Hepatotoxicity in HIV+ Postpartum Women Initiating Efavirenz-Containing Regimens

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Background

- Non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens have been a mainstay of WHO recommended first-line antiretroviral regimens (ARV)s [1]
- However increased toxicity (hypersensitivity and hepatotoxicity) with high CD4, especially in first 3 months of initiation[2]
- Efavirenz (EFV) has been considered safer than nevirapine but with limited clinical trial safety data among pregnant and postpartum women[3]
- EFV-containing regimens now are among the WHO recommended first-line ARV regimens (since 2013) including for pregnant and postpartum women[1]
- Recent reports of efavirenz-induced hepatotoxicity in South Africa[4]
- Three novel drug induced liver injury (DILI) patterns reported[4]
  - Non-specific hepatitis (mild ALT increase)
  - Mixed cholestatic-hepatitis (mild-moderate liver enzyme elevation (LEE) + jaundice)
  - Submassive necrosis (immunoallergic severe LEE, jaundice, coagulopathy)
    - High CD4, female sex, younger age

Objectives

- To characterize the incidence and predictors of hepatotoxicity in postpartum women initiating EFV-containing ARV in the Promoting Maternal and Infant Survival Everywhere (PROMISE) study

Methods

- In PROMISE 1077BF/FF, HIV+ antiretroviral treatment (ART) naïve pregnant women with **CD4>350 and ALT< 2.5 ULN** were assigned to antepartum (AP) and postpartum (PP) ART strategies to assess HIV vertical transmission, safety, and maternal disease progression.
- Sites participated between 4/2011-9/2016. In July 2015, based on the START study, participants were recommended to initiate ART, which included EFV at most sites.
- ALT was assessed at postpartum weeks 1, 6, 14, 26, 50 and q24 weeks until the end of follow-up
  - In the Maternal Health (MH) Component, ALT was assessed at screening, entry, weeks 4, 12, 24, and q24 weeks
  - Additional ALT measurements at early discontinuation, step change and 4 weeks afterwards, and event-driven visits
  - Hepatotoxicity was defined as grade 2 (2.6 - 5.0), grade 3 (5.1 - 10.0), or grade 4 (> 10.0) x ULN ALT elevation.
  - Grade 3/4 ALT elevation primary outcome in MV analysis
- Descriptive statistics
- Proportional hazards models (ratio (HR), 95% confidence interval (CI)) were run for each covariate and entered in a multivariable model. Covariates at EFV initiation included age, BMI, ALT, prior ALT elevation, HBsAg, ART regimen prior to EFV, CD4, country, EFV initiation study year , time from delivery to EFV initiation, receipt of EFV prior to delivery, NRTI in regimen, and AP and first PP randomized assignments.

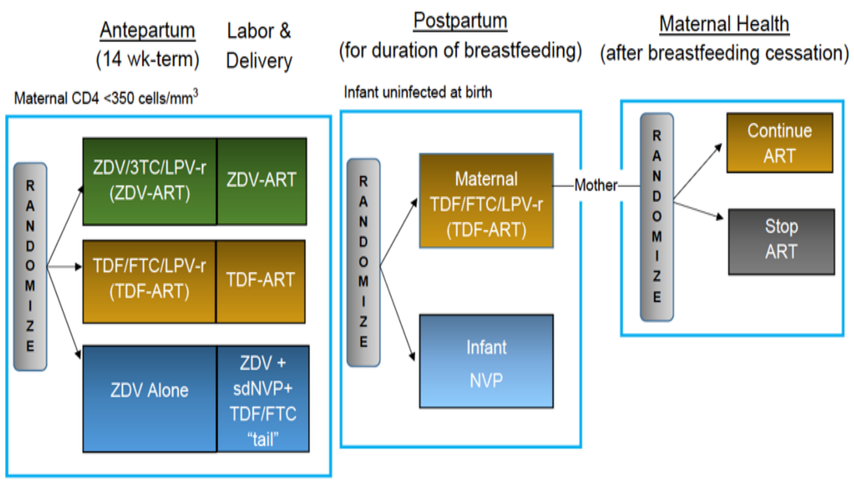

Figure 1. Study Method Arms. AP randomization: HIV+ women enrolled at 14 weeks of gestation or later to one of three regimens: zidovudine plus intrapartum single-dose nevirapine with 6 to 14 days of tenofovir and emtricitabine PP (zidovudine alone); zidovudine, lamivudine, and lopinavir–ritonavir (zidovudine- based ART); or tenofovir, emtricitabine, and lopinavir–ritonavir (tenofovir-based ART). All regimens continued through 6 to 14 days PP. All infants received nevirapine through 6 weeks PP per WHO. PP randomization differed by breast-feeding status; eligible breastfeeding women randomized to daily maternal ART or daily infant nevirapine prophylaxis. At cessation of breastfeeding, eligible mothers on ART in the PP component enrolled into "maternal health" component and randomized to either continue ART or stop ART. Eligible formula-feeding women: randomized into maternal health to stop or continue ART at delivery. Breast- feeding and formula-feeding settings began enrollment in April and July 2011, respectively.

Methods

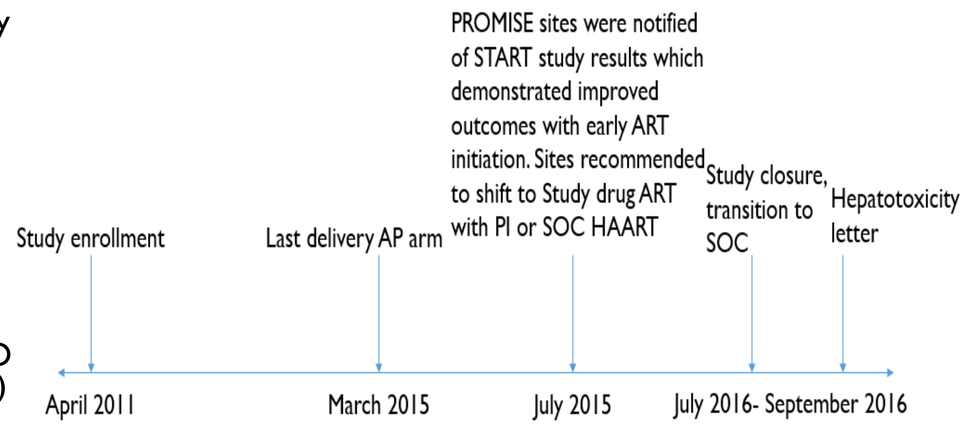

Figure 2. Key Events in PROMISE Timeline. Study enrollment began in April 2011, and the last delivery to a mother in the AP arm was in March 2015. In July 2015, the PROMISE sites were alerted to the results of the START[5] study, which had established enhanced outcomes with early ART initiation- it was suggested that the sites shift to Study drug ART with protease inhibitor (PI) or standard of care (SOC) which was often EFV-based ART. The study closed in July 2016 and transitioned to SOC through September 2016. From July-September 2016, a hepatotoxicity letter was sent to PROMISE investigators and HIV treatment providers outlining the risk of hepatotoxicity to women transitioning to EFV-based regimens, urging them to actively counsel women regarding risks and symptoms of hepatotoxicity.

Results

Table 1. Study Population Characteristics (n=2430) and ART Characteristics at Time of EFV Initiation.

Characteristic	n (%)
Median age (IQR), years	29 (25-33)
Median BMI	25 (22-29)
Median CD4 cells/mm^3	625 (466-839)
HBsAg+ at PROMISE entry	82 (4%)
Grade 3 or 4 ALT elevation prior to delivery	24 (1%)
EFV initiation Weeks from delivery, median (IQR)	114.1 (65.1-159.4)
EFV Initiation Study Year 2011- 2014 2015 (START): Jul 6 > July 6, 2015	 681 (29%) 401 (17%) 1236 (53%)
Prior Regimen Group	
PI+ 2NRTI	723 (31%)
No ARVs	1,434 (62%)
ZDV or ZDV+ sd NVP-TDF tail	58 (3%)
Other	103 (4%)

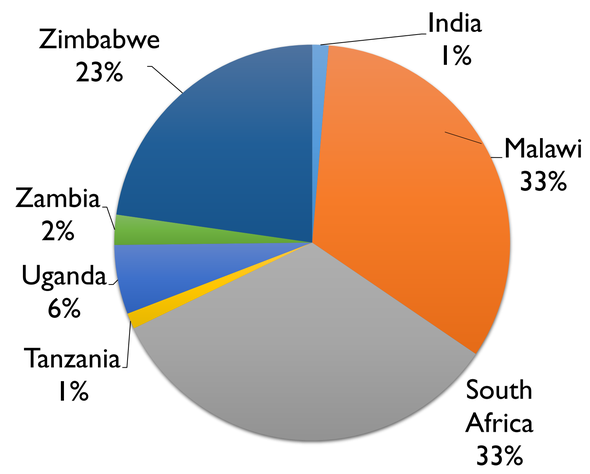

Figure 3. Population Breakdown by Country.

The majority of participants were either from South Africa or Malawi (33% each), with 23% from Zimbabwe, 6% from Uganda, 2% from Zambia, 1% from India, and 1% from Tanzania.

Of 2340 women who initiated on EFV:

- **180 (7.4%) Grade 2 or higher hepatotoxicity**
- **61 (2.5%) Grade 3 or higher hepatotoxicity**
  - 36 (1.5%) Grade 3
    - 5 symptomatic, 1 RUQ pain, anorexia
  - 25 (1.0%) Grade 4
    - 4 symptomatic, 3 of which were jaundiced
- 2 maternal deaths associated with grade 4 hepatotoxicity occurred at 16 and 25 weeks after EFV-ART and during the PROMISE study period
- 2 additional maternal deaths occurred after the PROMISE study period. On-study and post-study deaths are described in Table 2 but only on-study deaths are included as outcomes in MV analysis

Results

Table 2. Maternal Hepatitis Deaths in PROMISE 1077BF among those who initiated EFV

Participant	1 (South Africa)	2 (Malawi)	3 (Malawi)	4 (Zimbabwe)
Age	29yo	38yo	42yo	28yo
# weeks postpartum	77	105	125	146
Cause of Death	Hepatitis	Hepatitis	Hepatitis	Hepatitis
ARV	EFV	EFV	EFV	EFV
Death week since EFV initiation	25 weeks	16 weeks	22 weeks	48 weeks
Death from study drug	Possibly related	Probably related	Possibly related	Possibly related

Table 3. Factors Associated with Time to EFV Hepatotoxicity.

Covariate		Adjusted HR (95% CI)	p value
Age (per 5 years older)		**1.35 (1.06-1.71)**	**0.01**
BMI		0.99 (0.94-1.04)	0.64
CD4 cell count (per100 cells/mm^3 higher)		1.07 (0.97-1.18)	0.15
HBsAg+		0.48 (0.03-2.22)	0.47
EFV initiation weeks from delivery		1.00 (0.99, 1.01)	0.94
EFV study year (per 1 year)		1.31 (0.89-1.97)	0.18
Prior ARV			0.87*
	No ARVs	0.88 (0.44-1.84)	(0.73)
	AZT or AZT+SD NVP/TDF tail	1.77 (0.23-8.31)	(0.52)
	Other	1.01 (0.22-3.43)	(0.99)
	PI+2NRTI	ref	

*Overall p value is represented here, pair-wise p values for prior ARV are also presented in parentheses.

- In MV analysis, older age was significantly associated with increased risk of grade 3/4 LEE PP after EFV initiation (HR per 5 years 1.35 CI (1.06-1.71). There was a trend towards CD4 association with grade 3/4 LEE: CD4 per 50 cells higher 1.04 (0.986,1.086). Other covariates listed in methods and including HBsAg status were NS p> 0.14.

Conclusions

- EFV Grade 3 or higher hepatotoxicity rate in PROMISE similar to meta-analysis data of 2.3% and mortality of 0.2%.[3]
  - Most women asymptomatic, however
    - Serious toxicity resulting in deaths among women on EFV did occur (2 by end of PROMISE and 2 in follow up within 3 months of PROMISE ending)
- Older age was the only risk factor noted among this group with a median CD4 of 655
- Monitoring for ALT abnormalities may prevent unnecessary deaths but research needed to identify frequency and who is at highest risk for hepatotoxicity
- The PROMOTE study will monitor for hepatotoxicity in longer term follow up of PROMISE participants including during repeat pregnancies
- Limitation: Most women in PROMISE did not initiate EFV in pregnancy or early postpartum which is a higher risk period for hepatotoxicity

Acknowledgements

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References

1) Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. 2016. 2nd ed.WHO Guidelines
2) Sanne JID 2005
3) Shubber AIDS 2013
4) Sonderup AIDS 2016
5) The INSIGHT START Study Group. NEJM 2015.