HIV/HBV Coinfection in Pregnancy and Response to Antiretroviral Therapy in PROMISE P1077

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IMPAACT 1077
Promoting Maternal and Infant Survival Everywhere

Presented at the 24th IAS July 31, 2022

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Background

- Hepatitis B virus (HBV) affects 3-9% of pregnant women with HIV in Africa
- In ART initiation in those living with HIV/HBV, some studies in non-pregnant adults have demonstrated
  - delayed HIV virologic control and CD4 reconstitution
  - increased hepatotoxicity
- High HBV viral loads have been associated with hepatotoxicity in ART
- HBeAg is associated with high HBV viral loads
- Differences in these clinical outcomes may impact management strategies in pregnant women living with HIV and HBV
- Limited data in pregnancy

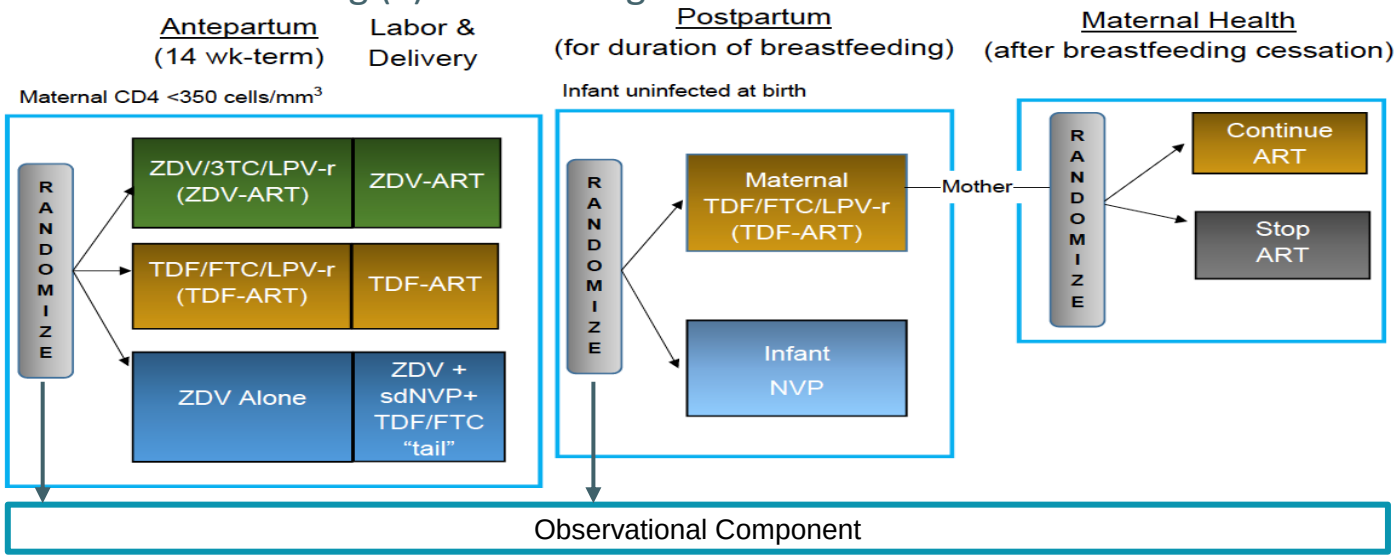
Fomulu BMC Preg Childbirth 2013. Rouet J Med Virol 2004. Chasela J Hepatol 2014. Andersson Vaccine 2013 Wandeler JID 2013, Law AIDS 2004, Yang Int J Inf Dis 2014, Hoffmann CID 2008

Research Question

- Do CD4 reconstitution, HIV virologic response, and hepatotoxicity differ by HBV status, in a cohort of pregnant women living with HIV alone and HIV/HBV coinfection initiating antiretroviral therapy?

Methods

- PROMISE: open-label study of pregnant women living with HIV who were ART- naive and had not met criteria for initiating ART that compared antepartum and postpartum HIV PMTCT strategies via sequential randomizations
- HBV defined as HBsAg (+) at screening



Fowler NEJM 2016

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

High CD4 criteria and low ALT indicate a healthier population living with HIV and HBV

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Assessments

Laboratory Test	Antepartum	Postpartum
CD4	Screening, week 12, delivery or week 1 postpartum	Week 14 then q12 weeks
HIV-1 RNA*	Entry, week 4, delivery	Week 1, weeks 6, 14, 26, 50, 74 then q24 weeks MH: Entry, weeks 4, 12, q 12 weeks
ALT	Entry, weeks 4 and 8, then q 4 weeks until delivery	Entry, weeks 6, 14, 26, 38, 50, then q24 weeks

Follow-up Time for Analysis→ Inclusive of Time off of ART

* HIV RNA assays performed in real time for women on triple ART, stored for those not on ART.
Stored specimens tested at delivery, post partum wks 6, 26, 50, 74, 98, 146/ MH entry, wks 4, 12, 48, 96,144

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Hepatotoxicity Definitions

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

Safety related events were graded per Division of AIDS (DAIDS) grading system (version 1.0, with clarification added August 2009)

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Statistical Considerations

- Outcome measures
  - CD4 cell count at Delivery and postpartum Week 74
  - HIV viral load (<400,>=400cp/ml) at Delivery and postpartum Week 50
  - Time to grade 3/4 ALT elevation
- Analyses
  - Two-group comparisons with HBsAg- group as reference
  - Covariate adjustment with logistic (odds ratio), Cox proportional hazards (hazard ratio), or linear (mean difference) regression for binary, time-to-event, and linear continuous outcome measures
    - adjusted by i) antepartum (AP) randomization assignment alone and ii) AP assignment + maternal baseline covariates.
    - Baseline covariates : baseline age, CD4 cell count, log10 HIV-RNA, geographic region

Analyses censored at July 6, 2015 with START study results and recommendation for all to initiate ART

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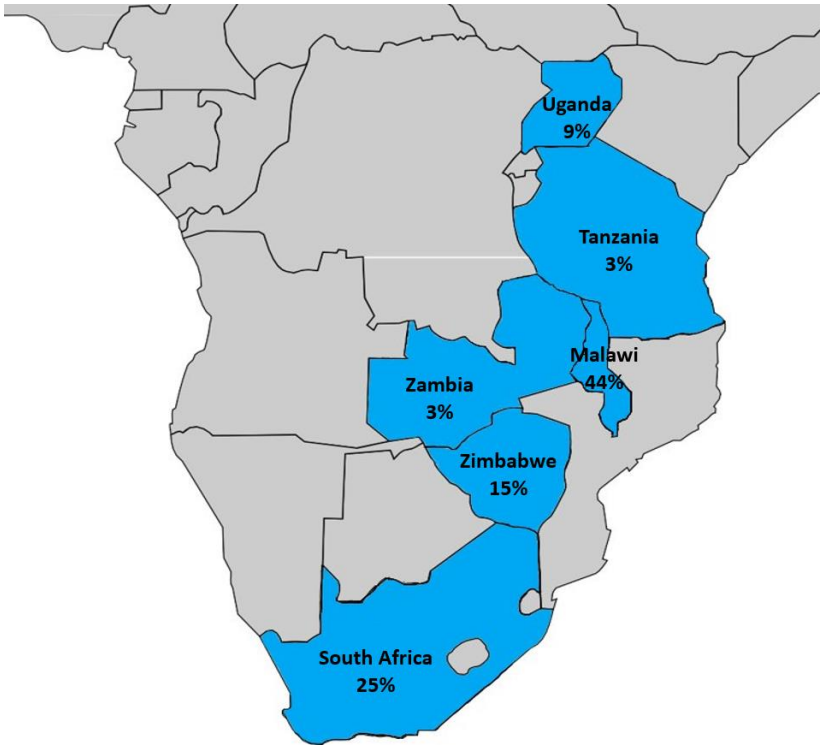
Baseline Characteristics of Pregnant Women with HIV and HIV/HBV

Enrolled 2011 -2014 with follow-up through September 2016

Maternal Characteristic		HIV/HBV (N=138)	HIV (N=3399)
Age (years)	Median (Q1-Q3)	27 (23-30)	27 (23-30)
Gestational age at AP Entry (weeks)	Median (Q1-Q3)	27 (22-31)	26 (21-30)
AP Randomization Arm*	No anti-HBV	42 (30%)	1,505 (44%)
	3TC	48 (35%)	1,497 (44%)
	FTC-TDF	48 (35%)	397 (12%)
CD4+ cell count (cells/mm^3)	Median (Q1-Q3)	505 (420-634)	533 (437-667)
Log_{10}HIV RNA (copies/mL)	Median (Q1-Q3)	4.0 (3.2-4.5)	3.9 (3.2-4.4)
Log_{10}HBV DNA (copies/mL)	Median (Q1-Q3)	2.58 (1.38-5.34)	-
HBeAg status	Negative	97 (74%)	-
TB Medications	Yes	13 (9%)	346 (10%)
ALT (IU/L)	Median (Q1-Q3)	15 (11-21)	12 (10-15)

*No anti-HBV: ZDV alone, 3TC: 3TC+ZDV+LPV/r, or FTC-TDF: FTC+TDF+LPV/r

Contribution to HIV/HBV Cohort (n=138) By Country



No Difference in CD4 Count at Delivery and 74 Weeks

	HIV alone	HIV/HBV	Unadjusted Comparisons (95% CI) P-value	Adjusted Comparisons (95% CI) P-value
Mean (se) Delivery CD4 count	755.3 (4.96)	749 (24.23)	-6.14 (-55.07, 42.79) 0.80	-1.76 (-41.61, 38.08) 0.93
Mean (se) 74 week CD4 count	726.4 (6.13)	747.2 (26.85)	20.71 (-33.93, 75.34) 0.45	22.07 (-31.03, 75.17) 0.42

Se: standard error; Adjusted for AP randomized arm and baseline age, CD4, VL, and geographic region

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No Difference in HIV VL Suppression at Delivery or Postpartum Week 50

	HIV alone	HIV/HBV	Unadjusted Comparisons Odds Ratio (95% CI) P-value	Adjusted Comparisons Odds Ratio (95% CI) P-value
Delivery HIV VL < 400 copies/ml	53% (1683/3150)	60% (76/126)	1.32 (0.91, 1.95) 0.14	1.18 (0.76, 1.82) 0.46
Postpartum Week 50 HIV VL< 400 cp/ml	51% (1168/2299)	52% (52/100)	1.05 (0.69, 1.60) 0.84	1.04 (0.69, 1.57) 0.86

Adjusted for AP randomized arm and baseline age, CD4, VL, and geographic region; 1 year= Wk 50 PP

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Women with HIV/HBV Coinfection: 2.9x Likely to Experience Grade 3 or 4 ALT Elevation

	HIV alone N=3399 No. Events (%)		HIV/HBV N=138 No. Events (%)		Unadjusted Comparisons Hazard Ratio (95% CI)	Adjusted Comparisons Hazard Ratio (95% CI)
Time to Grade 3/4 ALT	95	(2.8%)	11	(8.0%)	3.1 (1.6,5.5)	2.9 (1.5, 5.4)

Adjusted for randomized arm and baseline age, CD4, VL, and geographic region

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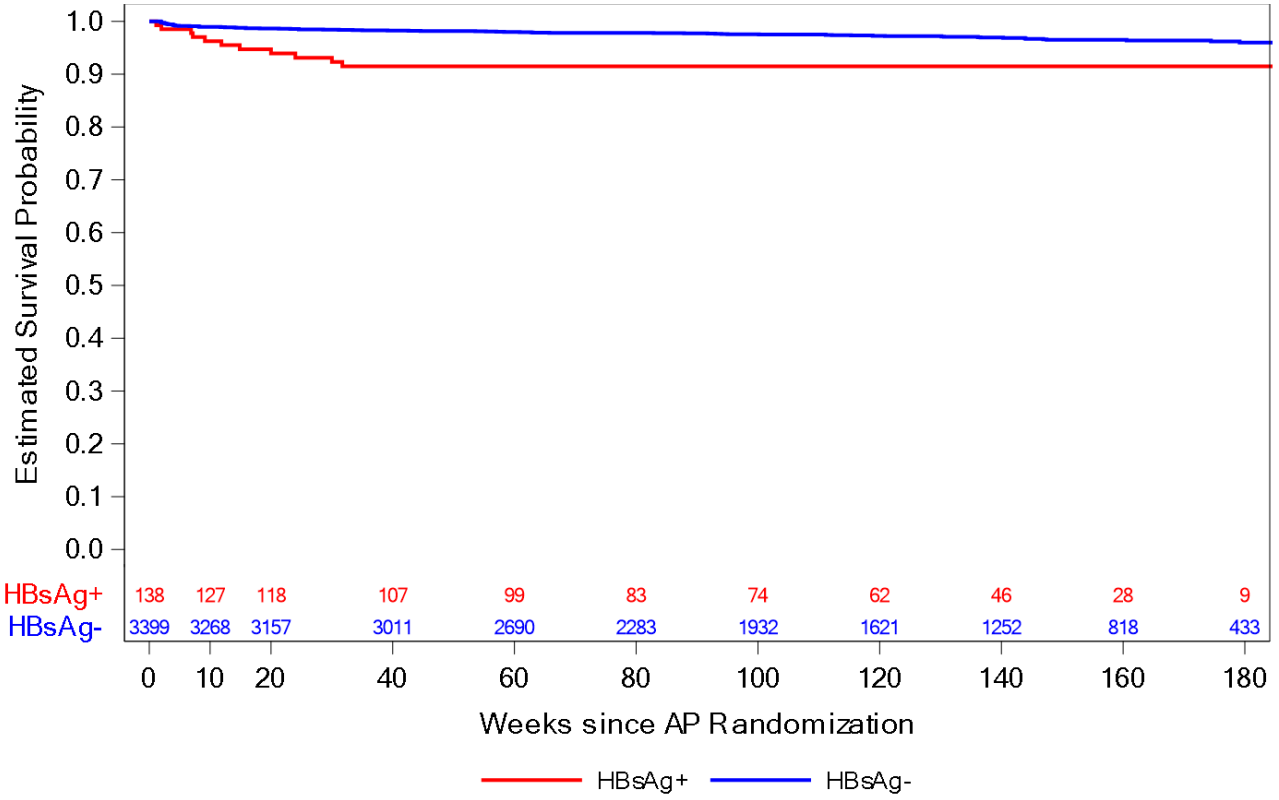
Time to First Grade 3 or 4 ALT: HBV vs No HBV



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Women with HIV/HBV(HBeAg+) Coinfection: 7.1 x Likely to Experience Grade 3 or 4 ALT Elevation

	HIV alone N=3399		HIV/HBV (HBeAg+) N=34		Unadjusted Comparisons Hazard Ratio (95% CI)	Adjusted Comparisons Hazard Ratio (95% CI)
Time to Grade 3/4 ALT	95	2.8%	6	17.6%	6.9 (2.7,14.7)	7.1 (2.7, 15.2)

Adjusted for AP randomized arm and baseline age, CD4, VL, and geographic region

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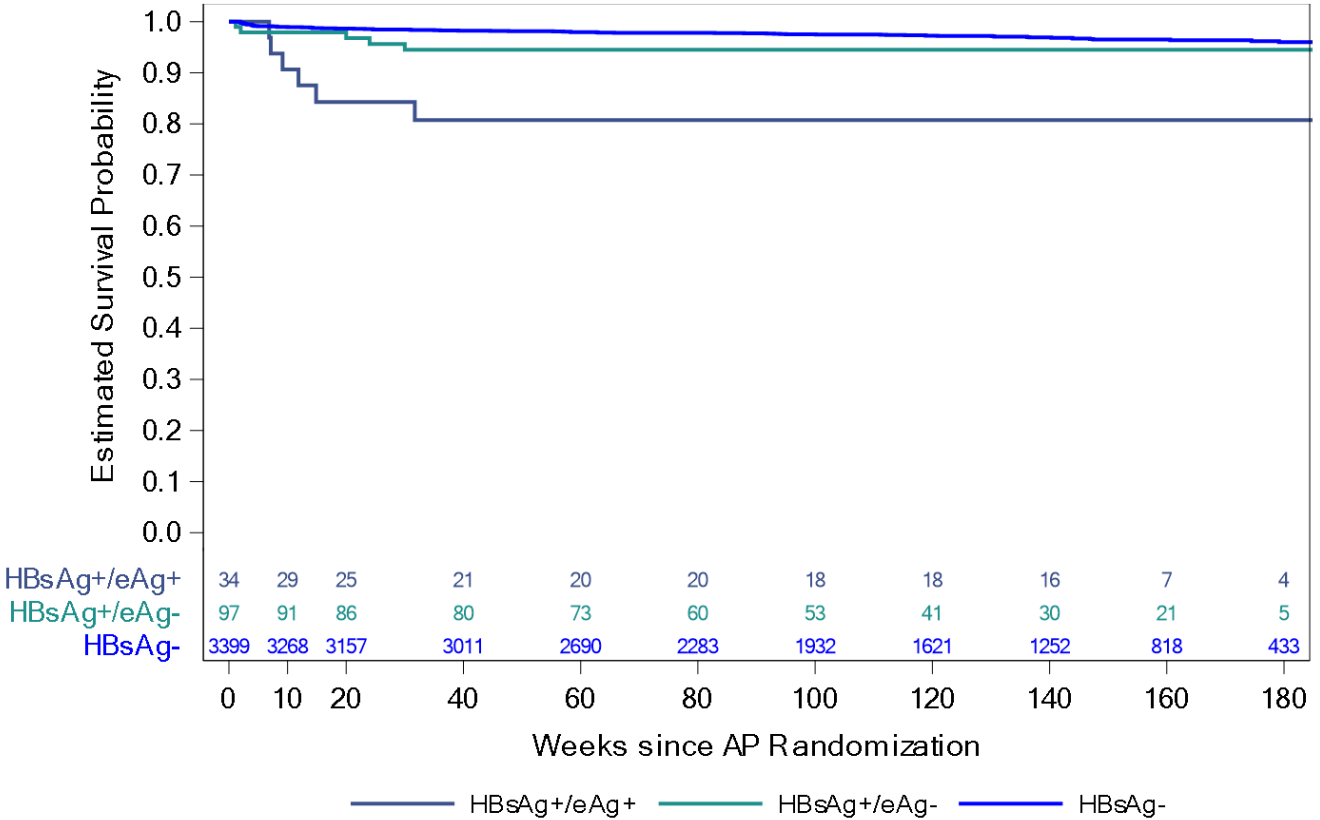
Time to First Grade 3 or 4 ALT: HBV (HBeAg+) vs No HBV



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Conclusions

- In pregnant women with HIV initiating ART, HIV RNA suppression and CD4 cell response did not differ between HIV and HIV/HBV coinfection.
- Grade 3 or 4 ALT elevations occurred at a higher rate in those with HBV, with HBeAg+ status conferring increased risk.

Limitations

- Unable to distinguish between acute and chronic HBV infection with a single timepoint assessment
- Use of LPV/r as backbone for TDF+3TC regimen
- Relatively small sample size for HBsAg+ group
- Women living with HIV/HBV in this cohort were relatively healthy (high CD4, low ALT)

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THANKS!

Any questions?

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Additional Slides

WHO Monitoring Guidelines

WHO HIV Perinatal Guidelines:

- HIV viral load test by six months and 12 months after initiating ART and every 12 months thereafter
- CD4 cell count every six months until established on ART
- Symptom-directed laboratory monitoring for safety and toxicity can be used for those receiving ART.
- WHO Europe:
    - Liver function test: just prior to initiation, week 4, week 12, 1 year, every 3-6 months thereafter, every year

WHO HBV Perinatal Guidelines:

- It is recommended that the following be monitored at least annually:
    - ALT levels (and AST for APRI), HBsAg, HBeAg and HBV DNA levels (where HBV DNA testing is available)
    - Non-invasive tests (APRI score or FibroScan) to assess for the presence of cirrhosis, in those without cirrhosis at baseline;
    - If on treatment, adherence should be monitored regularly and at each visit (Strong recommendation, moderate quality of evidence)

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Geographic Definitions for Covariates

- South Africa (South Africa)
- Southern Africa (Zambia and Zimbabwe)
- Eastern Africa (Malawi, Tanzania, Uganda)
- India (India)

WHO HIV Perinatal Guidelines:

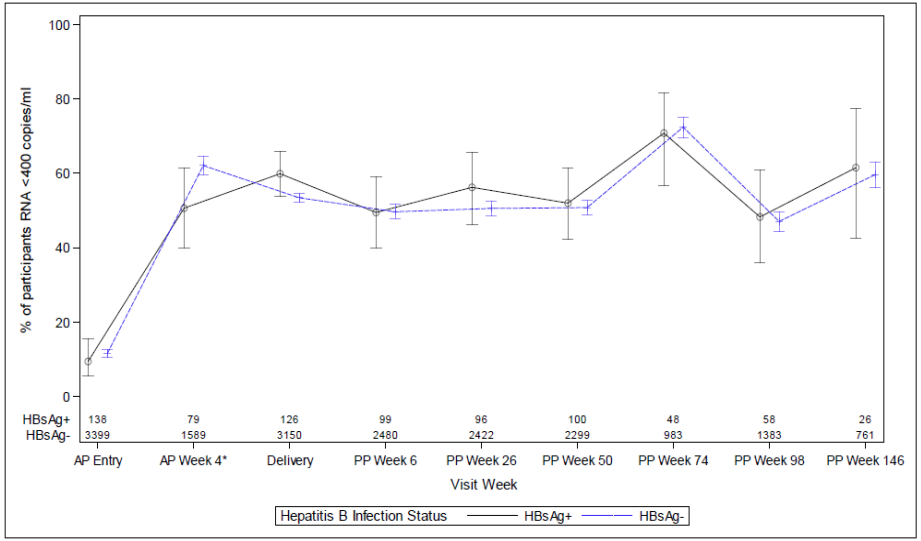
- HIV viral load test by six months and 12 months after initiating ART and every 12 months thereafter
- CD4 cell count every six months until established on ART

More detail:

- Routine viral load monitoring can be carried out by six months, at 12 months and then every 12 months thereafter if the person is established on ART to synchronize with routine monitoring and evaluation reporting (conditional recommendation, very-low-certainty evidence).
- In settings in which routine viral load monitoring is available, CD4 cell count monitoring can be stopped for individuals who are established on ART (conditional recommendation, low-certainty evidence)
- If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure (strong recommendation, moderate-certainty evidence).

Figure 2A/2B: HIV VL and CD4 Responses Over Time

Figure 2A: HIV VL Responses Over Time



** At AP Week 4, by the protocol, only mothers on Triple ARVs were tested for RNA in real time*
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Figure 2B: CD4 Responses Over Time

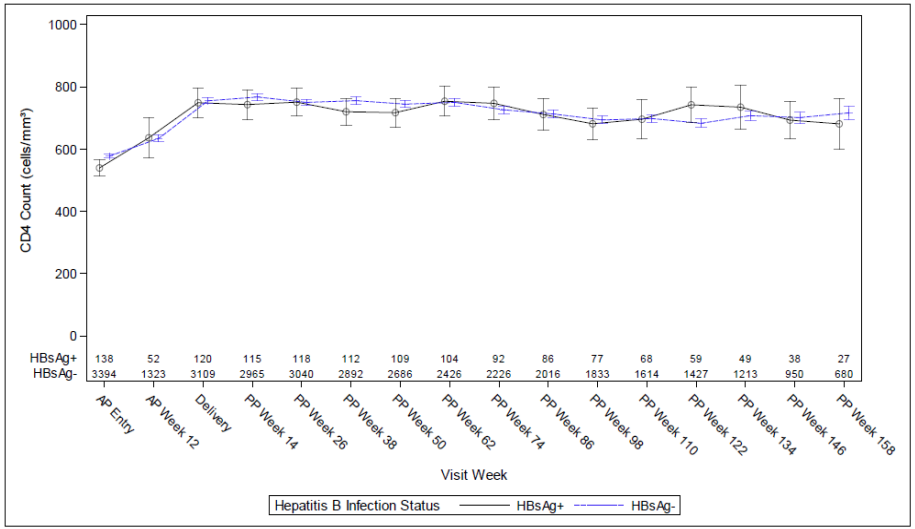

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Table 5b: ALT >19 Elevation Earlier in HIV/HBV Women

Hepatitis B Infection Status	Participants	Cumulative Events	Total person-years	Incidence Rate (95% CI) per 100 person-years	Hazard Ratio (95% CI), Logrank P-value HBsAg- (Ref) vs. HBsAg+
Time to ALT >19 (IU/L) Comparisons up to Delivery					
HIV/HBV	138	50	21.77	229.6 (179.1, 294.4)	3.25 (2.40, 4.30), <0.001
HIV	3399	494	736.65	67.1 (62.0, 72.6)	
Time to ALT >19 (IU/L) Comparisons					
HIV/HBV	138	121	47.9	252.6 (198.7, 321.2)	1.89 (1.57, 2.26), <0.001
HIV	3399	2697	2290.53	117.8 (111.9, 123.9)	

Figure 4A/4B: Time to ALT Comparisons

Figure 4A: Mean (95%) CI Maternal ALT from AP Randomization

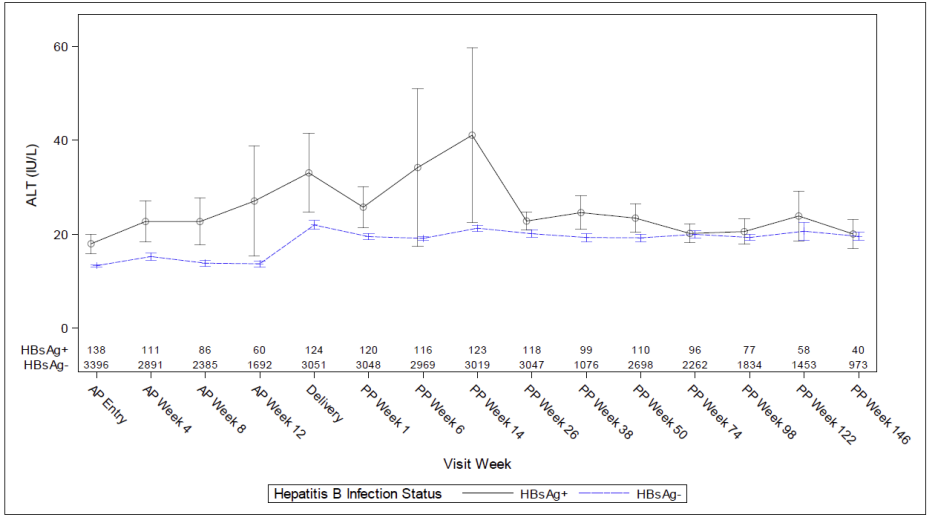

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Figure 4B: Mean (95%) CI Maternal ALT Change from BL from AP Randomization

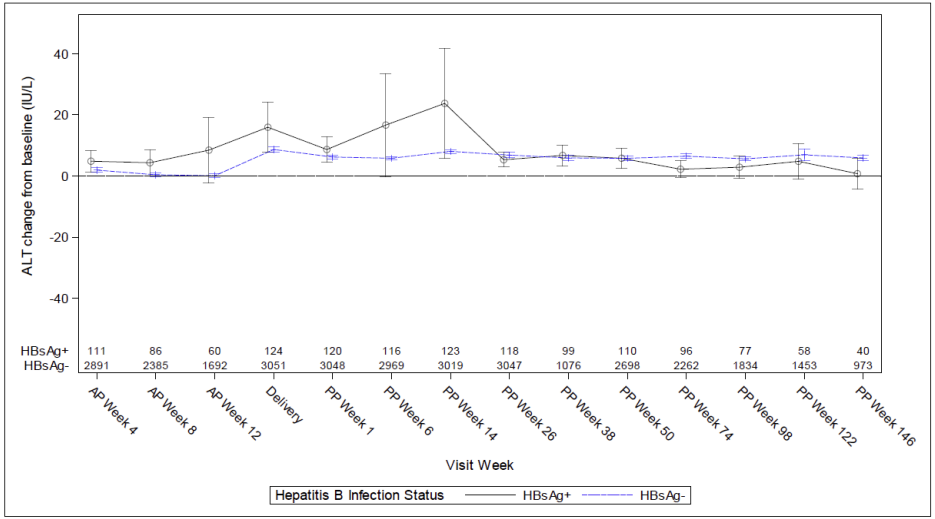

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Table 3: Maternal Grade 2, 3, or 4 Chemistries and Hematologies

	Hepatitis B Infection Status	
Toxicities	**HIV/HBV (N=138) Total**	**HIV (N=3399) Total**
Chemistries		
Any event	26 (19%)	254 (7%)
Any Liver/Hepatic, Chemistry	24 (17%)	236 (7%)
Any Renal, Chemistry	3 (2%)	16 (<0.5%)
Hematologies		
Any event	40 (29%)	834 (25%)
Any Hematology, Coagulation	5 (4%)	115 (3%)
Any Hematology, RBC	18 (13%)	367 (11%)
Any Hematology, WBC/Differential	23 (17%)	460 (14%)

In the above table each participant is counted once for the overall total.
For any given participant, the highest grade for each safety event is counted.

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Table 6: Comparisons of Maternal ALT Change from Baseline

		Hepatitis B Infection Status			Estimated Mean Difference (95% CI), P-value*
Study Visit Week	**ALT change from baseline (IU/L)**	**HIV/HBV (N=138)**	**HIV- (N=3399)**	**Total (N=3537)**	**HBsAg- (Ref) minus HBsAg+**
AP Wk 8	Mean (95% CI)	4.33 (0.08, 8.59)	0.39 (-0.29, 1.07)	0.53 (-0.14, 1.20)	3.95 (-0.36, 8.25), 0.072
Delivery	Mean (95% CI)	15.95 (7.85, 24.04)	8.67 (7.71, 9.63)	8.95 (7.98, 9.93)	7.28 (-0.87, 15.43), 0.080
PP Wk 6	Mean (95% CI)	16.65 (-0.22, 33.52)	5.80 (5.36, 6.25)	6.21 (5.45, 6.97)	10.85 (-6.03, 27.72), 0.21
PP Wk 14	Mean (95% CI)	23.73 (5.77, 41.70)	8.04 (7.40, 8.67)	8.65 (7.72, 9.58)	15.70 (-2.28, 33.68), 0.086
1 Year	Mean (95% CI)	5.80 (2.44, 9.16)	5.78 (4.95, 6.60)	5.78 (4.98, 6.58)	0.03 (-3.43, 3.48), 0.99
2 Years	Mean (95% CI)	2.87 (-0.75, 6.49)	5.61 (4.92, 6.30)	5.50 (4.82, 6.17)	-2.74 (-6.43, 0.95), 0.14

**2-sided, 2 sample T-test with unequal variances (Satterthwaite method)*

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Anemia

	HIV alone	HIV/HBV	Unadjusted[2] Comparisons(95% CI[1]) P-value	Adjusted Comparisons[3] (95% CI) P-value
Anemia (Hg<10ml g/dl) at Delivery[4]	23% (703/3045)	25% (31/125)	1.10 (0.70, 1.68) 0.67	1.10 (0.71, 1.66) 0.66

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No difference by treatment arm in HIV virologic suppression

Outcome Measure	Arm 1 vs. Arm2 (ref.)		Arm1: n/N (%)	Arm2: n/N (%)	Odds Ratio (95% CI)	p-value
Delivery HIV RNA <400 cp/ml	LPV/r+TDF/FTC vs LPV/r+ZDV/3TC	All	302/412 (73.3%)	1006/1462 (68.8%)	1.24 (0.98, 1.59)	0.080
		HBsAg+	31/45 (68.9%)	29/47 (61.7%)	1.37 (0.58, 3.29)	
		HBsAg-	271/367 (73.8%)	977/1415 (69.0%)	1.27 (0.98, 1.64)	
	LPV/r+TDF/FTC vs ZDV+sdNVP+TDF	All	302/412 (73.3%)	451/1402 (32.2%)	5.79 (4.54, 7.42)	
		HBsAg+	31/45 (68.9%)	16/34 (47.1%)	2.49 (1.00, 6.39)	
		HBsAg-	271/367 (73.8%)	435/1368 (31.8%)	6.05 (4.69, 7.88)	
	LPV/r+ZDV/3TC vs ZDV+sdNVP+TDF	All	1006/1462 (68.8%)	451/1402 (32.2%)	4.65 (3.98, 5.45)	
		HBsAg+	29/47 (61.7%)	16/34 (47.1%)	1.81 (0.74, 4.49)	
		HBsAg-	977/1415 (69.0%)	435/1368 (31.8%)	4.78 (4.08, 5.62)	

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No difference by treatment arm hepatotoxicity

	Outcome Measure	Arm 1 vs. Arm2 (ref.)		Arm1: n/N (%)	Arm2: n/N (%)	Hazard Ratio (95% CI)	p-value
Maternal	Time to Grade 3/4 ALT	LPV/r+TDF/FTC vs LPV/r+ZDV/3TC	All	14/445 (3.1%)	60/1545 (3.9%)	1.06 (0.57, 1.86)	0.65
			HBsAg+	5/48 (10.4%)	5/48 (10.4%)	1.08 (0.30, 3.89)	
			HBsAg-	9/397 (2.3%)	55/1497 (3.7%)	0.82 (0.38, 1.60)	
		LPV/r+TDF/FTC vs ZDV+sdNVP+TDF	All	14/445 (3.1%)	32/1547 (2.1%)	2.04 (1.05, 3.78)	
			HBsAg+	5/48 (10.4%)	1/42 (2.4%)	4.42 (0.71, 84.55)	
			HBsAg-	9/397 (2.3%)	31/1505 (2.1%)	1.50 (0.67, 3.06)	
		LPV/r+ZDV/3TC vs ZDV+sdNVP+TDF	All	60/1545 (3.9%)	32/1547 (2.1%)	1.92 (1.26, 2.98)	
			HBsAg+	5/48 (10.4%)	1/42 (2.4%)	4.08 (0.66, 78.11)	
			HBsAg-	55/1497 (3.7%)	31/1505 (2.1%)	1.83 (1.19, 2.87)	

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