BACKGROUND

HPTN 084 is a Phase 3 randomized, double-blind, double-dummy superiority trial that showed that long-acting injectable cabotegravir (CAB) and tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) were highly effective for HIV prevention in women in sub-Saharan Africa. Participants were randomized 1:1 to active CAB + TDF/FTC placebo or active TDF/FTC + CAB placebo. The blinded trial was stopped at a planned interim Data Safety Monitoring Board review in November 2020. CAB was superior, with an 89% lower risk of infection compared to TDF/FTC. We characterized the 40 observed infections in HPTN 084 (4 CAB, 36 TDF/FTC) using virology and pharmacology assays.

RESULTS

IDENTIFICATION OF HIV INFECTIONS

HIV infection was confirmed in four CAB arm participants including one who was found to have HIV infection at enrollment prior to CAB administration; this case was reclassified as a baseline infection (Case A1). (Figure 1 and 2). Ten participants with incident infection received no CAB injections and had no recent CAB exposure (Cases B1 and B2). B1 completed the oral lead in but failed to receive her first injection visit. B2 transitioned to open-label TDF/FTC due to pregnancy prior to the injection phase. The third incident infection occurred during the injection phase of the study in a participant with delayed injection visits (Case DX) (Figure 3). At 93 infections in the TDF/FTC arm were incident infections. When prevalent infections were excluded, the unadjusted hazard ratio for CAB vs. TDF/FTC was 0.08 (95% CI 0.03, 0.27) (Table 1).

STUDY DRUG EXPOSURES, DRUG CONCENTRATIONS AND HIV RESISTANCE

Cabotegravir cases

Case A1 (Figure 2) • The site first detected HIV infection 32.3 weeks post-enrollment. The participant received oral CAB and five CAB injections before the first site positive visit. • CAB concentrations indicated inconsistent use during the oral run-in period; by the 3rd injection CAB was 1.33 µg/mL, i.e., 28x PA-EIU and remained above this threshold through to the first site positive visit. At that time, the CAB concentration was 2.68 µg/mL. • Exposure to CAB was associated with diminished delayed inhibition and delayed HIV diagnosis. • Retrospective testing of samples revealed that the participant was infected at enrollment with a viral load of 21.4 copies/ml. • HIV RNA ranged from 500-600 copies/mL, during the oral lead in, but was not detectable using the qualitative RNA assay or the single-copy RNA assay at 0.77 copies/mL during CAB injections 2 weeks after the last CAB injection. • No major integrase strand transfer inhibitor (INSTI) mutations were detected. • The participant was successfully linked to antiretroviral therapy (ART) shortly after confirmation of infection.

FIGURE 2. Cabotegravir: case A1, reclassified as prevalent HIV infection

Case A1 (Figure 2) Step 1: CAB oral lead-in Step 2: CAB LA 900 mg/mL Step 2: CAB LA injection + 2 week overlap Step 3: CAB 60 mg/mL CAB RNA 60 ng/mL Open-label TDF/FTC for pregnancy No ART Blindfolded dispensed First site positive visit

Case DX, (Figure 3) • The site first detected HIV infection 72 weeks post-enrollment. • The participant received oral CAB and three CAB injections; the ninth injection was administered at the first site positive visit, before the site received the reactive Ag/Ab test result. • 5/9 injections were delayed (range: 2.57 days); the eighth injection occurred 16.1 weeks prior to the first HIV positive visit. • CAB concentrations in the oral lead-in phase were all BLO, indicating no adherence to oral study drug. CAB concentrations were 28x PA-EIU in plasma samples collected before the first HIV positive visit but were <4x PA-EIU (0.416 mcg/mL) at the first HIV positive visit. • HIV RNA was detectable at the first site positive visit. • No major INSTI mutations were detected. • The participant was successfully linked to ART.

FIGURE 3. Cabotegravir case DX, incident HIV infection after delayed injections

CONCLUSIONS

Most incident HIV infections in HPTN 084 occurred in the setting of unquantifiable or low drug concentrations. Detection of HIV infection may be delayed in this setting using routine diagnostic assays, particularly when long-acting products are used. Use of HIV RNA testing as primary screen for HIV infection will be assessed in the open-label extension. No major INSTI mutations were observed in the CAB arm. The prevalence of transmitted NNRTI drug resistance is a concern.

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