Hepatotoxicity in HIV+ Postpartum Women Initiating Efavirenz-Containing Regimens in PROMISE P1077

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Background

- Non-nucleoside reverse transcriptase inhibitor (NNRTI) containing regimens have been a mainstay of WHO-recommended first-line ARVs
  - Nevirapine 2002 to 2012
  - However increased toxicity (hypersensitivity and hepatotoxicity) with high CD4, especially in first 3 months of initiation
- Efavirenz (EFV) has been considered safer than nevirapine but with limited clinical trial safety data among pregnant and post partum women
- Recent reports of efavirenz-induced hepatotoxicity in South Africa and elsewhere (many initiated EFV in pregnancy)
  - Three novel drug induced liver injury (DILI) patterns reported
    - Non-specific hepatitis (mild ALT increase)
    - Mixed cholestatic-hepatitis (mild-moderate liver enzyme elevation (LEE) + jaundice)
    - Submassive necrosis (immunoallergic severe liver enzyme elevation, jaundice, coagulopathy)
      - High CD4, female sex, younger age
- Mixed and limited data about increased risk of DILI in pregnancy and postpartum

Sonderup AIDS 2016, Ouyang AIDS 2009,Huntington JIAS 2014

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PROMISE Hepatotoxicity Analyses Objectives

- To characterize the incidence, severity and predictors of hepatotoxicity in postpartum women initiating EFV-containing ART in the Promoting Maternal and Infant Survival Everywhere (PROMISE) 1077BF/FF trial as PROMISE maternal participants shifted to Standard of Care (SOC) regimens with the ending of PROMISE

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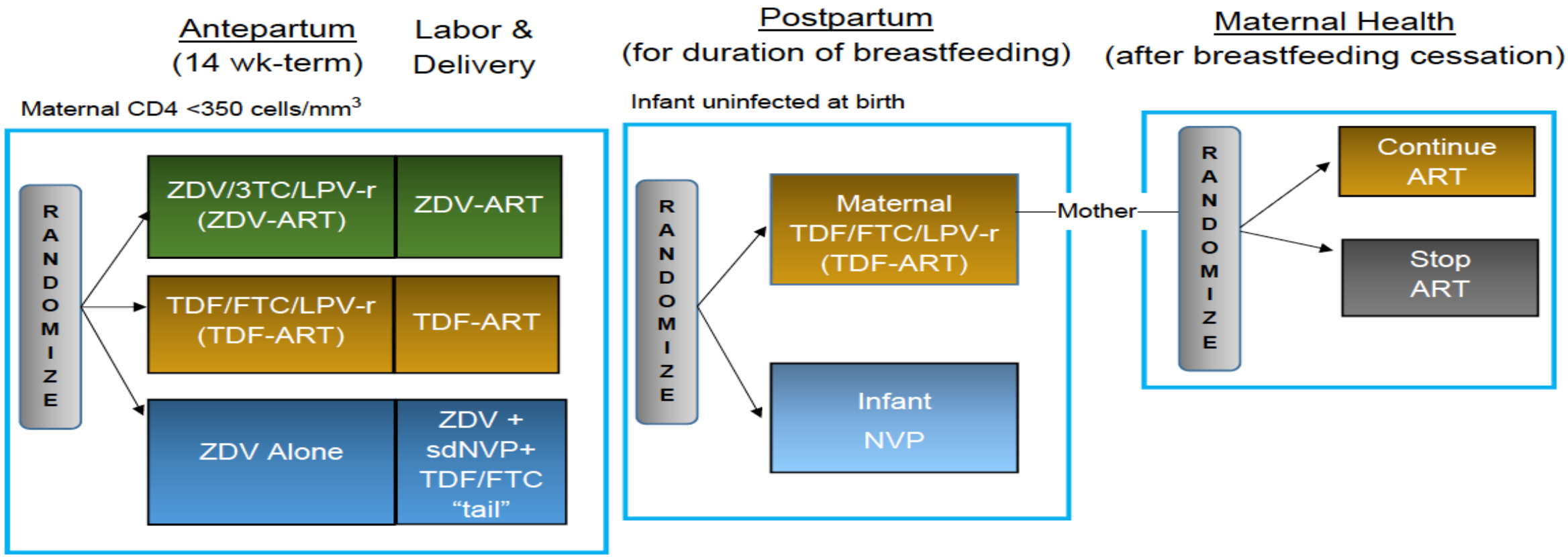
Methods

- PROMISE: an open-label study that compared antepartum and postpartum HIV PMTCT strategies via sequential randomizations



Methods

- Maternal Inclusion criteria
  - **CD4 ≥ 350 cells/mm³ or above country recommended CD4 threshold if that is higher**
  - Gestational age >14 weeks
  - No prior triple ART
  - Hemoglobin ≥ 7.5g/dL
  - ANC ≥ 750 cells/mm3
  - **ALT < 2.5 x ULN**
  - CrCl >60ml/min
  - No serious pregnancy complications prior to entry

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Toxicity Assessments and Definitions

- 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, q24 weeks
- Additional ALT measurements at early discontinuation, at step change and 4 weeks afterwards, and at event-driven visits

ALT	Degree of elevation	
Grade 2	**2.6-5.0 x ULN**	**Moderate**
Grade 3	**5.1-10.0 x ULN**	**Severe**
Grade 4	**>10.0 x ULN**	**Potentially Life threatening**

Methods: Key events in PROMISE Timeline

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

PROMISE sites were notified of START study results which demonstrated improved outcomes with early ART initiation. Sites recommended to shift to Study drug ART with PI or SOC HAART

Study closure, transition to SOC

Hepatotoxicity letter

Study enrollment

Last delivery AP arm

April 2011

March 2015

July 2015

July 2016-Sept 2016

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Analyses

- Descriptive statistics, incidence rates and 95% CI

- Cox proportional hazards model to assess factors associated with hepatotoxicity
  - 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.

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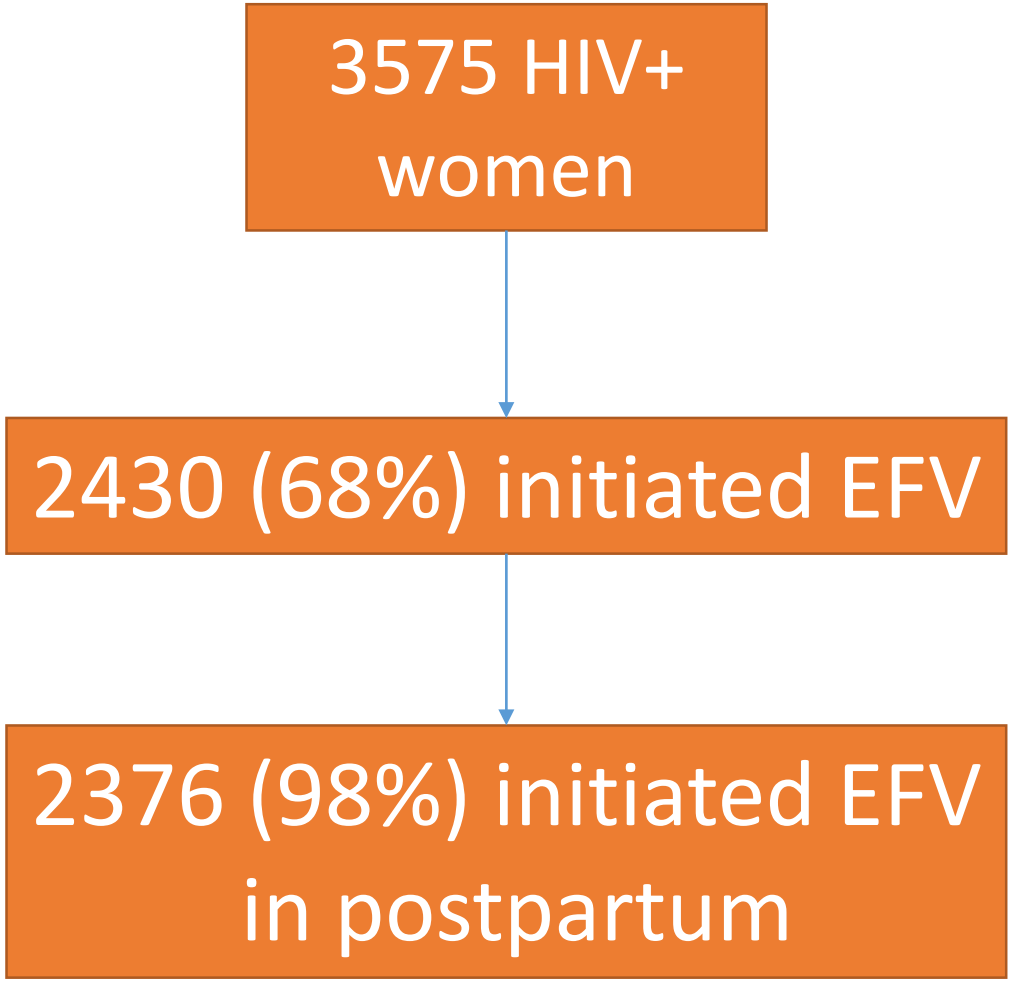
Results: Study population



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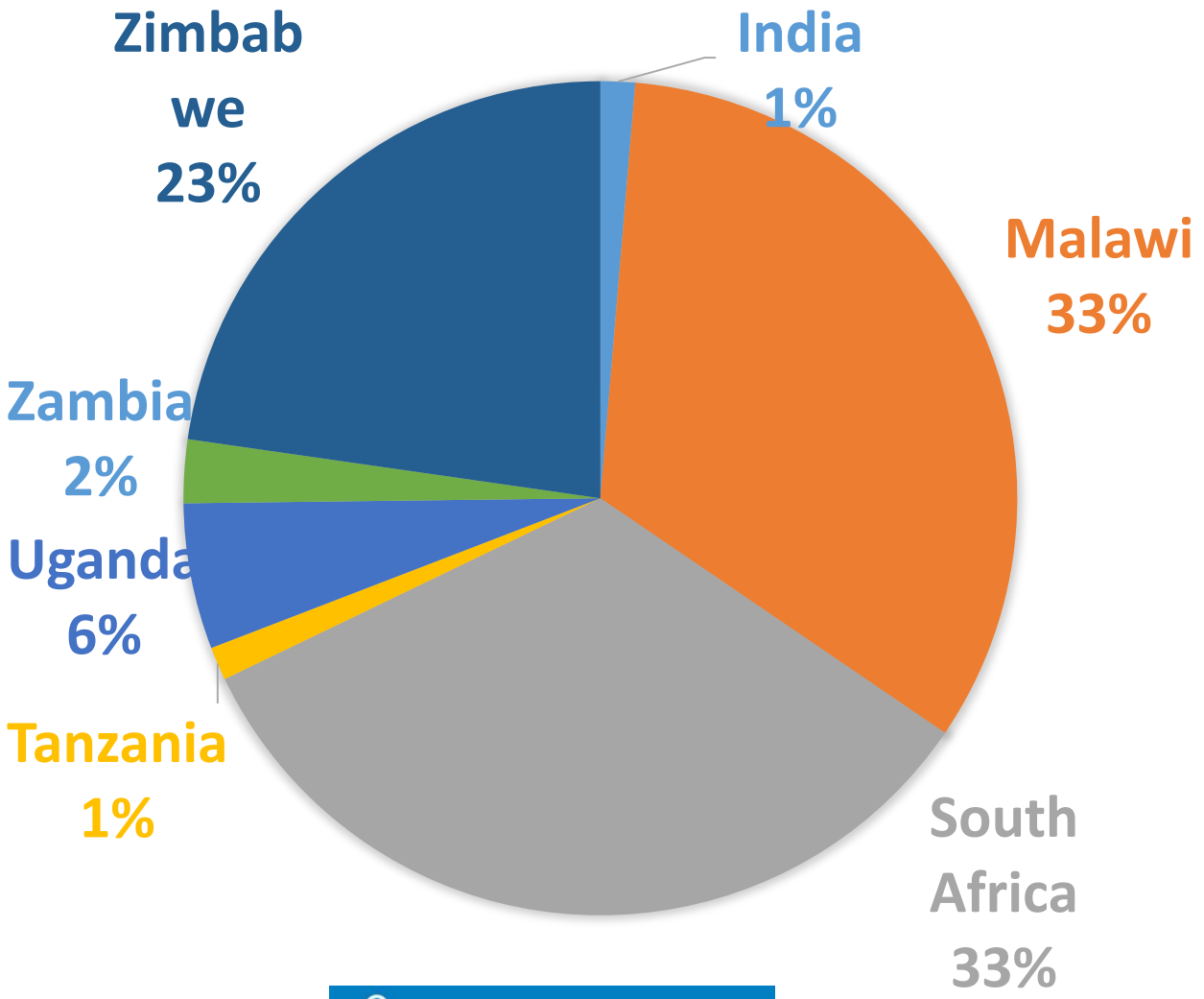
Results: Study population characteristics, n=2430

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%)



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ART Characteristics at Time of EFV Initiation

ART characteristic	Regimen	n (%)
Prior Regimen Group	PI+ 2NRTI	762 (31%)
	No ARVs	1,518 (62%)
	ZDV or ZDV+ sd NVP-TDF tail	51 (2%)
	Other	99 (4%)

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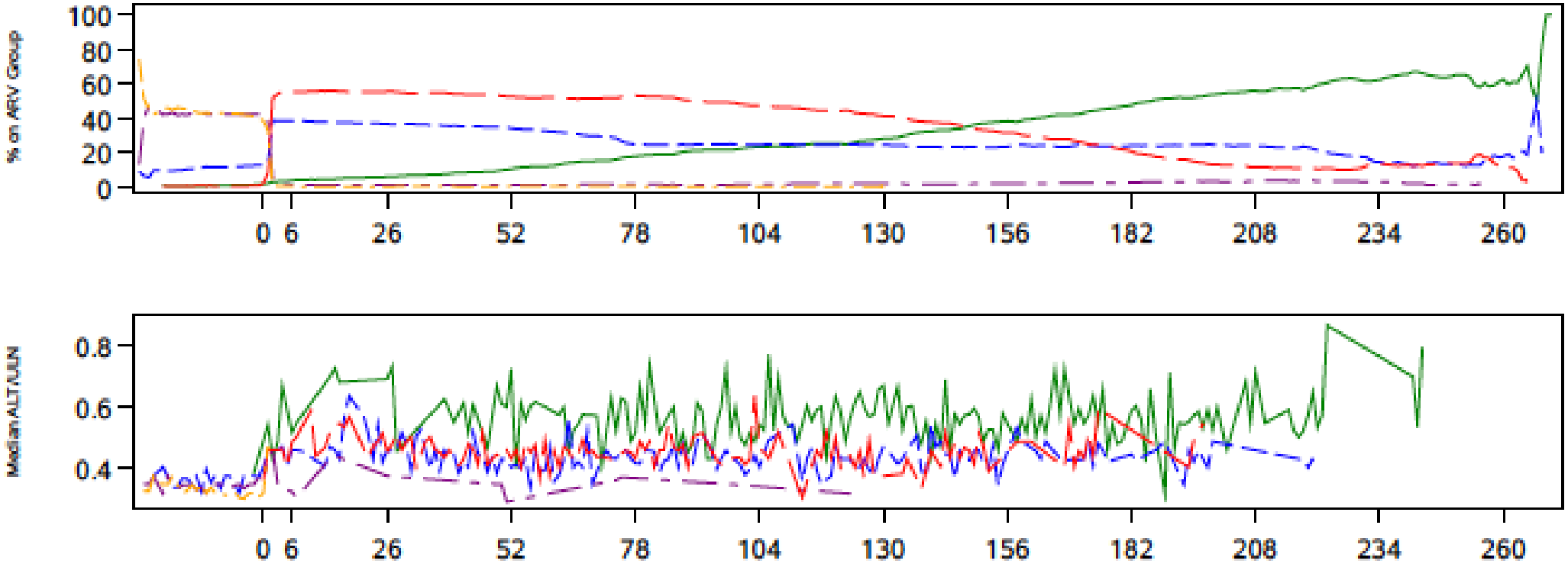
ARV regimens and ALT relative to Delivery



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Hepatotoxicity by Grade

- Of 2430 women initiated on EFV
  - 180 (7.4%) Grade 2 or higher
  - 61 (2.5%) Grade 3 or higher
    - 25 (1.0%) Grade 4
      - 4 symptomatic, 3 of which were jaundice
    - 36 (1.5%) Grade 3
      - 5 symptomatic, 1 of which RUQ pain, anorexia

- Incidence of Grade 3 or higher of 2.2 per 100PY

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Hospitalization by before/after EFV initiation post-delivery

	No of participants	Cumulative events	Total person-years	Incidence Rate (95%CI)
Before EFV initiation	**2377**	**88**	**5223**	**1.7 (1.5-1.9)**
After EFV initiation	**2372**	**86**	**2683**	**3.2 (2.9-3.6)**
Overall	**2377**	**168**	**7825**	**2.2 (1.9-2.4)**

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

N=2430 initiated EFV; 13 died, 4 EFV-related

2 occurred during PROMISE and 2 occurred 3 months after leaving PROMISE

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

Overall mortality incidence 0.44 per 100PY
EFV-related mortality incidence 0.13 per 100 PY

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	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	

In addition, no association of country, randomization arm, history of prior ALT abnormality or ALT at initiation, or receipt of EFV prior to delivery

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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 625
- Monitoring for ALT abnormalities may prevent unnecessary deaths but
  - research needed to identify frequency and who is at highest risk for hepatotoxicity
- Limitation:
  - Most women in PROMISE did not initiate EFV in pregnancy or early postpartum which is a higher risk period for hepatotoxicity
  - Generalizability: Study conducted in SSA where may be predisposing genetic factors.

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