Brief Report: Impact of ART on Maternal Health After Cessation of Breastfeeding

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Abstract:

IMPAACT PROMISE 1077BF/FF was a sequentially randomized study of pregnant and postpartum women living with HIV to investigate the efficacy and safety of antiretroviral therapy (ART). This Maternal Health Component investigated efficacy for the risk of developing AIDS or death; and safety among women randomized to continue ART (CTART: N = 289) or discontinue ART (N = 268) after cessation of breastfeeding or after confirmation of infant infection. No AIDS-defining illnesses were reported during follow-up in either arm. Adverse events of grade 3 or higher were more frequent in the CTART arm [hazard ratio = 1.78, 95% confidence interval: (1.05 to 3.02), *P*-value = 0.03]. The difference in adverse events in the 2 groups was mostly driven by moderate weight loss for women on the CTART arm.

Key Words: HIV, breastfeeding, ART, AIDS, mothers, adverse events

INTRODUCTION

When to start triple-drug antiretroviral therapy (ART) in people living with HIV was a principal scientific question facing the HIV research community over the past 30 years. Policy recommendations for starting ART have evolved over the past 2 decades. The CD4 cell count threshold to start ART increased from 200 CD4 cells/mm^3 up to 500 CD4 cells/mm^3, and then in 2015, WHO recommended starting ART as soon as possible after a diagnosis of HIV.[1] Two landmark studies in adults that strongly influenced current practice are the HPTN 052[2] study and the START study.[3] HPTN 052 demonstrated that starting ART immediately on diagnosis reduced the risk of transmission to an HIV-uninfected partner and also conferred a clinical benefit compared to starting ART at a CD4 cell count below 250 cells/mm^3. The START study demonstrated a clinical benefit to starting ART immediately compared with delaying ART until a decrease in CD4 cell count below 350 cells/mm^3.

Concurrent to the period of the START trial follow-up, 3 Promoting Maternal and Infant Survival Everywhere (PROMISE) studies designed to assess the risks and benefits of ART in pregnant and postpartum women, followed women living with HIV, who at the time of enrollment did not meet country criteria for treatment. Two of these studies randomized women after delivery to continue ART (CTART) or discontinue ART and restarted ART when clinically indicated (DCART). Both studies observed a low incidence of AIDS-defining illness with small by arm differences, but a lower rate of WHO II/III stage events in women who continued ART.[4,5] We present the results of the third randomized study that compares CTART to DCART after breastfeeding.

Given current guidelines to start lifetime ART after diagnosis, this study includes the only randomized data to estimate differences between CTART or DCART in a population of postpartum women. These data remain important, given the documented suboptimal rates of ART adherence among postpartum women in all settings, including resource-limited settings where HIV burden is highest.[6–8]

METHODS

The PROMISE studies, conducted from 2011 to 2016, were multisite, randomized, Phase III, open-labeled clinical trials that used 3 protocols: 1077HS, 1077BF, and 1077FF. In 1077HS,[4] formula-feeding women from areas where ART during pregnancy was standard of care for the prevention of perinatal HIV transmission were randomized to CTART or DCART after delivery. In 1077BF (breastfeeding) and 1077FF (formula-feeding), women could be sequentially randomized up to 3 times[9]: during pregnancy,[10,11] after delivery,[5,10,12] and after breastfeeding. 1077BF and 1077FF (1077BF/FF), which forms the basis for this study, was conducted in India, Malawi, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe where use of ZDV during pregnancy was standard of care for prevention of perinatal HIV transmission. The study by Hoffman et al[5] provides an important reference with further background information.

Important inclusion criteria for the postbreastfeeding randomization were HIV-1 infection, on ART in the postpartum component of 1077BF/FF, complete cessation of breastfeeding (infant received no breastmilk in the prior month) or were 18 months postpartum, CD4 cell count >350 cells/mm^3 or greater than the country-specific threshold, absolute neutrophil count >750 cells/mm^3, hemoglobin >7.0 gm/dL, platelet count > 50,000 cells/mm^3, ALT (SGPT) < 2.5 × ULN, and estimated creatinine clearance of > 60 mL/min13. Important exclusion criteria included WHO stage IV disease, significant illness or condition requiring systemic treatment or hospitalization 30 days before entry, current or history of TB disease, use of prohibited medications, documented conduction heart defect, or required ART for their own health. Randomization was stratified by country, infant age at randomization, and antepartum ARV arm. Adverse events (AEs) were graded using the DAIDS Table for Grading the

Severity of Adult and Pediatric AEs, 2004 Version 1.0.[14] Participants on the DCART arm restarted ART if they developed an indication for ART and women on ART switched to a second-line therapy when clinically indicated.

Endpoints and Statistical Analyses

The primary efficacy endpoint was the incidence of AIDS-defining illness (WHO clinical stage IV)[15] or all-cause mortality. Primary endpoints were reviewed by an independent endpoint review committee blinded to treatment arm. Two thousand one hundred women were planned to participate in the postbreastfeeding randomization to give 90% power for a comparison in the 2-year primary efficacy rate of 6.67% vs. 3.6%. Secondary efficacy endpoints included HIV-related illnesses: WHO stage IV, pulmonary tuberculosis, or bacterial infection (single episode of bacterial pneumonia, grade 4, within 3 days of an unscheduled hospitalization). Additional secondary efficacy endpoints included HIV-related illnesses or a new WHO Clinical Stage II or III event, HIV-related illnesses or death, pulmonary tuberculosis, and bacterial infection. The safety endpoint included time to first of selected grade 2 laboratory abnormalities (renal, hepatic, and hematologic), and all grade 3 or higher AEs.

The analyses were based on the principle of intent-to-treat. Time-to-event distributions were summarized using Kaplan–Meier estimators and compared between arms with the log-rank test and Cox proportional hazard models. Analyses of weight gain were conducted with generalized estimating equations. Incidence rates (IRs) were displayed per 100 person-years. Nominal unadjusted *P*-values and 95% confidence intervals were used to summarize results. Analyses were performed using Statistical Analysis System (SAS) software version 9.4 (SAS Institute).

RESULTS

Study Population

The first randomization for this analysis occurred on November 11th, 2011. On July 16th, 2014, accrual was halted due to slow enrollment. Randomized follow-up continued until July 7th, 2015, when the PROMISE study participants were notified about the START results and were recommended to start ART. The analysis data were censored at this date and frozen on March 1st, 2017.

Of the 1220 women randomized to ART during the earlier PROMISE postpartum component, 289 were subsequently randomized to CTART and 268 to DCART at cessation of breastfeeding. Of those not randomized, 361 women were breastfeeding when randomization was halted, 197 were off study before complete breastfeeding cessation, 84 needed ART for their own health, and 6 for other reasons. Baseline characteristics were similar across arms. Ninety-four percent were Black African, with a median age of 28 years, and median BMI of 23.1 kg/m^2. Ninety-three percent were at WHO Clinical Stage I, and 95% had a CD4 cell count ≥500 cells/mm^3. Ninety-eight percent of women were on LPV/r+FTC-TDF at the time of randomization.

Sixteen women prematurely discontinued study follow-up: 6 due to site closure, 2 died, and 8 were lost to follow-up. The overall median follow-up time was 84 weeks (range: 4–171) for a total of 871 person-years. Ninety-eight (37%) of women on the DCART arm restarted ART: 91 for a clinical indication consistent with protocol requirements and 7 without a recorded clinical indication. Thirty women on the CTART arm discontinued ART early.

CD4 Cell Counts and Viral Loads Over Time

Median CD4 cell counts were stable, above 350 cells/mm3 over time in the CTART arm but decayed slowly in the DCART arm, with higher median CD4 cell counts in CTART (Fig. 1A). Median HIV-1 RNA levels were lower in the CTART arm compared with the DCART arm for all time points after randomization (Fig. 1B). The proportion of women with a viral load below 400 copies/mL increased after week 12, from 84% to 92% at week 96 in the CTART arm (Fig. 1B).

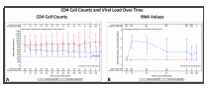

FIGURE 1.

CD4 cell counts cells/mm^3 and log HIV-RNA over time with median, 25th and 75th percentiles; percentage of participants with (A) CD4 cell percentage <350 cells/mm^3 and (B) HIV-RNA ≤400 copies. Both subfigures used the midpoint between visits ...

Safety: AE Analysis

More women experienced a composite grade 2, 3, or 4 AE in the CTART arm compared with the DCART arm [hazard ratio (HR) = 1.36, 95% confidence interval (CI) (0.96 to 1.94), *P*-value = 0.08] (Table 1). Results were similar when restricting the analysis to grade 3 or higher AEs [HR = 1.78, 95% CI (1.05 to 3.02), *P*-value = 0.03]. Differences were mostly due to grade 3 weight loss (CTART: 13 grade 3 and 1 grade 4; DCART:

5 grade 3) (Table 1). Contributing to the imbalance in the composite AE endpoint, the estimated IR of grade 3 or higher hematologic AEs was higher for women on the CTART arm (IR = 15.4) compared with the DCART arm (IR = 12.3) (*P*-value = 0.28). No women with an AE for weight loss experienced an AE for nausea or vomiting. Women on the DCART arm gained more weight after randomization than those on the CTART arm {CTART:1.9 kg/yr [95% CI (1.4 to 2.3)]; DCART:2.8 kilograms/yr [95% CI (2.3 to 3.3)]; *P*-value = 0.006}.

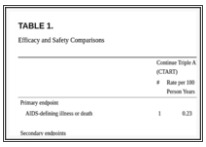
TABLE 1.
Efficacy and Safety Comparisons

	Continue Triple A (CTART)	
	#	Rate per 100 Person Years
Primary endpoint		
AIDS-defining illness or death	1	0.23
Secondary endpoints		

TABLE 1.

Efficacy and Safety Comparisons

Efficacy

The incidence of the primary efficacy endpoint of AIDS or death was similar across the DCART and CTART arms (Table 1). There were no AIDS-defining illnesses, and 2 deaths—one in each arm. HIV/AIDS-related events were also similar across arms [HR = 1.03, 95% CI (0.26 to 4.12), *P*-value = 0.97]. There were 5 tuberculosis events (3 in CTART and 2 in DCART) and 3 bacterial pneumonia events (1 in CTART and 2 in DCART). HIV/AIDS-related events or WHO stage II/III events were more frequent in the CTART arm [HR = 1.83, 95% CI (0.84 to 3.97), *P*-value = 0.12]. In post hoc analyses, WHO stage II and III events were more frequent in the CTART arm [HR = 2.18, 95% CI (0.94 to 5.06), *P*-value = 0.06]. Consistent with the AE analysis, differences in WHO stage II and III were primarily due to WHO stage II moderate unexplained weight loss at less than 10% of body weight (13 events in CTART and 1 event in DCART); there was one WHO stage III severe weight loss in CTART and none in DCART. There were 4 herpes zoster infections in DCART and zero herpes zoster infections in CTART.

DISCUSSION/CONCLUSION

This analysis compares maternal HIV disease progression and adverse safety events in a trial that randomized postpartum women living with HIV to CTART or DCART after the end of breastfeeding, at a time when the standard of care used CD4 thresholds and clinical staging to recommend ART initiation. We observed higher CD4 cell counts and better viral load control among women randomized to CTART, both of which are important surrogates for progression to AIDS. Nevertheless, progression to AIDS or death was similar by arm and rare: 0.23/100 person-years in the CTART and DCART arms. The low risk of progression to AIDS or death is consistent with both the previously published PROMISE 1077HS[4] and in PROMISE 1077BF/FF[5] trial (<0.49/100 person-years across all arms). These very low endpoint rates may be related to the mothers' young age, female sex, high CD4 counts, high CD4 threshold for starting ART, or the relative short duration of follow-up.

The 2 previous PROMISE manuscripts favored continuation of ART, whereas estimated rates of AEs and WHO stage II or III events were higher in this study comparing CTART to DCART. In the previous 1077BF/FF postdelivery analysis, the reduction of WHO stage II or III events were primarily due to weight loss and herpes zoster events. In the 1077HS study, the imbalance was primarily due to herpes zoster and bacterial infections but with similar WHO II weight loss events by arm. This analysis showed a similar trend for herpes zoster as the previous studies, but not for weight loss. We observed weight gain in both arms, but weight gain was higher in the DCART arm.

The low rate of AIDS-defining illness provides reassurances for the recommendation from the consensus meeting on analytical antiretroviral treatment interruptions[16] of studies in healthy female participants when the time off ART is shorter than in this study, ART is restarted soon after viral rebound, safety monitoring of disease progression is frequent, and risk of HIV transmission to uninfected persons can be minimized or eliminated.

The study strengths include the rigorous randomized clinical trial conducted in a diverse number of countries. The limitations include the fewer than planned randomizations, the lower than expected primary endpoint rate, and the use of an older ARV regimen.

In conclusion, we found that, over an average of 84 weeks of follow-up, relatively healthy young mothers living with HIV-1 from resource-limited breastfeeding settings had low rates of AIDS or death, regardless of randomization. Given the well-documented challenges with ART adherence postpartum mothers, these findings suggest that short-term pauses in ART that may occur with suboptimal drug adherence are unlikely to lead to rapid disease progression to AIDS or death. Our findings are in contrast to studies in other adult populations[17,18] and imply the need for further investigations in populations of young mothers.

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