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

- EFV-containing regimens now are among the WHO recommended first line antiretroviral (ARV) regimens (since 2013)
  - Including for pregnant and postpartum women

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Background

- 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 LEE, 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 Hepatic Toxicity 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

- To compare rates of LEE for women initiating EFV compared to the PROMISE study antiretroviral regimens

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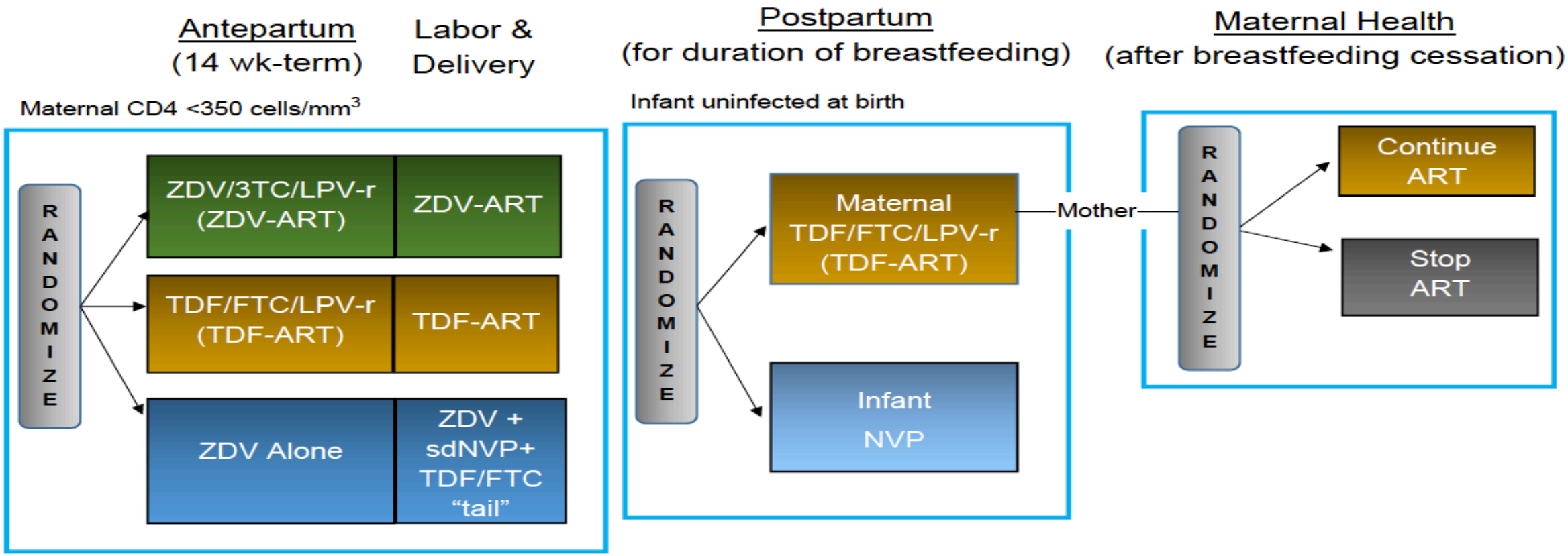
Methods

- 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 cut off 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 event driven

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 enrollment

Last delivery AP arm

Study closure, transition to SOC

Hepatotoxicity letter

April 2011

March 2015

July 2015

July 2016-Sept 2016

July 2016-Sept 2016

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27 September 2016

Dear PROMISE Investigators and HIV Care and Treatment Providers,

Thank you for the continued care of the PROMISE study participants as they transition off study.

The PROMISE team would like to make you aware of several events of significant hepatotoxicity that we have noted recently in the PROMISE study as women have transitioned to efavirenz-based regimens. In the past, non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been associated with hepatotoxicity, but this has usually been associated with nevirapine among women with high CD4 counts.

However, in several recent PROMISE cases, women participants who had begun efavirenz-based standard of care treatment have presented to routine study visits with generally asymptomatic grade 3 to 4 hepatotoxicity (ALT>500), most of whom had resolution with discontinuation of efavirenz-based regimens. In the rare instances where women were re-challenged with efavirenz, the liver enzyme hepatotoxicity recurred. There was no history of liver disease in these patients, nor receipt of potentially hepatotoxic medications at the time of hepatotoxicity presentation. Testing for viral hepatitis was also negative. A number of these participants experienced this hepatic toxicity postpartum and the events were sometimes delayed for up to as long as 9 months after starting efavirenz-based ART regimens. Their CD4 counts were generally high.

In addition, Sonderup and colleagues recently reported on 81 cases of efavirenz-associated hepatotoxicity in South Africa (enclosed), 18 of which occurred in pregnant women. Three patterns were described: 1. Nonspecific hepatitis with grade 1-2 elevation of serum transaminases; 2. Mixed cholestatic-hepatitis; 3. Submassive necrosis with grade 4 elevation of ALT/AST with severe jaundice and coagulopathy. Although the mechanism is unknown, immune reactivation in the postpartum period may play a role.

Based on the recent PROMISE cases of hepatotoxicity among participants when they were

Analyses

- Descriptive statistics, incidence rates and 95% CI

- Cox proportional hazards model to assess factors associated with LEE
  - covariates included age, BMI, prior ALT elevation, HBsAg, ART regimen before EFV, CD4, country, EFV initiation date, time from delivery to EFV initiation, receipt of EFV prior to delivery, NRTI in regimen, antepartum and postpartum randomization assignments

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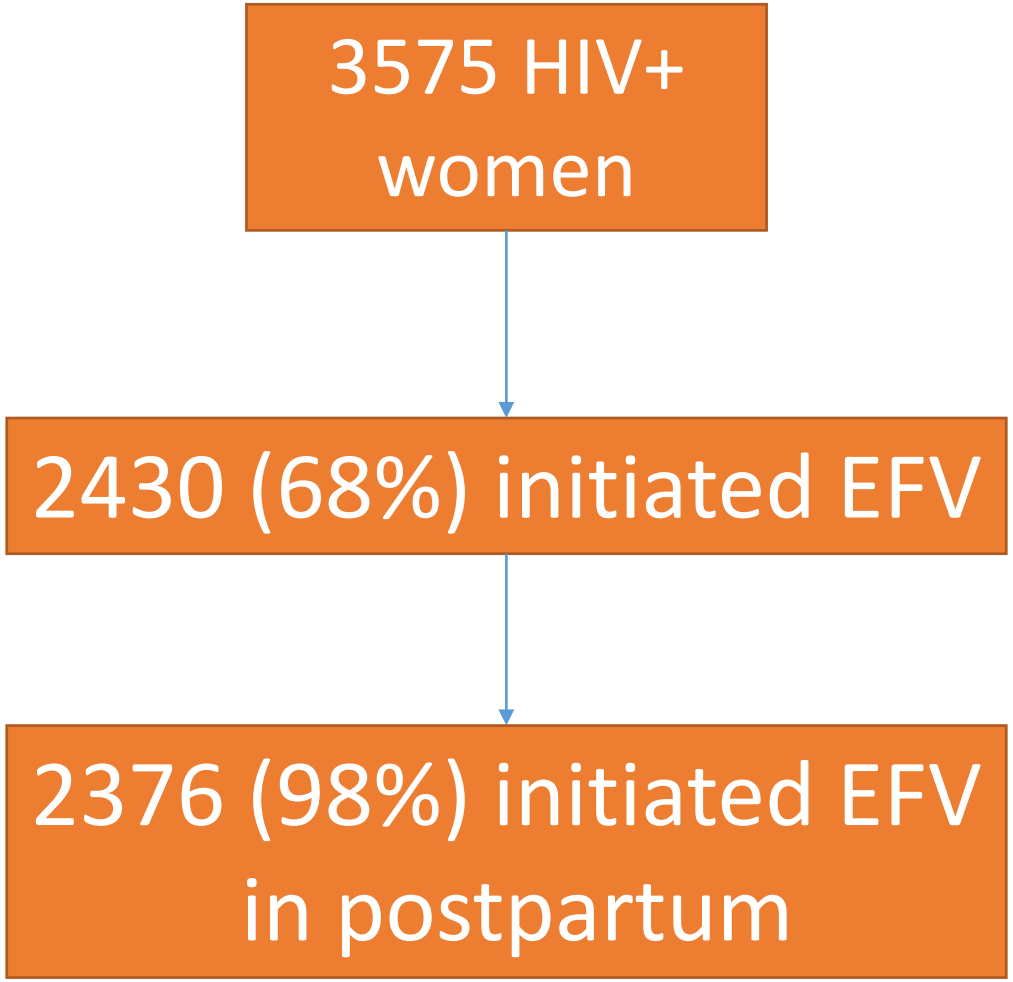
Results: Study population



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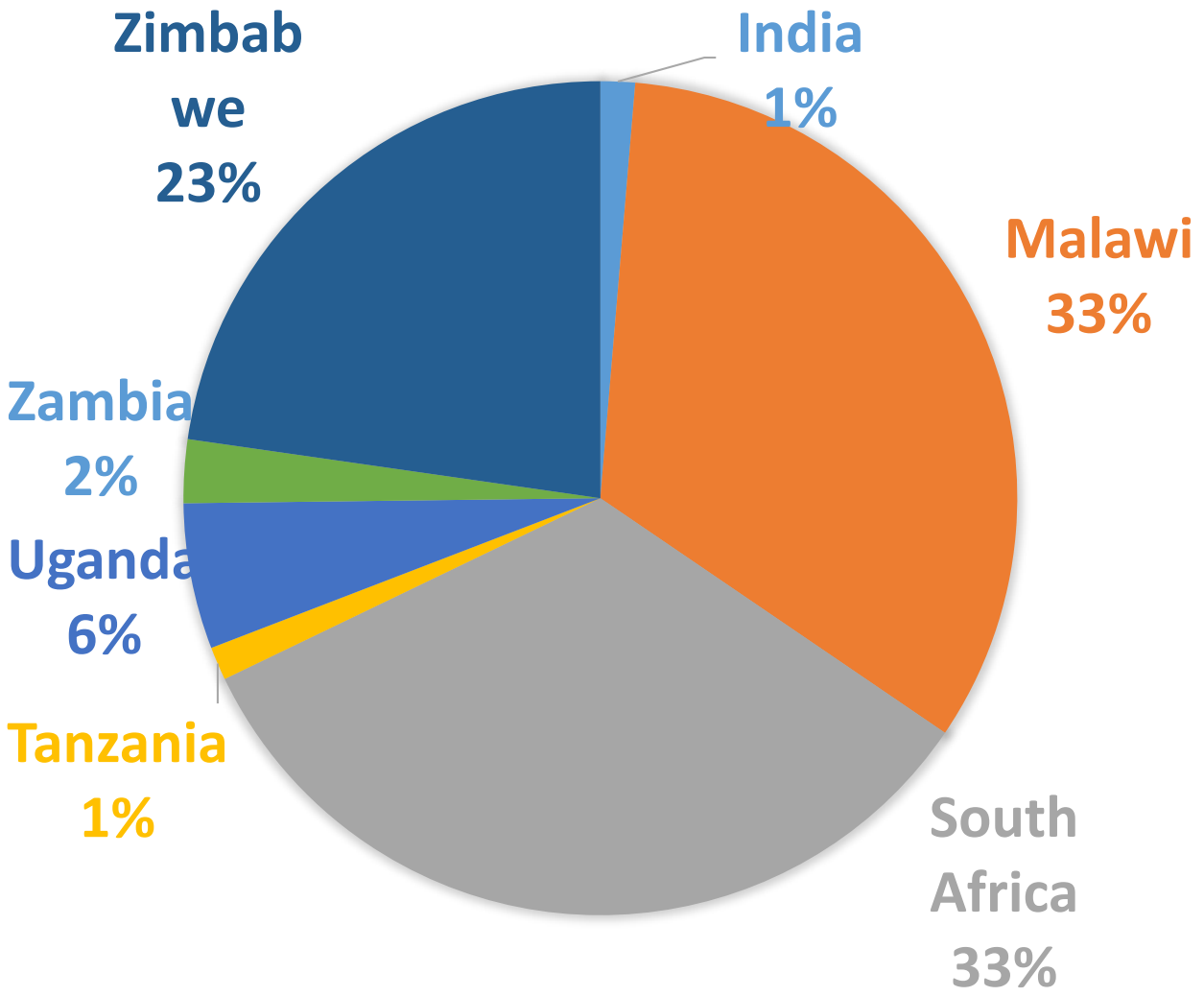
Results: Study population characteristics, n=2430

Characteristic	n (%)
Median Age (IQR) , years	29 (25-33)
Median BMI	25 (22-29)
Median CD4 cells/mm3	625 (466-839)
HBsAg+	82 (4%)
Grade 3 or 4 ALT elevation prior to delivery	24 (1%)



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ART Characteristics at Time of EFV Initiation

ART characteristic	Regimen	n (%)
Prior Regimen Group	PI+ 2NRTI	723 (31%)
	No ARVs	1,434 (62%)
	ZDV or ZDV+ sd NVP-TDF tail	58 (3%)
	Other	103 (4%)

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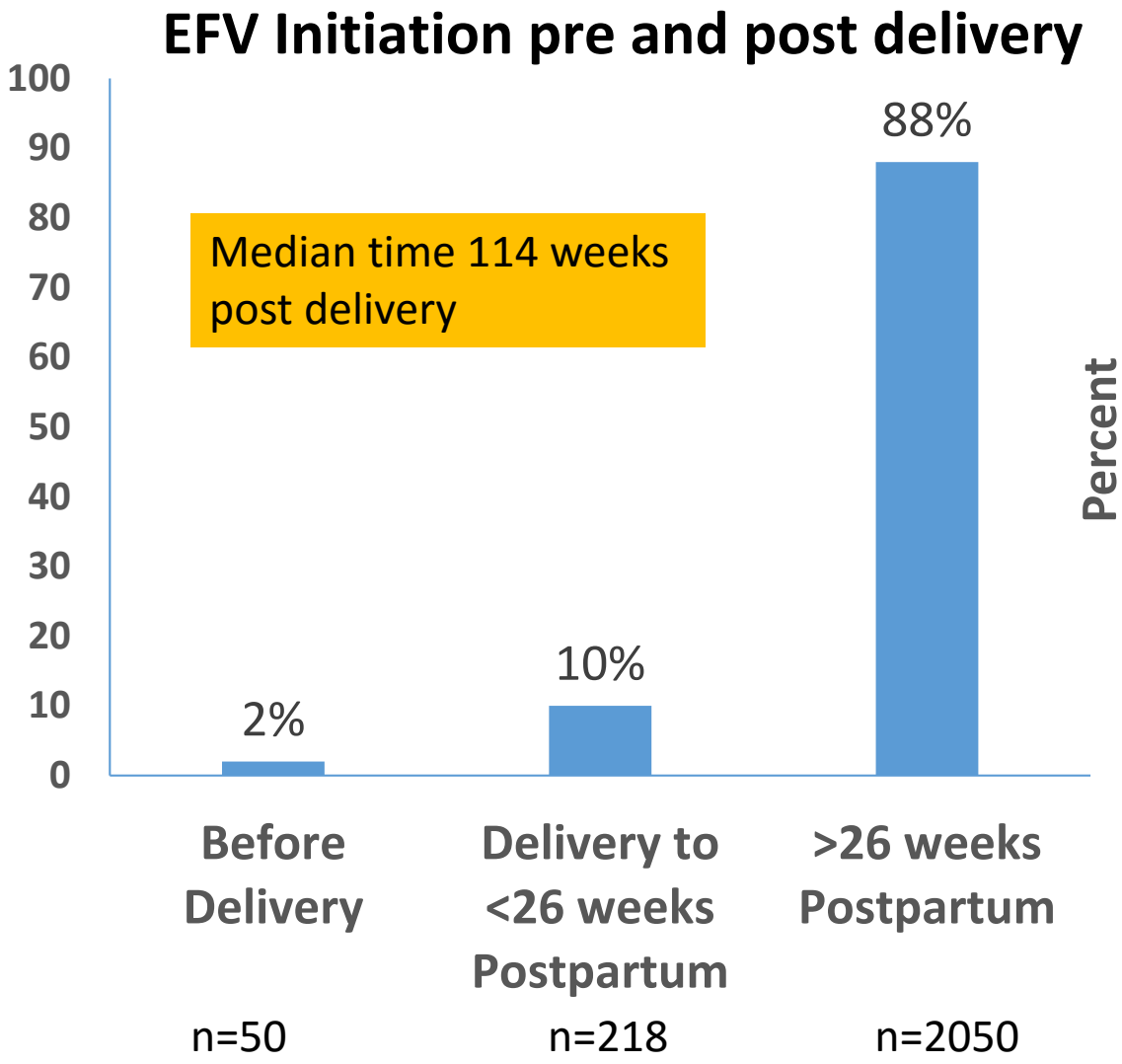
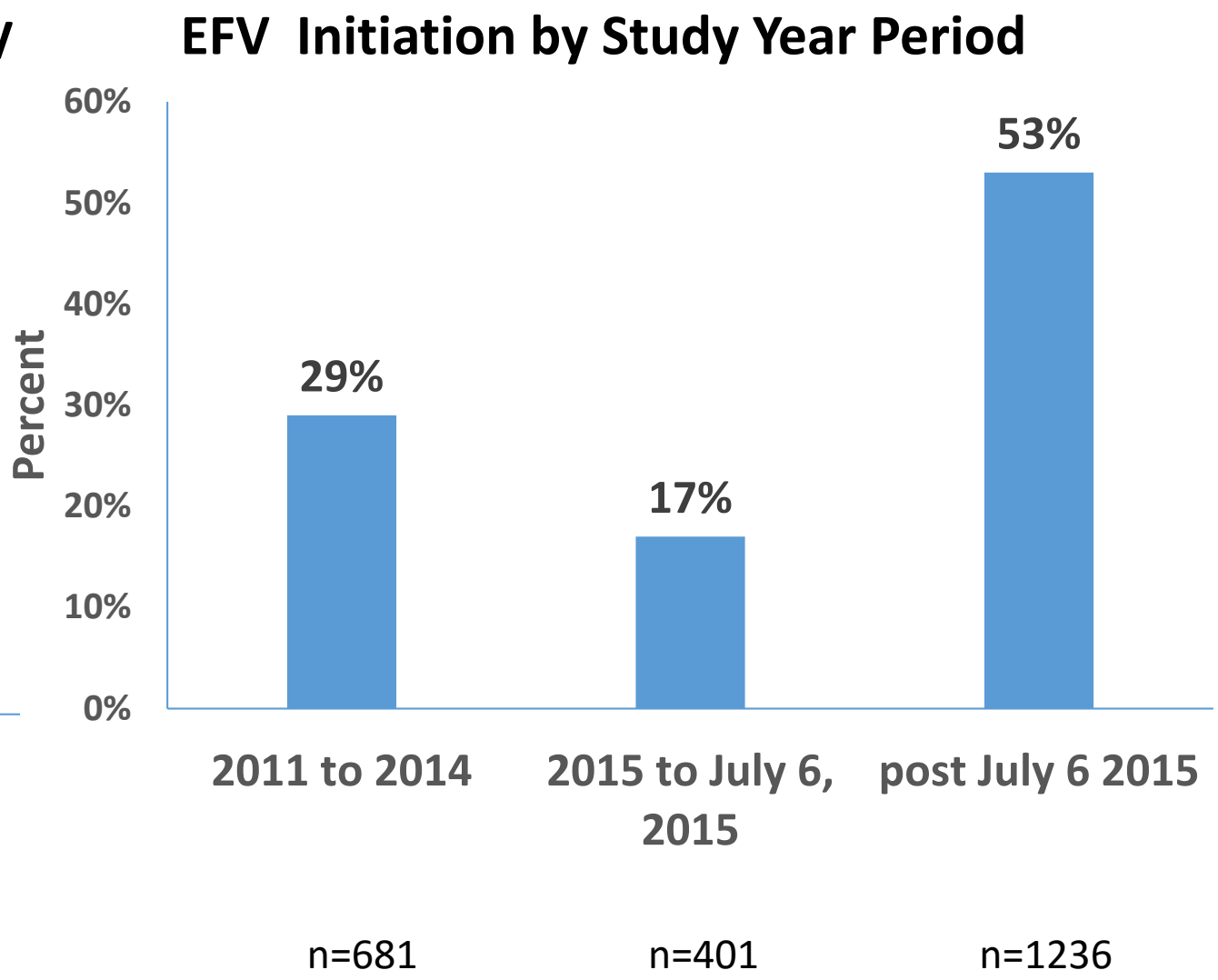
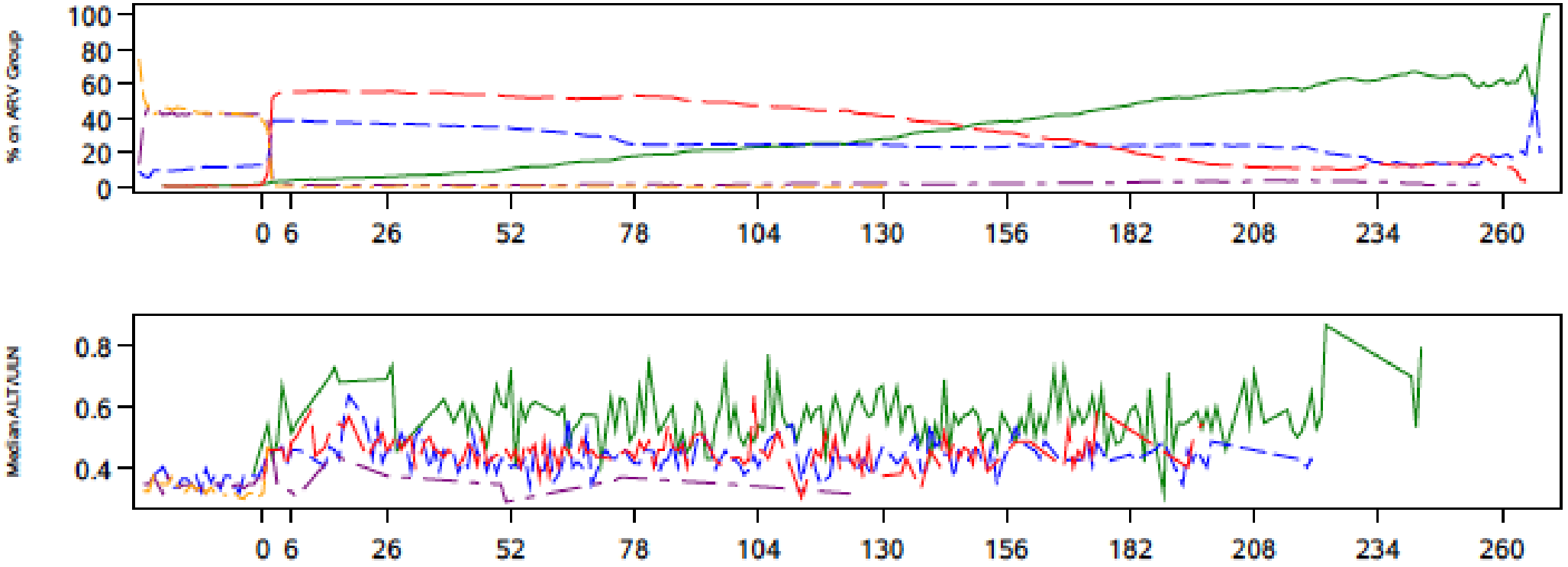
Timing of EFV initiation





ARV regimens and ALT relative to Delivery



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Incidence of Maternal ALT Elevation (Grade 3 or higher) after Delivery by Regimen

ARV Regimen	No of participants	Cumulative events	Total Person Years	Incidence Rate/100PY
EFV/TDF/3TC or FTC	2430	61	2726	2.2
LPV/r/TDF/FTC or 3TC	1241	8	2139	0.4
no ARVs	1809	21	3319	0.6

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Maternal Incidence of ALT Elevation (Grade3 or higher) after EFV Initiation by Country

Country	No of participants	Cumulative events	Total person years	Incidence rate (95% CI)
South Africa	783	20	1006	2.0 (1.6-2.5)
Malawi	841	18	800.5	2.3 (1.8-2.8)
Uganda	136	6	183.0	3.3 (2.2-4.9)
Zimbabwe	549	12	579.4	2.1 (1.6-2.7)
Zambia	60	1	67.6	1.5 (0.6-3.9)
Tanzania	30	1	37.1	2.7 (1.0-7.1)
India	31	3	59.1	5.1 (2.9-8.9)
Overall	2430	61	2733	2.2 (2.0-2.5)

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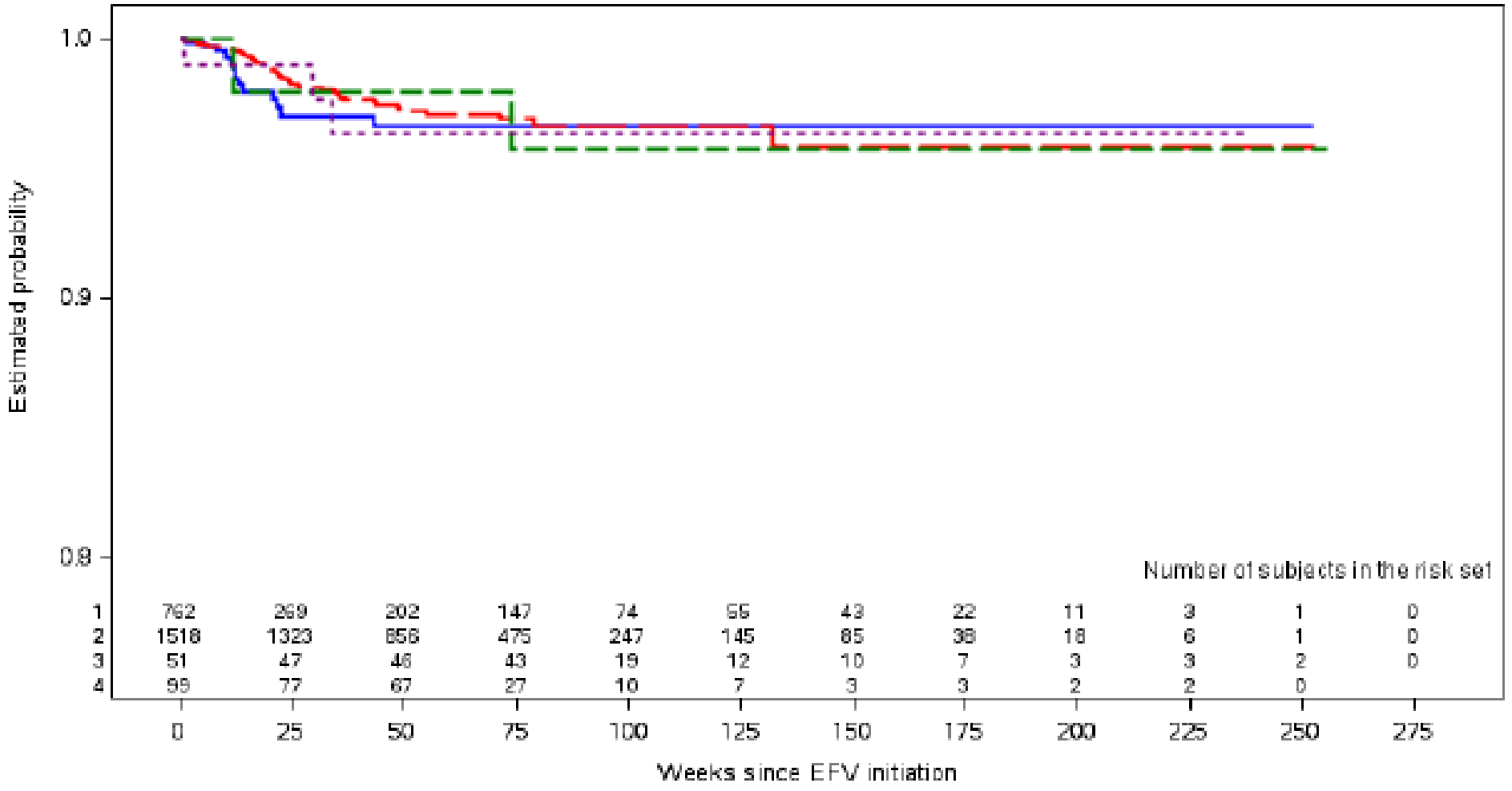
KM plot for the First Grade 3 or higher ALT Elevation after EFV Initiation



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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 by study end

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

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

Participant	1	2 (Malawi)	3 (Malawi)	4 (Zimbabwe)
Age		29yo	39yo	
# weeks postpartum	77	105	125	
Cause of Death	Hepatitis	Hepatitis	Hepatitis	Hepatitis
ARV	EFV	EFV	EFV	EFV
Death week since EFV initiation	25 weeks	16 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/mm3 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

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Conclusions

- Limitation: Most women in PROMISE did not initiate EFV in pregnancy or early postpartum which is a higher risk period for hepatotoxicity
- EFV was associated with higher incidence of hepatotoxicity compared to LPV/r or no ARV regimens
  - Most women were asymptomatic but
  - Serious toxicity resulting in hospitalization and deaths among women on EFV did occur (2 by end of PROMISE and 2 in follow up within 3 months of PROMISE ending)
- EFV Grade 3 or higher hepatotoxicity rate in PROMISE appears similar to meta-analysis published literature of 2.3% and mortality of 0.2% (Shubber AIDS 2013).
- Monitoring for ALT abnormalities may prevent unnecessary deaths but research needed to identify frequency and who is at highest risk for hepatotoxicity
- PROMISE analyses ongoing to further assess rates and risk factors of hepatotoxicity
- The PROMOTE study will continue to monitor for hepatic toxicity in longer term follow up of PROMISE participants including during repeat pregnancies.

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Acknowledgments

- Study participants who participated of the PROMISE 1077BF/1077FF study along with their infants
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Extra slides

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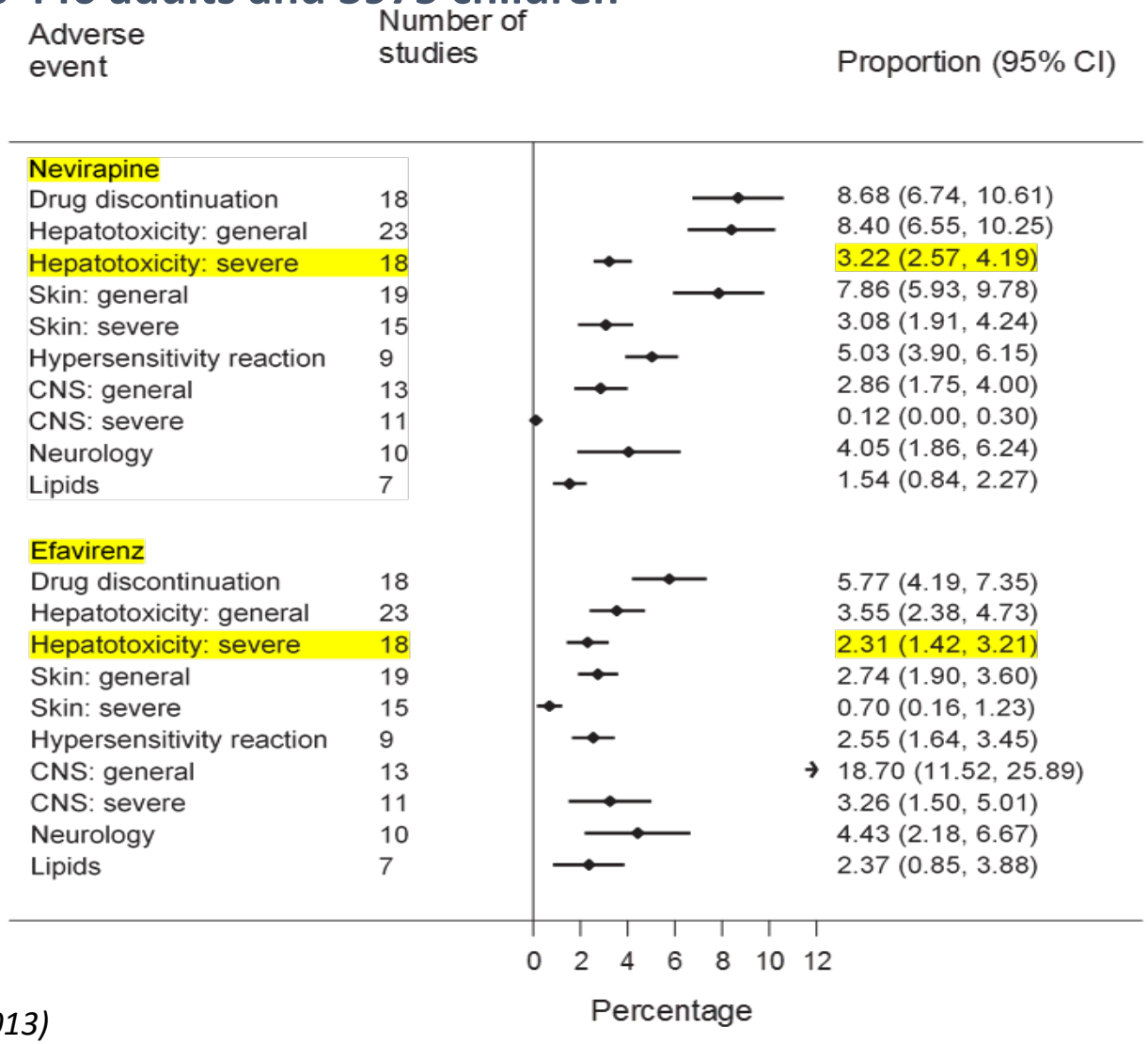
Severe Hepatotoxicity: NVP vs. EFV

Data from 8 RCTs and 26 cohorts
26 446 adults and 3975 children

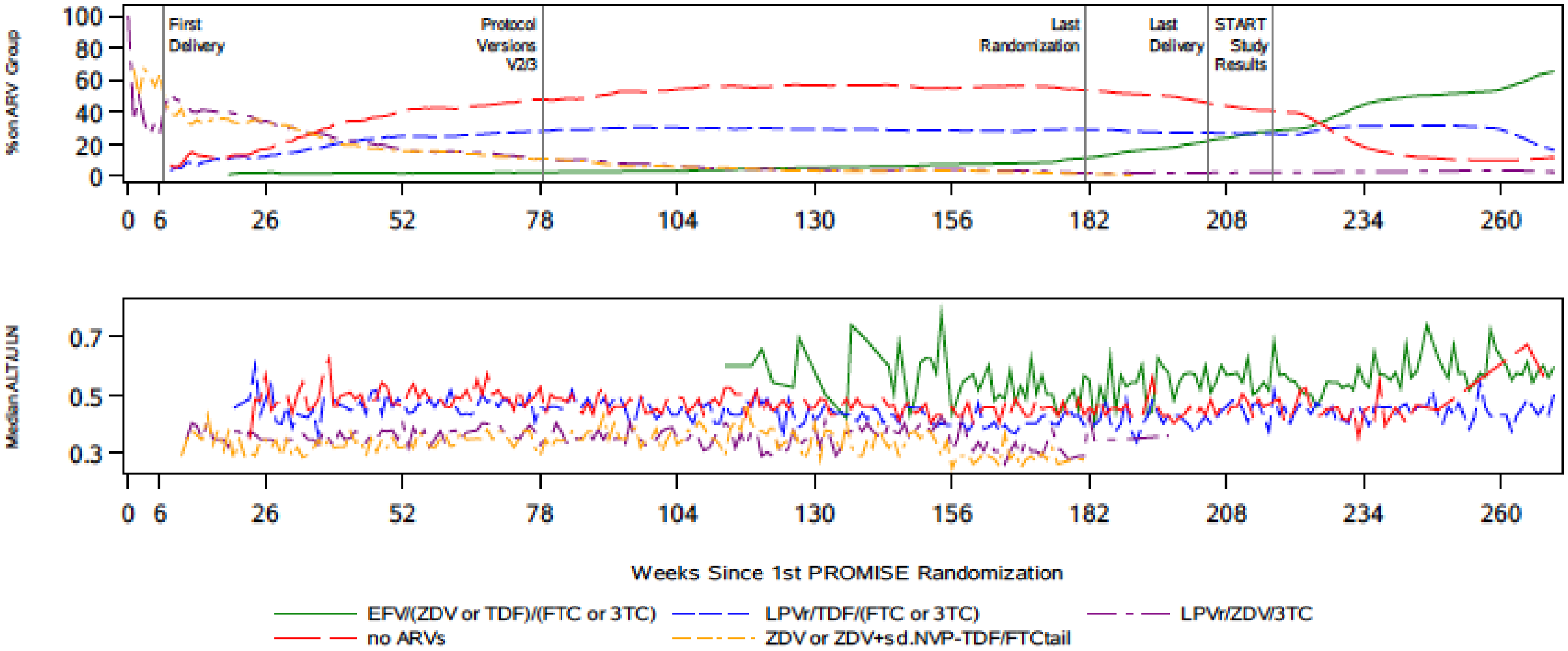


Shubber, Z., et al., AIDS (2013)

Fig. 2. Pooled proportion of adverse events by drug

*Severe hepatotoxicity defined as Grade 3,4 or drug discontinuation

ARV regimens and ALT from first PROMISE randomization



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