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Hepatotoxicity and Liver-Related Mortality in Women of Childbearing Potential Living With Human Immunodeficiency Virus and High CD4 Cell Counts Initiating Efavirenz-Containing Regimens

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Background. Severe hepatotoxicity in people with human immunodeficiency virus (HIV) receiving efavirenz (EFV) has been reported. We assessed the incidence and risk factors of hepatotoxicity in women of childbearing age initiating EFV-containing regimens.

Methods. In the Promoting Maternal and Infant Survival Everywhere (PROMISE) trial, ART-naive pregnant women with HIV and CD4 count ≥ 350 cells/μL and alanine aminotransferase ≤ 2.5 the upper limit of normal were randomized during the antepartum and postpartum periods to antiretroviral therapy (ART) strategies to assess HIV vertical transmission, safety, and maternal disease progression. Hepatotoxicity was defined per the Division of AIDS Toxicity Tables. Cox proportional hazards models were constructed with covariates including participant characteristics, ART regimens, and timing of EFV initiation.

Results. Among 3576 women, 2435 (68%) initiated EFV at a median 121.1 weeks post delivery. After EFV initiation, 2.5% (61/2435) had severe (grade 3 or higher) hepatotoxicity with an incidence of 2.3 (95% confidence interval [CI], 2.0–2.6) per 100 person-years. Events occurred between 1 and 132 weeks postpartum. Of those with severe hepatotoxicity, 8.2% (5/61) were symptomatic, and 3.3% (2/61) of those with severe hepatotoxicity died from EFV-related hepatotoxicity, 1 of whom was symptomatic. The incidence of liver-related mortality was 0.07 (95% CI, .06–.08) per 100 person-years. In multivariable analysis, older age was associated with severe hepatotoxicity (adjusted hazard ratio per 5 years, 1.35 [95% CI, 1.06–1.70]).

Conclusions. Severe hepatotoxicity after EFV initiation occurred in 2.5% of women and liver-related mortality occurred in 3% of those with severe hepatotoxicity. The occurrence of fatal events underscores the need for safer treatments for women of childbearing age.

Keywords. HIV; real-world; hepatotoxicity; liver enzyme elevation.

Efavirenz (EFV)–containing antiretroviral therapy (EFV-ART) is currently a World Health Organization–recommended first-line regimen. EFV is a nonnucleoside reverse transcriptase inhibitor. Another agent in the same class, nevirapine (NVP), has been associated with fulminant hepatotoxicity, especially at high CD4 cell counts [1–3]. However, the extent of severe hepatotoxicity associated with EFV-ART in women of childbearing age with high CD4 cell counts in resource-limited settings has not been well characterized.

A large meta-analysis of 8 randomized trials and 26 prospective cohorts identified severe hepatotoxicity in 2.3% (95% confidence interval [CI], 1.42%–3.21%) of individuals receiving EFV-ART [4]. In African observational adult cohorts on EFV-ART, severe hepatotoxicity was found in 1%–5% of patients, with concomitant hepatitis B virus (HBV) infection and tuberculosis (TB) individually conferring higher overall risks. These observational cohorts did not include a high proportion of women or individuals with high CD4 cell counts [5–7].

Risk factors for NVP-associated hepatotoxicity include coinfection with viral hepatitis, female sex, and CD4 count > 250 cells/μL [3, 8, 9]. Hepatotoxicity occurs within the first 6–8 weeks of therapy initiation [10–12]. NVP has been associated with rare cases of fulminant liver-related mortality in 0.1% of patients [2]. EFV-ART has generally been regarded as safe, although EFV-ART has also occasionally been associated with fulminant hepatic failure [13–15]. More recently, investigators in South Africa have described 3 novel patterns

of drug-induced liver injury among patients with human immunodeficiency virus (HIV) initiating EFV-ART [16], including submassive hepatic necrosis. Additionally, the period after delivery may be a risk factor for drug-related hepatotoxicity, as has been seen with isoniazid during TB treatment [17, 18].

Given these reports of hepatotoxicity with EFV-ART and the widespread implementation of EFV-ART including in prevention of mother-to-child transmission (PMTCT) programs in many African settings, we sought to characterize the incidence and risk factors for severe hepatotoxicity in women of childbearing age with high CD4 cell counts initiating EFV-ART therapy in a large PMTCT trial, PROMISE (Promoting Maternal and Infant Survival Everywhere) 1077BF/1077FF.

METHODS

The PROMISE multicountry randomized trial [19] compared antepartum and postpartum HIV PMTCT strategies in pregnant women with high CD4 cell counts through sequential antepartum and postpartum randomizations. The full methodology has been presented previously [19, 20]. In brief, antepartum women were randomized to 1 of 3 regimens: (1) zidovudine (ZDV) plus intrapartum single-dose nevirapine (sd-NVP) followed by 6–14 days of tenofovir disproxil fumarate (TDF) and emtricitabine (FTC) "tail" postpartum (ZDV alone); (2) ZDV, lamivudine, and ritonavir-boosted lopinavir (LPV/r) (ZDV-based ART); or (3) TDF, FTC, and LPV/r (TDF-based ART). After delivery, women were randomized again to postpartum ART or no ART. In the last randomization (maternal health component), mothers on ART were randomized to either continue or stop ART. Mothers who did not want to be randomized or meet criteria for randomization were followed in observational follow-up. The first randomization occurred in 2011 with follow-up ending in September 2016. Supplementary Figure 1 outlines the PROMISE randomizations.

On 7 July 2015, PROMISE sites were notified of the results of the Strategic Timing of Antiretroviral Therapy (START) study, which demonstrated a lower risk of developing AIDS or other serious illnesses with ART initiation in early asymptomatic HIV infection [21], and sites were instructed to recommend that all women enrolled in PROMISE initiate ART regardless of prior randomization or CD4 cell count. Sites offered either local standard of care ART (generally EFV-ART) or, if access was unavailable, study-supplied ART. Consequently, EFV-ART became more common in the last 15 months of the study. This analysis focuses on women enrolled in PROMISE who received EFV-ART, the majority of who first received EFV-ART after delivery. Figure 1A demonstrates the uptake of EFV-ART and other ART regimens during the study period from the first randomization.

Toxicity management included drug discontinuation for any symptomatic alanine aminotransferase (ALT) elevation deemed possibly, probably, or definitely related to EFV-ART and study treatment hold for asymptomatic grade 3 or higher ALT elevation. Permanent discontinuation of individual ART regimens was performed with guidance from a clinical monitoring committee.

The PROMISE1077BF/1077FF study inclusion criteria included pretreatment CD4 count ≥ 350 cells/μL, or greater than or equal to the country-specific threshold of treatment initiation if the threshold was > 350 cells/μL; gestation ≥ 14 weeks; no previous use of triple ART except for PMTCT in previous pregnancies; a hemoglobin level of at least 7.5 g/dL; an absolute neutrophil count of ≥ 750 cells/μL; an ALT ≤ 2.5 times the upper limit of normal (ULN); a calculated creatinine clearance of at least 60 mL/minute; and no serious pregnancy complications.

After delivery, ALT was assessed at weeks 1, 6, 14, 26, and 50 and every 24 weeks until the end of follow-up. In the maternal health component, ALT was assessed at screening, entry, and at weeks 4, 12, 24, and every 24 weeks until the end of follow-up. Additional ALT measurements occurred at early ART discontinuation and when women met criteria for ART initiation; ALT was then repeated 4 weeks afterward. ALT was also assessed at an event-driven visit, defined as confirmation of immunologic or virologic failure, discontinuation of ART for toxicity reasons, or a clinically significant event suggestive of acute exacerbation of hepatitis B. Women who were hepatitis B surface antigen (HBsAg) positive at enrollment had an additional ALT assessment at postpartum week 38.

Severe hepatotoxicity was defined as grade 3 (5.1–10.0) or grade 4 (> 10.0) × ULN ALT elevation using the Division of AIDS toxicity tables (2004/2009) [22]; grade 2 ALT elevation was defined as 1.25–2.5 times the ULN. Symptomatic events were defined as scleral icterus or jaundice, abdominal, or lower extremity swelling, or otherwise unexplained petechiae or abdominal pain. We defined a medication to be hepatotoxic if it was 1 of 72 medications identified as a cause of drug-induced liver injury (DILI) in 5 or more adjudicated DILI cases in 3 DILI registries [23]. We also included albendazole and antimalarial medications. Cox proportional hazards models were run for each covariate and entered in a multivariable model. Covariates included age, body mass index, ALT, prior ALT elevation, HBsAg status, ART regimen prior to EFV-ART and duration, CD4 cell count, country, EFV-ART initiation date, time from delivery to EFV-ART initiation, receipt of EFV-ART prior to delivery, nucleos(t)ide reverse transcriptase inhibitor (NRTI) in EFV-ART, and antepartum and postpartum randomizations. Two-sided 95% confidence intervals (CIs) are presented and associations were assessed at a .05 significance level. Analyses were carried out in SAS software version 9.4.
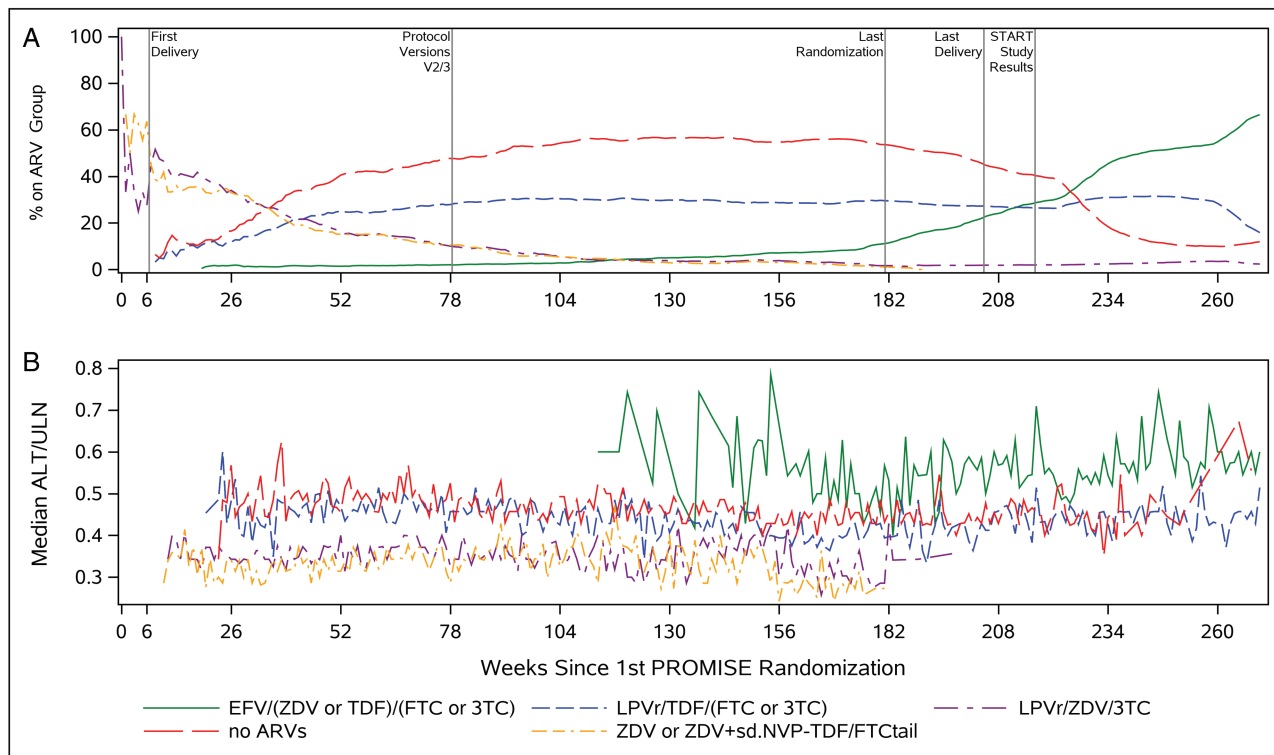
Figure 1. Antiretroviral therapy (ART) distribution and median alanine aminotransferase (ALT) over Promoting Maternal and Infant Survival Everywhere (PROMISE) study period. *A*, Proportion of women in major antiretroviral regimen groups as percentage in each ART group across time (week) since the first PROMISE randomization. *B*, Median ALT/upper limit of normal in each ART group across time (week) since the first PROMISE randomization (1-week time window for sample sizes > 10). Abbreviations: 3TC, lamivudine; ALT, alanine aminotransferase; ARV, antiretroviral; EFV, efavirenz; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; sd-NVP, single-dose nevirapine; START, Strategic Timing of Antiretroviral Therapy; TDF, tenofovir disoproxil fumarate; TDF-FTC tail, 1 week of tenofovir disoproxil fumarate–emtricitabine administered postpartum in the women who were randomized to ZDV alone in the antepartum period; ULN, upper limit of normal; ZDV, zidovudine.

RESULTS

Characteristics of Women Initiating EFV-ART

Among 3576 participants, 2435 (65%) initiated EFV and 2381 (98%) did so after delivery (Figure 2). The majority started EFV-ART as countries' CD4 ART initiation threshold increased over time and after the START study results. Three (0.12%) initiated EFV-ART for prior elevated ALT, 3 (0.12%) for TB (0.12%), 2 for toxicity (0.08%), and 6 for virologic or immunologic failure (0.25%).

Table 1 describes the participant characteristics at EFV-ART initiation. The median age was 29.3 years and the median CD4 count was 623 cells/μL. Most (90%) were from Malawi, South Africa, and Zimbabwe. The median time of EFV-ART initiation after delivery was 121.1 weeks. Ninety-one women (4%) were HBsAg positive. Twenty-five (1%) and 43 women (2%) had TB or were on isoniazid (INH), respectively, prior to EFV-ART.

Incidence, Clinical Characteristics, and Course of Hepatotoxicity

Figure 1 demonstrates the proportion of women on ART regimens over time and the median ALT with each regimen over time. Median ALT levels were higher with EFV-ART over time. After EFV-ART, 7.4% (181/2435), 2.5% (61/2435), and 1.0%

(26/2435) had grade 2 or higher, grade 3 or higher, and grade 4 elevated ALT, respectively, with an incidence of severe (grade 3 or higher) hepatotoxicity of 2.3 (95% CI, 2.0–2.6) per 100 person-years (PY) (Figure 2). Among women who had grade 1 or higher ALT elevation after EFV initiation, 5% (25/533) had hepatitis-specific symptoms. Of the 181 women who had grade 2 or higher ALT, 12 of 181 (6.6%) were symptomatic; 2 had jaundice, 4 had a rash, and 6 had abdominal pain within 1 week of the grade 2 or higher ALT. In 141 participants (78%) with grade 2 or lower ALT elevation, ALT resolved to grade 1 or lower, and 119 (66%) resolved to a normal ALT value.

Focusing on those with severe hepatotoxicity, the majority (42 of 61 [69%]) were not on ART prior to initiating EFV-ART. The median CD4 count was 635 cells/μL and the median age was 29.8 years. Only 1 participant was HBsAg positive and 7% (4/61) had a grade 3/4 ALT elevation prior to initiating EFV-ART. Of the 61 with severe (ie, grade 3/4) hepatotoxicity, 5 of 61 (8.2%) were symptomatic, 2 had jaundice, 2 had a rash, and 1 had abdominal pain. Severe hepatotoxicity occurred a median of 20.6 weeks after EFV initiation. In 47 participants (77%), severe hepatotoxicity resolved to grade 2 or lower ALT elevation. The median time to grade 2 ALT decline was 6.9 weeks and the
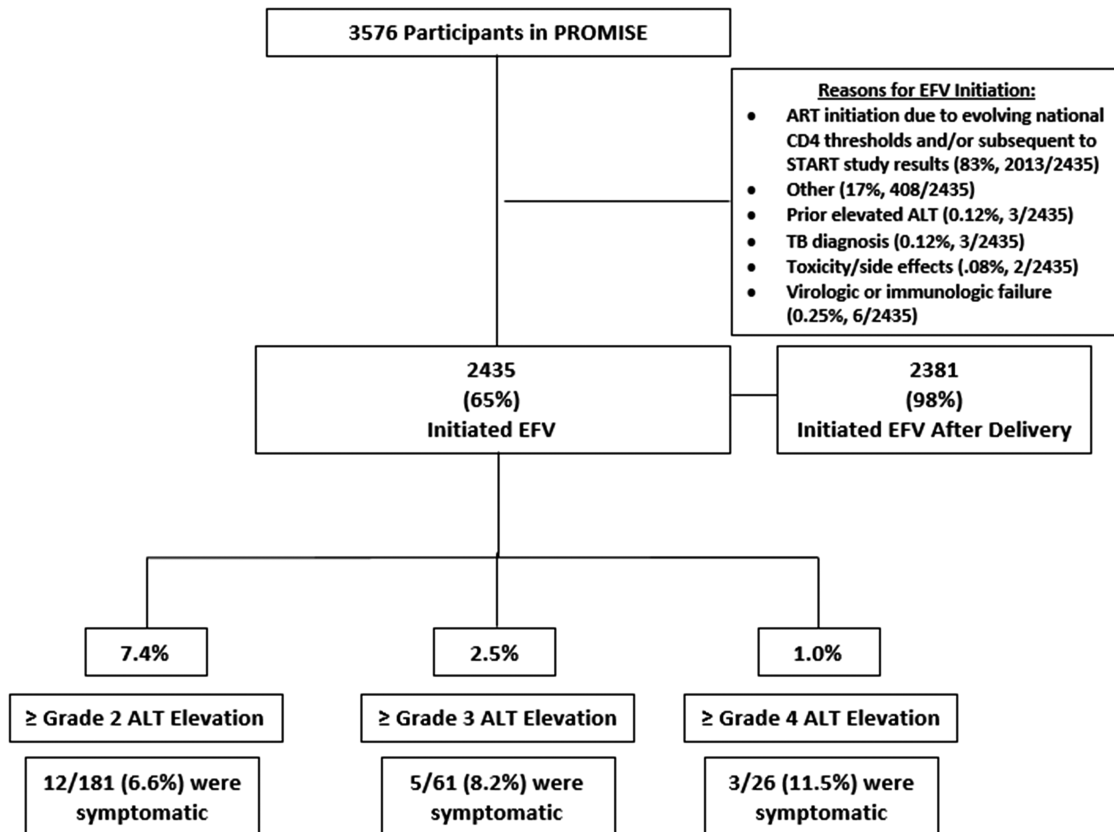
Figure 2. Cohort diagram of women who initiated efavirenz-containing antiretroviral therapy and incidence of hepatotoxicity. Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; EFV, efavirenz; PROMISE, Promoting Maternal and Infant Survival Everywhere; START, Strategic Timing of Antiretroviral Therapy; TB, tuberculosis.

time to grade 2 ALT did not differ by whether EFV was discontinued before a follow-up measurement to the initial ALT elevation (P = .74). Among these 61 women with severe hepatotoxicity, 7 (11%) discontinued EFV a median of 0.14 weeks before severe hepatotoxicity and 11 (18%) discontinued EFV a median of 2.43 weeks after their ALT elevation.

We also evaluated other factors associated with hepatotoxicity in those with severe hepatotoxicity. Among the 61 women on EFV-ART with severe hepatotoxicity, only 2 (3.2%) were on monotherapy or combination INH or had a TB diagnosis prior to their initial elevation. The incidence per 100 PY of severe hepatotoxicity was 0.8 (95% CI, .4–1.7 [2 events]) among 140 who initiated INH for TB disease treatment or had TB within 3 months prior to or after EFV initiation, and 2.4 (95% CI, 2.1–2.7 [59 events]) among 2995 who did not report taking INH or have a TB diagnosis. None had diagnoses of viral hepatitis. Reported alcohol use was uncommon; 11% (7/61) reported drinking > 1 drink per month of alcohol at least once during follow-up. None reported the use of traditional medications. Two women were diagnosed after EFV initiation with pelvic inflammatory disease or a reproductive disorder, which may sometimes cause liver dysfunction. Among all 2435 women, 43% used potentially hepatotoxic medications at the time of EFV-ART initiation. Focusing on those with severe hepatotoxicity,

43% used potentially hepatotoxic drugs within 4 weeks of ALT elevation. The most common medications were acetaminophen-, co-trimoxazole-, and diclofenac/ibuprofen– containing regimens in 16%, 15%, and 13% of women, respectively. Other medications included other antibiotics (10%), enalapril (2%), phenytoin (2%), and ranitidine (2%).

Mortality While on EFV-ART

Thirteen women died after EFV initiation through 30 September 2016 (end of PROMISE). Two had severe hepatotoxicity prior to death. Death was deemed as possibly or probably related to EFV in these 2 women and occurred 1 week after hospitalization for both. They died 105 and 77 weeks after delivery, 16 and 25 weeks after EFV initiation, and 3 and 3.14 weeks after ALT elevation, respectively. The incidence of maternal mortality assessed as related to EFV was 0.07 (95% CI, .06–.08) per 100 PY over 2878 total PY. As the clinical monitoring committee was notified of ongoing toxicities off-study, we learned that 4 additional women on EFV died with hepatic complications following the end of PROMISE, all of which were considered potentially related to efavirenz. We did not include these as outcomes in the analyses as they occurred after the end of PROMISE, but we include them in the descriptive table (Table 2). Among the 6 deaths in combined follow-up,

Table 1. Characteristics of Study Population at Initiation of Efavirenz-Containing Antiretroviral Therapy

Characteristic	Total (N = 2435)
Prior ART regimen	
PI + 2 NRTIs	750 (31)
No ART[a]	1546 (63)
ZDV or ZDV + sd-NVP–TDF/FTC tail	50 (2)
Other	89 (4)
CD4 count, cells/μL	
Min–Max	75–1938
Median (Q1–Q3)	623 (463–839)
Country	
India	34 (1)
Malawi	841 (35)
South Africa	785 (32)
Tanzania	29 (1)
Uganda	136 (6)
Zambia	60 (2)
Zimbabwe	550 (23)
EFV-ART initiation year	
2011–2014	661 (27)
6 July 2015 (START date)[b]	423 (17)
Later than 6 July 2015	1351 (55)
EFV-ART initiation, wk after delivery	
Min–Max	–21.1 to 255.7
Median (Q1–Q3)	121.1 (73.7–160.9)
Before delivery	52 (2)
0–29 d	90 (4)
>30 d to 6 wk	15 (1)
> 6 wk to 26 wk	80 (3)
>26 wk	2198 (90)
Receipt of EFV-ART before delivery	
No	2381 (98)
Yes	54 (2)
Age, y	
Min–Max	18.5–50.5
Median (Q1–Q3)	29.3 (25.5–33.2)
HBsAg positive	
No	2344 (96)
Yes	91 (4)
Grade 3/4 ALT elevation at EFV-ART initiation	
Any grade 3/4 elevation	72 (3)
No grade 3/4 elevation	363 (97)
Grade 3/4 ALT elevation before or during delivery	
Any grade 3/4 elevation	25 (1)
No grade 3/4 elevation	2329 (96)
Randomization in BP late presenter[c]	81 (3)
NRTI in EFV-ART regimen	
3TC/TDF	1428 (59)
FTC/TDF	937 (38)
Other	70 (3)
Antepartum randomization	
ZDV + sd-NVP–TDF/FTC tail	1029 (42)
LPV/r/ZDV/3TC	1019 (42)
LPV/r/TDF/3TC	304 (12)
Late presenter[c]	83 (3)

Table 1. Continued

Postpartum first randomization	
Triple ART	906 (37)
No ART	990 (41)
Observation[d]	539 (22)
New TB prior to EFV-ART initiation	
Yes	25 (1)
No	2410 (99)
INH in 3 mo before EFV-ART initation	
Yes	43 (2)
No	2392 (98)

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: 3TC, lamivudine; ALT, alanine aminotransferase; ART, antiretroviral therapy; BMI, body mass index; BP, breastfeeding postpartum component; EFV, efavirenz; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; INH, isoniazid; LPV/r, ritonavir-boosted lopinavir; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor; Q1–Q3, first–third quartile; sd-NVP, single-dose nevirapine; START, Strategic Timing of Antiretroviral Therapy; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; TDF-FTC tail, 1 week of tenofovir disoproxil fumarate–emtricitabine administered postpartum in the women who were randomized to no antiretrovirals in the antepartum period; ZDV, zidovudine.

[a]Sixty-three percent were not on ART prior to starting EFV-ART as subsets of participants were randomized to discontinue ART (unless they met country treatment initiation criteria) in the postpartum and maternal health randomizations or may not have been eligible to be randomized to the next step.

[b]START date refers to date of the dissemination of START study findings.

[c]Late-presenter women did not access antiretroviral strategies for prevention of perinatal transmission during pregnancy.

[d]Women in observation were those who did not randomize to ART/no ART postpartum or were ineligible to be randomized.

the last previous normal ALT during PROMISE follow-up was measured a median of 4 weeks after EFV initiation and a median of 37.9 weeks prior to death. One woman was receiving INH and 1 had malaria, but these were still thought to be related to EFV. None had heavy alcohol use, use of traditional medications, diagnoses of viral hepatitis, sexually transmitted diseases, or opportunistic infections.

Risk Factors of EFV-ART Hepatotoxicity

Cox proportional hazards model analysis of EFV hepatotoxicity risk factors are presented in Table 3. Older age was significantly associated with an increased risk of severe hepatotoxicity in both unadjusted and adjusted analysis (adjusted hazard ratio per 5 years older, 1.35 [95% CI, 1.06–1.70]). Neither CD4 cell count, HBV coinfection, NRTI selection in EFV regimen, nor prior ARV regimen were significantly associated with severe hepatotoxicity ($P \geq .08$).

DISCUSSION

Severe hepatotoxicity occurred in 2.5% of women initiating EFV-ART, of whom only 4 of 61 were symptomatic. Older age was associated with increased risk of severe hepatotoxicity. Notably, there were 2 deaths related to EFV-ART hepatotoxicity and 4 additional hepatic-related deaths among participants on EFV-ART that occurred in the year after PROMISE ended. The 2 hepatotoxicity events leading to death during PROMISE follow-up occurred late, up to 6 months after

Table 2. Maternal Hepatitis Deaths Among Women Enrolled in the Promoting Maternal and Infant Survival Everywhere (PROMISE) 1077BF Trial Who Initiated Efavirenz

Characteristic	Participant Number					
	1	2	3	4	5	6
Death observed during PROMISE follow-up	Yes	Yes	No	No	No	No
Weeks between EFV initiation and death	25 wk	16 wk	59 wk	22 wk	52 wk	102 wk
Last CD4 count, cells/μL	497	575	604	596	387	483
Site assessment of relation of death to EFV[a]	Possibly related	Probably related	Potentially related	Potentially related	Potentially related	Potentially related
Last CD4 count, cells/μL	497	575	604	596	387	483
Last measured normal ALT on PROMISE						
Weeks after EFV initiation	3.86	4.14	18.57	−12.57[b]	9.0	−12.29[b]
Weeks before death	21.14	12.14	40.71	35.14	43.0	114.57
Laboratory results						
Hepatitis E IgM	NR	…	…	…	…	…
Hepatitis A IgM	NR	…	…	…	…	…
HBV DNA	ND	…	…	…	…	…
HCV RNA	SI	…	…	…	…	…
Additional relevant diagnoses						
TB or INH receipt	No	No	No	No	No	Yes
HBsAg positive at screening	No	No	No	No	No	No
Malaria	No	No	No	No	Yes	No
DVT or PE	No	No	No	No	No	No
Hepatobiliary diagnoses[c]	No[d]	No[e]	No	No	No	No
Genitourinary/sexually transmitted diseases[f]	No	No	No	No	No	No

This table describes the maternal deaths attributable to EFV that occurred during PROMISE follow-up and afterward. INH and malaria may have been contributing causes in each of 2 individuals.

Abbreviations: ALT, alanine aminotransferase; DVT, deep vein thrombosis; EFV, efavirenz; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgM, immunoglobulin M; INH, isoniazid; ND, not detectable; NR, nonreactive: PE, pulmonary embolism; SI, sample insufficient; TB, tuberculosis.

[a]Deaths of participants 1 and 2 were designated as possibly and probably related to EFV by site investigators. As deaths in participants 3–6 occurred off-study, investigators were not required to designate relatedness for reporting purposes. However, site investigators, the clinical monitoring committee, and/or study chairs felt that these deaths were potentially related to EFV in email communications.

[b]Negative integer represents time before EFV-containing antiretroviral therapy initiation.

[c]Hepatobiliary diagnoses were obtained from case report forms that included hepatitis A and B.

[d]For participant 1, "hepatitis, etiology unknown (death)" and "hepatitis, drug induced" were listed, respectively, consistent with no alternate etiology for hepatitis.

[e]For participant 2, "hepatitis, etiology unknown (death)" and "hepatitis, drug induced" were listed, respectively, consistent with no alternate etiology for hepatitis.

[f]Genitourinary/sexually transmitted diseases were obtained from case report forms with relevant diagnoses, including syphilis, chancroid, pelvic inflammatory disease, trichomoniasis, urethritis, and/or venereal disease.

EFV-ART initiation, in contrast to reports of fulminant hepatotoxicity with nevirapine, which occur within the first 6–8 weeks [10–12].

Risk factors for liver-related mortality with EFV-ART are not well understood. Shubber et al found that <1% of deaths were related to toxicity among patients on EFV-ART, but they did not specify whether the toxicity was hepatotoxicity [4]. Our study supports the findings of other smaller case series of EFV-ART hepatotoxicity and fulminant liver failure. In South Africa, Sonderup et al reported novel patterns of EFV-ART DILI including submassive hepatic necrosis associated with an "immune-allergic pattern" of inflammatory cell infiltrates of eosinophils, plasma cells, and lymphocytes on liver biopsy, a mixed cholestatic hepatitis associated with grade 2–3 hepatotoxicity, and a nonspecific mild hepatitis [16]. Risk factors for each pattern differed with female sex, higher CD4 cell count, and younger age predictive for submassive hepatic necrosis, whereas older age and lower CD4 count were associated with the mixed cholestatic pattern. Participants in the PROMISE study may have had various patterns of hepatic injury, accounting for our differing results with regards to age.

Although our general hepatotoxicity rates were similar to other African cohorts [5–7], our findings of liver-related mortality from hepatotoxicity with relatively late onset after EFV-ART initiation has not been consistently reported in other studies [5–7]. The findings of liver-related mortality among women living with HIV raise concern, particularly since there are no recommendations to routinely monitor liver function tests in HIV treatment programs. It is possible that the deaths reported would not have occurred if hepatotoxicity had been recognized and EFV-ART discontinued earlier.

Also notable was the mild but persistent greater median ALT over time with EFV-ART (Figure 1). Our study population was predominantly black African. There are supporting data that persons of black African ethnicity are at increased risk of severe hepatotoxicity, hospitalizations, and liver transplant or liver-related death after DILI [24]. Mechanisms for an increased risk of hepatotoxicity to EFV in African cohorts are unknown but

Table 3. Predictors of Grade 3/4 Alanine Aminotransferase (ALT) Elevation After Efavirenz Antiretroviral Therapy (EFV-ART) Initiation

Covariate at EFV-ART Initiation and Category	Unadjusted		Adjusted	
	Hazard Ratio (95% CI)	P Value (Overall)	Hazard Ratio (95% CI)	P Value (Overall)
Prior ART (ref: PI + 2 NRTIs)				
No ART	0.75 (.42–1.41)	.35 (.80)	0.89 (.44–1.87)	.76 (.82)
ZDV or ZDV + sd-NVP–TDF/FTC tail	0.94 (.15–3.35)	.93	1.88 (.24–9.36)	.48
Other	0.66 (.10–2.35)	.58	0.69 (.10–2.84)	.65
CD4 count (per 100 cells/µL)	1.08 (.99–1.17)	.08	1.07 (.96–1.17)	.19
EFV-ART initiation study y (per 1 y)	1.14 (.86–1.56)	.39	1.17 (.81–1.74)	.41
EFV-ART initiation study y (ref: 2011–2014)[a]				
6 July 2015 (START date[b])	0.52 (.21–1.18)	.14 (.09)	…	
Later than 6 July 2015	1.29 (.73–2.34)	.38	…	
Age (per 5 y older)	1.25 (1.00–1.55)	.05	1.35 (1.06–1.70)	.01
BMI (per 1 kg/m² higher)	1.00 (.95–1.04)	.88	0.99 (.94–1.04)	.78
HBsAg positive (yes)	0.44 (.02–1.99)	.40	0.43 (.01–1.98)	.41
ALT/ALT × ULN (per 1 higher)	1.07 (.81–1.21)	.43	1.09 (.82–1.24)	.36
ALT grade 3/4[a] elevation prior to EFV-ART initiation (ref: no grade 3/4 elevation)	1.86 (.56–4.53)	.23	…	

Covariates not presented in the table that were not statistically significant ($P \geq .15$) in univariate or multivariable analysis: country enrolled, EFV initiation weeks from delivery, receipt of EFV prior to delivery, categorical BMI, ALT elevation prior to delivery, CD4 cell count by quartile, NRTI in regimen, antepartum and postpartum (ART vs no ART) assignments. The values in the parenthesis of the hazard ratio are the 95% confidence intervals. For grade 3/4 ALT elevation before delivery, there were no postpartum events among those with a prior event, so this covariate was not included in the adjusted model. Continuous covariates were adjusted as applicable.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; HBsAg, hepatitis B surface antigen; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor; sd-NVP, single-dose nevirapine; START, Strategic Timing of Antiretroviral Therapy; TDF-FTC tail, 1 week of tenofovir disoproxil fumarate–emtricitabine administered postpartum in the women who were randomized to no antiretrovirals in the antepartum period; ULN, upper limit of normal; ZDV, zidovudine.

[a]Results were similar in an adjusted model with categorical versions for covariates.

[b]START date refers to date of the dissemination of START study findings.

may be related to the genetics of EFV metabolism. EFV is metabolized by the cytochrome P450 (CYP) 2B6 and CYP3A4/5 liver enzymes [25]. A CYP2B6 variant allele that was found in 43%–49% of South African and Zimbabwean populations was associated with higher plasma EFV concentrations [26, 27] and, in 1 study in Tanzania, was associated with an increased risk of DILI [7]. One hypothesis is that elevated serum EFV may predispose to higher rates of hepatotoxicity or hypersensitivity reactions.

We could not compare rates of hepatotoxicity to women with lower CD4 counts. We cannot exclude the possibility that such an association would have been present if the cohort had included more women with lower CD4 counts.

Hepatitis B infection was not a risk factor for severe hepatotoxicity. The prevalence of hepatitis B e antigenemia and elevated HBV viral loads, both risk factors for hepatotoxicity, are low in African populations [5]. Additionally, participants with grade 2 or higher ALT were excluded, potentially enriching this cohort for less hepatic inflammation.

Limitations of our study include the lack of corroborative liver biopsy and pharmacogenomics or pharmacokinetic information. However, this information is rarely available in resource-limited settings and only endorses the need for more regular ALT monitoring as a proxy for clinically important hepatic events. More than 40% of the overall population received potentially hepatotoxic medications. We did not have dosing information for these medications but given that equivalent proportions of the overall cohort and those with severe

hepatotoxicity received potentially hepatotoxic medications and that the most common medications included acetaminophen, nonsteroidal anti-inflammatory medications, and co-trimoxazole–containing regimens, we did not believe that this was a significant contributing factor, although this cannot be excluded. Another limitation was that participants were excluded at study entry if their ALT was > 2.5 times the ULN (grade 2 or higher). Given that prior ALT elevation is a previously reported risk factor for subsequent ALT elevation with EFV-ART [28, 29], rates may have been higher in a population that included this group. To address this, we assessed ALT elevations after entry and screening failures as proxies for potential exclusionary ALT. Only 1.7% had grade 2 or higher ALT after entry and within 3 months before EFV-ART. Among 2723 recorded screening failures, only 5 indicated ALT as reason for failure. These data suggest that only a small proportion of otherwise eligible participants would have been excluded due to an elevated ALT. The PROMISE study was also not specifically designed or powered for the objectives of this secondary analysis and the number of severe hepatotoxicity events was relatively small. Finally, follow-up ended 30 September 2016 with the possibility of later events occurring after the end of data collection.

In summary, we found that in women living with HIV of childbearing age who were initiating EFV at a median of 121 weeks postdelivery, severe (grade 3 or 4) hepatotoxicity after EFV-containing ART initiation occurred at rates seen in prior cohorts. However, liver-related mortality from EFV drug-induced liver injury was unexpected and concerning, as severe

hepatotoxicity and mortality occurred late after EFV initiation, generally with no early symptoms. As ART continues to roll out to millions of individuals in sub-Saharan Africa living with HIV, clinicians should be aware of the rare but notable risk of liver-related mortality with EFV-ART and the risk-benefit ratio should be closely weighed. It remains unclear how best to identify women who are at an increased risk of hepatotoxicity. We advise that ALT monitoring should be considered with EFV-ART in older women of childbearing age. Further investigation into the risk factors for DILI in persons living with HIV and receiving EFV-ART should be conducted. With the rollout of lifelong ART for women living with HIV of childbearing age, these results underscore the need for safer treatment options.

Supplementary Data

Supplementary materials are available at *Clinical 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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