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EDITORIAL COMMENTARY

Long-Acting Cabotegravir and Rilpivirine: Innovation, New Challenges, and Opportunities

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(See the Major Article by Overton et al. on pages 1646–54.)

Cabotegravir (an integrase strand transfer inhibitor [INSTI] that is structurally similar to dolutegravir) and rilpivirine (a nonnucleoside reverse transcriptase inhibitor [NNRTI]) formulated as a nanoparticle suspension for intramuscular injection (CAB + RPV LA) are the first complete long-acting maintenance antiretroviral treatment (ART) approved for clinical use. To date, the drugs have not been coformulated, so each administration requires 2 simultaneous intramuscular jabs.

This singular therapy emerged from research and innovation related to long-acting ART. Multiple drugs and drug combinations through oral, parenteral, or subcutaneous implant formulations, including ultra–long-acting refillable subcutaneous implants and microarray patches, are being assessed.

If access criteria are met and there are no constraints regarding intramuscular administration capabilities at the treatment center, this will be the first ART option to be solely a patient's choice. Patients with daily oral pill fatigue or human immunodeficiency virus (HIV) disclosure and ART privacy issues will be able to decide about their treatment choice.

The registrational phase 3 studies, ATLAS and FLAIR, compared every 4-week (Q4W) dosing of CAB + RPV LA with daily oral combination ART and led to the approval of this dosing strategy [1, 2].

Phase 2 results of every 8-week (Q8W) dosing and supportive modeling underpinned further evaluation of Q8W dosing. The ATLAS-2M study, a head-to-head comparison of Q8W vs Q4W, demonstrated noninferiority of the Q8W strategy and led to the approval of this dosing regimen [3]. There have been no direct comparisons of Q8W CAB + RPV LA vs oral ART. Despite the approval of both Q4W and Q8W dosing by both the European Medicines Agency and the US Food and Drug Administration (FDA), in many countries (including several European countries and the United Kingdom) the only dosing available will be Q8W.

In this issue of *Clinical Infectious Diseases*, investigators from the ATLAS-2M trial make a substantial step toward establishing the long-term efficacy of the Q8W strategy, reporting the 152-week data [4]. Most notable among their trial findings was confirmation of the long-term efficacy, safety, and tolerability of CAB + RPV LA and, not unexpectedly, preference by participants for Q8W instead of Q4W administration.

In the 152-week study, CAB + RPV LA Q8W demonstrated noninferior efficacy vs Q4W dosing, with 2.7% (n = 14) and 1.0% (n = 5) of participants having HIV-1 RNA ≥50 copies/mL, respectively (adjusted treatment difference, 1.7%; 95% confidence interval [CI]: .1 to 3.3), in the efficacy end point. Though meeting the prespecified noninferiority threshold of 4% (commonly acknowledged by the FDA in switch trials), this rate of nonvirological suppression (≥50 copies/mL) was significantly higher in the Q8W arm (the lower bound of the 95% confidence limit did not cross 0). This curious finding is occasionally encountered in noninferiority trials [5] and must be interpreted cautiously. This difference was not observed in the primary end point (48 weeks) [3] or at the 96-week analysis [6] nor was it observed in the per-protocol analysis at 152 weeks, which showed an adjusted treatment difference of 1.4% (95% CI: −.2% to 2.9%). Moreover, because the 95% confidence limits of the difference lie entirely within the prespecified boundary of 4%, this minimal difference should not be interpreted as having clinical significance [7].

Q4W and Q8W safety profiles were comparable, with no new safety signals observed since week 48. Drug-related adverse events were common and comparable across arms, largely attributable to injection site reactions, which represent 64% of all participants with drug-related adverse events.

Two additional participants experienced protocol-defined confirmed virological failures (CVFs) and a third experienced nonprotocol-defined virologic failure

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between week 96 and week 152 (all in the Q8W arm). Mutations associated with RPV resistance were detected in virus from all 3 participants, and CAB resistance mutations were detected in the 2 with protocol-defined CVFs. This small but measurable rate of resistance emergence was unevenly distributed between the 2 dosing arms in the long term. These additional data bring the total number of participants with emergent drug resistance at 152 weeks to 12 of 452 (2.7%) in the Q8W arm compared with only 2 of 447 (0.5%) in the Q4W arm.

Although the proportion of participants with emergent drug resistance was small, in a majority of CVF cases was associated with selection of resistance to 2 drug classes: INSTIs and NNRTIs. In some cases, the resistance mutations that were selected rendered all INSTIs and NNRTIs inactive. So, a question arises: how high a risk of resistance selection at treatment failure can be tolerated in a novel switch regimen, considering that most switch strategies accepted in guidelines have zero resistance selection?

Of potential concern is the observation that protocol-defined CVFs with resistance occurred in some participants despite confirmed on-time (±7-day window) injection of CAB + RPV LA, effectively excluding nonadherence as a potential cause of CVF. In this regard, it is notable that plasma drug concentrations for participants with CVF were generally in the first quartile of the overall study geometric mean values, albeit above the protein-adjusted concentration required for 90% inhibition (PA-IC_{90}) for both agents. Similarly, a Swiss HIV cohort study of people receiving the Q8W regimen reported low RPV concentrations that were approximately 2 times the PA-IC_{90} of 12 ng/mL in 13% of their participants [8]. The relevance of this finding is still unknown, but it reinforces the importance of close adherence to the recommended dosing interval for CAB + RPV LA of every 8 weeks, ±7 days. It will be important to determine the contribution of various patient-specific factors, including body mass index (BMI), injection practice, and genetically determined variation in the rate of drug metabolism, to the observed interpatient variability in plasma concentrations of these long-acting drugs.

A separate analysis identified baseline factors associated with increased risk of CVF, including presence of RPV resistance-associated mutations (RAMs), HIV-1 subtype A6/A1, and BMI ≥30 kg/m^2. A multivariable analysis that included post-baseline model-predicted CAB/RPV trough concentrations identified RPV RAMs, HIV-1 subtype A6/A1, and predicted CAB or RPV trough plasma concentrations (baseline BMI was no longer significant in this model) [9]. The presence of a combination of ≥2 baseline factors predicted an increased risk of CVF with a specificity of 98% but a sensitivity of only 48%.

Reassuringly, the proportion of participants with HIV-1 RNA blips, target nondetected HIV-1 RNA, HIV-1-RNA <2 copies/mL, and mean CD4+-to-CD8+ ratio (with and without blips) was similar between the Q8W and Q4W CAB + RPV LA groups through week 152 in ATLAS-2M [10]; blips were not associated with CVF.

Some antiretroviral guidelines include specific recommendations regarding this 2-drug injectable regimen, and the British HIV Association guidelines are the first to do so [11]. They recommend use of CAB + RPV LA for people who accept the risk of virological failure despite complete adherence and monitoring HIV-1 RNA every 2 months. Their rationale for frequent virus load monitoring is that since HIV-1 RNA quantification was performed at each visit in the trial, until trial and/or real-world evidence emerges to support otherwise, they recommend viral load monitoring at all visits and prompt recall for repeat testing and resistance testing if viral rebound occurs.

Therefore, treating clinicians must understand that it is of the outmost importance to protect this novel long-acting regimen against a potential risk of CVF and HIV resistance selection. The best way to minimize the risk of CVF and resistance selection might be to exclude people with any prior virological failure. Prior unplanned treatment interruptions on NNRTI (particularly first-generation NNRTIs) must be carefully evaluated. Specifically, patients with known or suspected NNRTI or INSTI resistance should be excluded. Finally, some experts might recommend excluding persons with HIV-1 A6/A1 virus as well [11], though low numbers with an A6/A1 subtype as the single baseline factor experienced CVF in a multivariable analysis [9]. Importantly, it should be prescribed only for people who can commit to receiving injections every 2 months and do not need a tenofovir-containing regimen for the treatment or prevention of hepatitis B.

Long-acting ART poses new opportunities and challenges. Together, let us protect these new amazing treatment strategies and the amazing landscape they open to lifelong ART.

Note

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