype A6 was relatively common (n = 180 [13%]), whereas subtype A1 was rare (n = 19 [1%]) [1–3, 8 (including Supplementary data)]. Among 23 recorded CVFs, 11 were in subtype A6 (11/180, 6.1%) and 2 in subtype A1. The multivariable analysis combined the 2 subtypes into the unified variable "A6/A1" [8], and this terminology was reflected in the label. Given the limited number of trial participants with subtype A1, a key question was whether CVF risk should be associated with this subtype. The randomized Cabotegravir and Rilpivirine Efficacy and Safety (CARES) trial of CAB + RPV-LA implementation in 3 African countries recently provided reassurance [10, 11]. Based mainly on reverse transcriptase sequences, purely subtype A1 (ie, excluding 12 mixed subtypes) was found in 101/213 (47%) participants of the CAB + RPV-LA arm [10 (including Supplementary data)]. At week 48, the efficacy of CAB + RPV-LA in maintaining virological suppression was 246/255 (96%) and comparable to that of oral ART (250/257 [97%]). Virological suppression was sustained through week 96 (247/255 [97%] on CAB + RPV-LA vs 250/257 [97%] on oral ART); among 4 CVFs in the CAB + RPV-LA arm, 2 were in subtype A1 [11].

The genetic mechanisms linking subtype A6 to CVF remain poorly understood. Subtype A6 likely evolved from A1 in Central Africa, diverging genetically while spreading to countries of the former Soviet Union, where A6 is fuelling an expanding HIV epidemic [12, 13]. Distinctive mutations, including multiple integrase substitutions, differentiate A6 from A1. One distinction is the presence of isoleucine (I) instead of leucine (L) at integrase position 74. Isoleucine is the consensus amino acid in subtype A6 but occurs in only ~10% of A1 strains [12, 14]. Located in the enzyme catalytic core domain near the active site, L74I does not reduce CAB susceptibility [15]. However, L74I enhances the replication capacity of viruses harboring major RAMs in subtype A6 integrase (G118R, G140R, Q148H, R263K) [16]. This enhancement may partly explain the association between subtype A6 and CVF, although it presumes that other factors allow virus replication to resume.

Implications for Clinical Practice

- The CARES trial data support the notion that subtype A1 is not associated with CVF risk.
- Although subtype A6 as a sole factor carries a small CVF risk, determining the subtype enables a thorough risk/benefit assessment.
- During virological suppression, the subtype may be identified from historical genotypes, which can be reanalyzed for precise subtype assignment; furthermore, the absence of L74I in integrase would argue against subtype A6. The subtype may also be determined through HIV DNA sequencing (if available), ideally using integrase in addition to reverse transcriptase sequences. If none of these options is feasible, the geographical origin of the infection is a proxy indicator. A6 is dominant in countries of the former Soviet Union (eg, Ukraine); it is uncommon in other countries, although increasing in areas with extensive migration from the region [17].

HIV Drug Resistance

Although individuals with known NNRTI/INSTI resistance were excluded from the CAB + RPV-LA registrational trials, retrospective analyses found preexisting RPV RAMs (any of L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L) in 56 participants, 8 of whom (14%) experienced CVF [8 (including Supplementary data)]. In ATLAS and ATLAS-2M, historical RAMs were analyzed in HIV DNA sequences obtained from peripheral blood mononuclear cells, a method known as archived or proviral resistance testing [18, 19]. This method allows detection of historical RAMs when plasma HIV RNA is undetectable; however, several factors complicate interpretation (Supplementary Figure 1) [18, 19].

Archived resistance testing may both underestimate and overestimate resistance [18, 19]. Sensitivity is influenced by HIV DNA load, the circumstances of and time elapsed since the initial emergence, sample quality, and sequencing method (Sanger sequencing vs next-generation sequencing). Next-generation sequencing offers greater sensitivity, but technical artefacts may occur below a 5%–10% frequency threshold. The method may also overestimate resistance by detecting RAMs in defective proviruses incapable of producing infectious viruses. Notably, when sequencing HIV DNA, mutations may be found at drug-resistance sites that arise from the editing activity of APOBEC3 rather than antiretroviral exposure [18–20]. These host cell enzymes (primarily APOBEC3G and APOBEC3F) are incorporated into HIV virions. After virus entry and initiation of reverse transcription, they catalyze cytosine-to-uracil deamination, resulting in G-to-A mutations (GG→AG and GA→AA) in the plus-strand HIV DNA. APOBEC3 editing can be associated with several major and some minor RAMs (**Box 1**) [14]. However, multiple defects in hypermutated proviruses prevent the production of infectious viruses, negating clinical relevance of APOBEC3-associated RAMs [18–20].

Box 1. Common resistance-associated mutations that can occur in the context of APOBEC3-linked hypermutation. All are major mutations except G73S, G163K/R, and D232N, which are minor mutations [14].

- Reverse transcriptase—NRTIs: D67N, M184I; NNRTIs: E138K, G190E, G190S, M230I
- Protease—D30N, M46I, G48S, G73S
- Integrase—G118R, E138K, G140S, G140R, G163K, G163R, D232N, R263K

Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor.

An illustration of this issue may be found in the CARES study, which recruited virologically suppressed adults without a history of virological failure [10]. Participants had frequent prior exposure to NNRTIs (74%) and INSTIs (92%). Peripheral blood mononuclear cells collected at study entry were retrospectively tested for archived resistance by Sanger sequencing. In the CAB + RPV-LA arm, the investigators initially reported detection of CAB RAMs in 15/95 (16%) samples and RPV RAMs in 25/200 (13%) samples. However, the study methodology had not included hypermutation screening. Yet, most of the reported RAMs were among those potentially linked to APOBEC3 editing, including the NNRTI RAMs E138K and M230I and the INSTI RAMs E138K, G140R/S, and R263K [10 (including Supplementary data)]. Alerted to this issue, the investigators revised the analysis to account for APOBEC3-related effects. Although more data are needed on the methodology, this reduced the number of individuals with CAB RAMs (8/99, 8%) and RPV RAMs (14/208, 7%; largely the E138A polymorphism) [11]. Among the 4 CVFs described through week 96, 2 had baseline RPV/NNRTI RAMs (E138A + K103N/S and E138K (or possibly E138A or E138G), respectively), totalling 2/14 (14%) CVFs among individuals with archived RPV RAMs [11].

Implications For Clinical Practice

- The CAB + RPV-LA registrational trials indicate that archived RPV RAMs increase CVF risk. NNRTI-resistant variants typically exhibit high resistance with negligible fitness cost and can expand rapidly under NNRTI-selective pressure unless promptly suppressed by other agents in the regimen [21, 22]. A CVF risk may also be anticipated for preexisting CAB RAMs.
- The data from the CARES study initially appeared to contradict these concepts. However, a revised analysis accounting for APOBEC3-related effects yielded results consistent with those observed in the registrational trials.
- Treatment and viral load history are the key factors in guiding treatment decisions, alongside available historical genotypes.
- Archived resistance testing can unveil valuable data in virologically suppressed individuals with incomplete or unclear history. However, the test requires expert review to avoid misinterpretations. It should complement—not replace—the historical data, and should not be seen as a prerequisite to initiating CAB + RPV-LA.
- Based on available evidence, the presence of resistance—whether documented historically, inferred from the treatment and viral load history, or detected through appropriately analyzed HIV DNA sequences—remains an important consideration for any ART regimen, including CAB + RPV-LA.
- Although the data specifically refer to RPV/CAB RAMs, caution is advised when assessing risk in the presence of any NNRTI or INSTI RAMs that emerged during viremic episodes. Multiple RAMs may emerge during virological failure, and they may not all be evidenced by routine tests.
- Limited evidence indirectly supports the notion that a history of transmitted K103N in reverse transcriptase may still permit CAB + RPV-LA use [23].

Body Mass Index

A post hoc analysis of the CAB + RPV-LA registration trials found similar safety and efficacy among participants with BMI <30 or ≥30 kg/m^2 through 48 weeks [24]. In both groups, CAB and RPV $C_{troughs}$ remained above the protein-adjusted 90% inhibitory concentration (PA-IC_{90}). Among 1245 participants, 213 (17%) had a BMI ≥30 kg/m^2 (including 20 with BMI ≥40 kg/m^2), of whom 72% received Q4W dosing and 28% Q8W, with limited use (15%–18%) of long (2-inch) needles. Including data beyond week 48, of 10 CVFs, 8 occurred in participants with BMI ≥30 kg/m^2, but all had RPV RAMs and/or subtype A6/A1 [24].

Similarly, a post hoc analysis of SOLAR found comparable 12-month CAB + RPV-LA Q8W efficacy across BMI groups [25]. Among 447 participants in the CAB + RPV-LA arm, 93 (21%) had a BMI ≥30 kg/m². Of 3 CVFs, 1 (excluded from the primary analysis) involved an individual with BMI ≥30 kg/m² (subtype C; baseline RPV RAMs unknown).

Observational studies support these findings. Maguire et al. analyzed CAB + RPV-LA efficacy in 374 virologically suppressed participants [26]. Most (68%) received Q8W dosing. There were 148 (40%) participants with BMI ≥30 kg/m^2, with ~8% receiving initial injections with long needles. Over a median follow-up of ~36 weeks, CVF (confirmed HIV RNA ≥200 copies/mL) occurred in 3 participants, including 2 with BMI ≥30 kg/m² as the sole factor. The 2 received on-time injections (Q4W and Q8W, respectively) using 1.5-inch needles, and 1 had gluteal implants. Notably, no CVFs occurred among 34 participants with BMI ≥40 kg/m^2 (40–44.9, n = 18; 45–49.9, n = 11; ≥ 50, n = 5). A last-observed HIV RNA ≥50 copies/mL occurred in 21/226 (9%) versus 18/148 (12%) participants with BMI <30 versus ≥30 kg/m^2, largely as low-level viremia (50–199 copies/mL), with no association with BMI. Preliminary data from the cohorts Observational Pharmaco-Epidemiology Research & Analysis (OPERA) (n = 450/1543 [29%] with BMI ≥30 kg/m^2) [27] and RELATIVITY (n = 113 with BMI >30 kg/m^2) [28] confirm efficacy across BMI categories.

Implications for Clinical Practice

- A high BMI as a sole factor does not significantly increase CVF risk, with both trial and real-world evidence supporting CAB + RPV-LA efficacy.
- 2-inch needles are indicated at high BMI to ensure proper intramuscular delivery. However, data from trials with low use of 2-inch needles suggest that lack of access may not substantially affect outcomes in practice.
- More evidence is needed for very high BMI and for gluteal implants, and on alternative injection sites.

Pharmacokinetics

The low number of CVFs in CAB + RPV-LA studies has hindered efforts to establish pharmacokinetic (PK)/pharmacodynamic relationships. A consensus on minimal concentration thresholds is also lacking. Various thresholds have been applied, including the PA-IC_{90} (CAB 166 ng/mL, RPV 12 ng/mL) [24, 29, 30] or 4× $PAIC_{90}$, and those based on drug level distributions, such as the upper limit of the first quartile of the distribution of $C_{troughs}$ in the registrational trials (CAB 1120 ng/mL, RPV 32 ng/mL) [29, 31] In the trials, 14/22 (60%) participants with CVF had "low" CAB and/or RPV, ie, levels ≤1st quartile, at week 4 after first injection [8]. However, few with low C_{trough} as the sole factor experienced CVF [8 (including Supplementary data)] (Figure 1).

A cohort study suggested thresholds of 664 ng/mL for CAB and 50 ng/mL for RPV, which mirror the 4x $PAIC_{90}$, although these were based on limited data that did not demonstrate a clear correlation between drug concentrations and CVF [32]. In a prospective study of 173 individuals switching to CAB + RPV-LA Q8W, participants with viremia ≥50 copies/mL had lower CAB and RPV $C_{troughs}$ than those with consistent suppression [29]. However, adding PK parameters to predictive models did not improve accuracy, indicating that PK alone was not a key determinant of viraemia.

CAB and RPV $C_{troughs}$ show wide inter- and intra-individual variability [8, 29, 33]. CAB $C_{troughs}$ are initially slightly lower at higher BMI [8, 31, 34, 35]. In the registrational trials, with Q8W dosing, week 8 CAB $C_{troughs}$ were 2.0 µg/mL at BMI <30 kg/m^2 and 1.1 at higher BMI, but no difference was observed from week 16 through week 48; at BMI ≥30 kg/m^2, plasma concentrations increased if using 2-inch needles [24]. The trials did not detect an effect of higher BMI on RPV $C_{troughs}$ with either Q4W or Q8W dosing over 48 weeks [24]. However, cohort data suggest a possible effect with Q8W dosing [34]. The trials found no influence of BMI on week 48 CAB and RPV $C_{troughs}$ [8]. However, modelling predicts lower CAB and RPV $C_{troughs}$ at steady-state with BMI >35 kg/m^2 and >40 kg/m^2, respectively, particularly with Q8W dosing [36]. CAB exposure may also show minor variations by age and sex; however, post hoc analyses of the SOLAR [25] and CARISEL [37] trials demonstrated consistent efficacy of CAB + RPV-LA Q8W across age, sex, and ethnicity subgroups.

Although evidence is limited, some investigators have suggested therapeutic drug monitoring (TDM) for selected individuals, particularly for those with high BMI, populations underrepresented in clinical trials, or individuals with unexplained viremia [31, 32, 36]. One approach proposes using low C_{trough} measurements to trigger intensified virological monitoring, repeat TDM, and a review of other CVF risk [31], whereas another advocates TDM in people with morbid obesity to adjust dosing intervals [36].

Implications for Clinical Practice

- The relationship between BMI and CAB/RPV concentrations is complex. However, a direct relationship between drug concentrations and CVF has not been established.
- Multiple factors complicate use and interpretation of TDM (Box 2), necessitating further evidence of clinical utility.
- TDM is not currently recommended outside of research settings until more robust evidence is available.

Box 2. Factors complicating the use and interpretation of therapeutic drug monitoring of CAB + RPV-LA in routine practice.

- Wide intra-individual variability in drug concentrations
- Lack of established therapeutic thresholds
- Interpretation requires specialist knowledge
- The clinical relevance of detecting low drug concentrations remains to be demonstrated, with limited evidence on how results should guide practice, including introducing any variations in dose or dosing intervals
- Logistical challenges in sampling for C_{trough} measurement
- Limited test availability outside of research centers
- The cost-benefit has not been established

Abbreviations: CAB, cabotegravir; C_{trough}, trough plasma concentration; LA, long acting; RPV, rilpivirine.

Dosing in renal and hepatic impairment and notable drug-drug interactions are summarized in Supplementary Boxes 1 and 2.

IMPLEMENTATION CHALLENGES

Pregnancy

In the CAB + RPV-LA registration trials, fewer than one third of participants were female at birth, and those who were pregnant, breastfeeding, or planning conception were excluded [1–3]. For RPV, sufficient first-trimester exposures have been monitored to detect a ≥ 2-fold increase in birth defect risk, and no such increase has been detected [38]. Although pregnancy CAB data remain limited, no safety signals have been observed to date [38–44]. Animal studies showed no adverse effects with CAB doses ≤13 times the human exposure [39]. The HPTN-084 open-label extension study of CAB-LA for preexposure prophylaxis reported good tolerability and no adverse pregnancy outcomes among 212 pregnancies on active CAB-LA and 68 pregnancies with prior CAB-LA [42].

CAB is primarily metabolized by UGT1A1 and RPV by CYP3A4, with enzyme induction in the second and third trimesters, potentially lowering plasma concentrations [45]. PK modelling suggests CAB Q4W may maintain adequate levels throughout pregnancy, but caution is advised with CAB Q8W; with both dosing regimens, RPV levels may fall below efficacy thresholds [46]. Clinical data are limited. A retrospective case series reported high virological suppression among 18 women who started or continued CAB + RPV-LA Q4W/Q8W through pregnancy [43]. A case report (CAB + RPV-LA Q8W) showed CAB levels comparable to nonpregnant individuals but a 70%–75% reduction in RPV levels; neither virological failure nor perinatal transmission occurred [41].

Implications for Clinical Practice

- Pregnancy guidelines do not endorse CAB + RPV-LA due to limited safety and efficacy data [39]. Although available data raise no safety concerns in relation to the effects of CAB/RPV exposure on pregnancy outcomes, evidence remains insufficient.
- More studies are needed to support CAB + RPV-LA use in pregnancy. Importantly, after discontinuation in early pregnancy, the PK tails of CAB/RPV extend to 6 months postpartum [44].
- Since women of childbearing potential are willing to try injectable ART, often preferring it to oral ART [47], shared decision-making is advised when initiating treatment for individuals who wish to conceive.
- For individuals who become pregnant on CAB + RPV-LA, the preferred approach is switching to oral ART [39].

Hepatitis B Virus

An oral regimen with dual HIV/HBV activity is recommended for individuals with chronic HBV infection [4–7]. HBV acquisition in nonimmune individuals and reactivation in those with past infection are concerns when considering HBV-inactive ART.

In nonimmune individuals, responses to conventional alum-adjuvant HBV vaccines are often suboptimal, with reduced hepatitis B surface antibody (anti-HBs) seroconversion rates, anti-HBs titers, and duration of seroprotection [48]. Factors associated with poor vaccine immunogenicity include male sex, age >40 years, smoking, detectable HIV RNA, CD4 counts <350 cells/mm^3, and low nadir CD4 counts [48, 49]. higher and more frequent doses [48, 50] or newer adjuvant vaccines [48, 51–54] are recommended to improve responses (Figure 2).

With past infection, moderate-to-low-quality evidence indicates that HBV-inactive ART carries a low (~1.6%) risk of reactivation, identified through hepatitis B surface antigen (HBsAg) and/or HBV DNA detection using routine diagnostics [55]. Across studies, reactivations were typically less common with preswitch anti-HBs ≥10 IU/L than with anti-HBs lack or loss, and were variably associated with alanine transaminase elevations, including severe hepatic flares [55]. Reassuringly, hepatic flares typically resolved after introducing HBV-active agents, with HBsAg loss documented within 2–5 months [55].

Implications for Clinical Practice

Testing for HBV infection and immunity is recommended when considering CAB + RPV-LA, with results necessitating appropriate follow-up and management (Figure 2).

Variations in HBV testing practices before and after initiating HBV-inactive ART [55] highlight the need for standardized monitoring protocols.

- Nonimmune individuals (HBsAg, anti-HBs, and hepatitis B core antibody (anti-HBc) negative)Regardless of exposure risk, individuals should have documented seroprotection (anti-HBs ≥10 IU/L) [48] prior to initiating HBV-inactive regimens. An ideal threshold has not been established but may be >100 IU/L [48].

Six months are typically required to complete a standard vaccination series (Supplementary Table 1), with anti-HBs measured 4–8 weeks after last dose [48]. To accelerate a switch to HBV-inactive ART, anti-HBs may be measured after ≥3 doses of alum-adjuvant vaccines or ≥2 doses of newer adjuvant vaccines [52]; if seroprotection is demonstrated, switching may proceed while continuing the vaccination series.

Ultra-rapid vaccination (3 doses of an alum-adjuvant vaccine over 3 weeks) may be considered in individuals with CD4 counts >500 cells/mm^3, preferably without risk factors for nonresponse [48].

If no response is achieved by series end, further cycles can be attempted, preferring high-dose or newer adjuvant vaccines [48, 51–54].

Individuals with a previous vaccine response should be offered a booster dose [48].

A booster dose may also be considered if post-vaccination anti-HBs titers fall between 10 and 99 U/L to increase the longevity of seroprotection [48].

- Individuals with prior HBV infection (HBsAg-negative, anti-HBc positive)
- Prior HBV infection requires a careful assessment of HIV-related and non–HIV-related risk factors for HBV reactivation preswitch and on an ongoing basis. These include lack or loss of anti-HBs, low current or nadir CD4 count, HIV viremia, detectable HBV DNA preswitch, immunosuppression, and poorly controlled diabetes or advanced chronic renal disease; the presence of anti-HBs reduces but does not abolish the risk [55, 56].
- Postswitch monitoring involves testing for both HBsAg and HBV DNA; the interval is yet to be defined and may be every 1 to 6 months based on clinical judgment [6].
- HBsAg and/or HBV DNA detection postswitch signals a heightened risk of hepatic flares [55] and should be confirmed and managed promptly.
- Individuals with HBV reactivation should either switch to HBV-active ART or start an oral anti-HBV agent such as tenofovir or entecavir [6].

Adherence Challenges

Emerging evidence suggests that injectable therapy may benefit those struggling with daily oral ART, provided appropriate support is in place (Table 1) [57–61]. Ward 86, a publicly

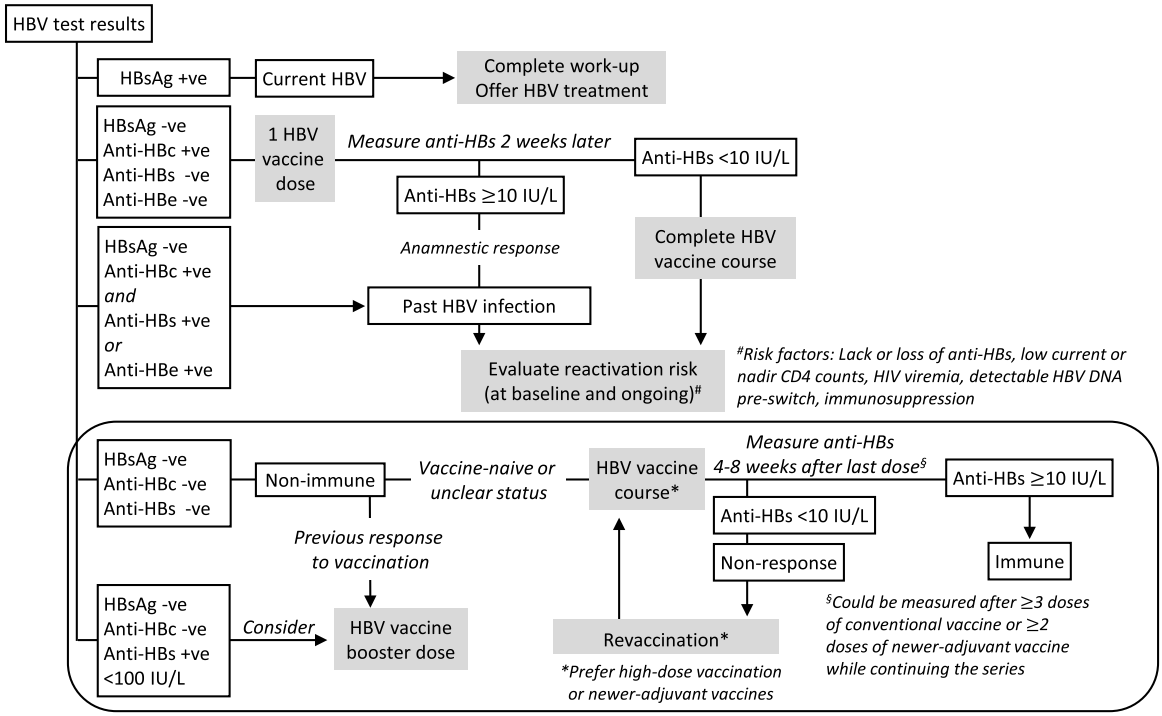

Figure 2. Proposed algorithm for managing the results of HBV serological testing. Abbreviations: +ve, positive; -ve, negative; anti-HBc, hepatitis B core antibody; anti-HBe, antibody to hepatitis B e-antigen; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Table 1. Studies Providing Proof-of-concept Evidence for CAB + RPV-LA Implementation in Populations With Psychosocial Complexity and Adherence Challenges.

Study Country	Design Population	Regimen	Outcomes
San Francisco WARD 86 clinic [57] US	Retrospective cohort study N = 59 All HIV RNA ≥50 copies/mL (median 4.6 $\log_{10}$ copies/mL) 29 (49%) CD4 < 200 cells/mm^3	CAB + RPV-LA Q4W (no OLI) with optional switch to Q8W after 3–6 m of VS Low-barrier care model with social work outreach, financial incentives, and flexibility in injection sites	• At 48 wk: 47 (80%) continued CAB + RPV-LA with VS • 5 (8%) discontinued; 5 (8%) had VF (all with CAB and/or RPV RAMs); 1 was lost to follow-up; 1 added lenacapavir due to low-level viremia (without CAB + RPV RAMs) • 94% of injections in dosing window, 0.6% missed
LATITUDE [59] US	Phase III, multicentre, open-label randomized N = 294 All with HIV RNA >200 copies/mL No CAB/RPV RAMs	Induction phase: Incentivized oral ART (≥2 active drugs) for ≤24 wk to reach virological milestones Randomization phase: Participants achieving HIV RNA <200 copies/mL randomized to CAB + RPV-LA Q4W (± OLI) (n = 146) versus continue oral ART (n = 148)	• Interim analysis: Judging CAB + RPV-LA overall superior to oral ART, the DSMB recommended to stop randomization and offer CAB + RPV-LA to all eligible participants • CAB + RPV-LA versus oral ART: VF 7% versus 25%, treatment-related failure 10% versus 26%, permanent treatment discontinuation 21% versus 25% • CAB + RPV-LA arm: 2 with VF acquired CAB/RPV RAMs • 93% of injections in dosing window, 3% missed
San Diego Owen Clinic [61] US	Retrospective cohort study N = 62 15 (24%) HIV RNA >200 copies/mL 7 (11%) HIV RNA >10 000 copies/mL Median CD4 count 497 cells/mm^3	CAB + RPV-LA (primarily Q8W without OLI) 9 also received lenacapavir 3 also received oral agents	• At 48 wk: 53 (86%) continued CAB + RPV-LA with VS • 6 (10%) discontinued (3 were lost to follow-up); 5 (8%) had VF (3 with CAB/RPV RAMs; 2 resuppressed without ART change) • 82% of injections in dosing window

Table 1. Continued

Study Country	Design Population	Regimen	Outcomes
JABS [60] Australia	Phase IV, single-center, open-label N = 60 with VS, no CAB + RPV RAMs No active HBV	CAB + RPV-LA Q8W (+ OLI) Multidisciplinary support program (nurse practitioner, social worker, welfare assistant)	• Effective implementation at 48 wk • 97% of injections in dosing window • Similar injection adherence regardless of adherence history • 6 discontinuations, no VFs

Abbreviations: ART, antiretroviral therapy; CAB, cabotegravir; DSMB, Data Safety Monitoring Board; HBV, hepatitis B virus; JABS, Injectable Antiretroviral Therapy Feasibility Study; LA, long-acting; OLI, oral-lead-in; Q4W, every 4 weeks; Q8W, every 8 weeks; RAMs, resistance-associated mutations; RPV, rilpivirine; VS, virological suppression; VF, virological failure.

funded HIV clinic in San Francisco, pioneered the study of CAB + RPV-LA Q4W (with an optional switch to Q8W after achieving stable virological suppression) in a viremic population with financial and housing insecurity, mental health problems, substance use disorders and suboptimal adherence, reporting overall favorable outcomes [57]. A low-barrier care model incorporating social work outreach, financial incentives, and flexible injection site options was key to supporting participants [58]. In the United States, an interim analysis of the Long-Acting Therapy to Improve Treatment Success in Daily Life (LATITUDE) trial showed greater efficacy of CAB + RPV-LA Q4W versus standard oral ART in adults with adherence challenges, adopting an approach of incentivizing the attainment of virological suppression before randomization [59]. Data from the United States and Australia demonstrated the feasibility of implementing CAB + RPV-LA Q8W in similar populations [60, 61]. These studies achieved low rates of missed injections through robust adherence support. However, the strategy is not without risks. The prolonged PK tails of CAB and RPV mean that treatment discontinuation without oral ART cover will lead to viral rebound, prolonged subtherapeutic drug levels, and drug resistance.

Migrating and displaced populations often face challenges in maintaining stable ART, including limited access to care, stigma, language barriers, financial and housing instability, and frequent relocations or ongoing migration. When considering CAB + RPV-LA, additional issues arise, such as incomplete HIV treatment history, high prevalence of HBV infection and tuberculosis, and potential drug–drug interactions (eg, with rifampicin). Ukrainian migrants to Poland and Germany exemplify these challenges: subtype A6 is nearly universal, RPV resistance rates are high, HBV vaccine coverage is suboptimal, and tuberculosis is prevalent [62, 63]. While delinkage from care exceeds 10% [62], ensuring treatment continuity is complicated by the variable availability of CAB + RPV-LA across Central and Eastern Europe.

Implications for Clinical Practice

- Injectable therapy has the potential to benefit individuals struggling with adherence for a multiplicity of reasons, including stigma-driven challenges, pill fatigue, housing instability, or harmful substance use.
- While the original registration trials included virologically suppressed individuals with good adherence, preliminary data have led several panels to cautiously endorse CAB + RPV-LA for individuals with or without viremia who cannot take oral ART consistently despite adherence support, have no CAB/RPV resistance, and are at risk of clinical progression [5–7].
- Provider concerns include adherence to injection schedules, rapid initiation of oral ART after missed injections, resistance development, and potential onward transmission of resistant strains, which could undermine population-level control efforts, including the prophylactic efficacy of CAB-LA.
- There are logistic challenges, such as providing the required harm reduction, multidisciplinary case management, appointment reminders, flexible scheduling, transportation support, financial incentives, and alternative injection locations, which are exacerbated when caring for migrant populations.
- The potential advantages of closer follow-up with Q4W dosing remain uncertain; Q4W dosing is approved but not available across Europe.

CONCLUSIONS AND FUTURE DIRECTIONS

CAB + RPV-LA represents a significant innovation in HIV treatment, with trials and observational studies demonstrating robust efficacy across diverse populations. Although clinical research gaps remain (Box 3), successful

Box 3. Priority research areas for enhancing the clinical impact of CAB + RPV-LA.

- Expand predictive models to guide individualized therapy
- Develop standardized tools for archived resistance testing and establish its clinical utility
- Investigate the role of therapeutic drug monitoring in enhancing safety and efficacy, especially in populations with potential pharmacokinetic challenges
- Expand the evidence on alternative injection sites
- Investigate rapid HBV vaccination strategies
- Expand studies in key populations, including pregnant individuals, people with very high BMI, and those with past HBV, to strengthen clinical recommendations
- Enhance adherence-focused interventions by integrating flexible delivery models and addressing socioeconomic barriers, exploring implementation strategies across different settings

Abbreviations: BMI, body mass index; CAB, cabotegravir; HBV, hepatitis B virus; LA, long acting; RPV, rilpivirine.

implementation relies on carefully weighing individual-specific risks and benefits, including viral, host, and PK factors. Additionally, the risk/benefit assessment should consider how switching from oral ART to injectable therapy may improve the experience of stigma and other parameters of psychosocial wellbeing [9]. A tailored approach can maximize the potential of CAB + RPV-LA to improve outcomes for people with HIV.

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

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