Pharmacokinetics of Etravirine (ETR) in HIV-1–Infected Pregnant Women

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Introduction

- Highly active antiretroviral (ARV) therapy is recommended during pregnancy.[1] As pregnancy may impact the pharmacokinetics (PK) of drugs,[2] it is important to evaluate PK during pregnancy
  - There are limited data on etravirine (ETR) during pregnancy[3-5]; in 1 small study (n = 4), similar ETR PK were reported for the third trimester of pregnancy and in nonpregnant adults (historic controls)[3]

1. HHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission—A Working Group of the Office of AIDS Research Advisory Council (OARAC). http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed February 12, 2015.
2. Colbers A, et al. *Curr Opin Infect Dis*. 2013;26(6):575-588.4.):434-435
3. Izurieta P, et al. *HIV Med*. 2011;12(4):257-258.
4. Jaworsky D, et al. *Antivir Ther*. 2010;15(4):677-680.
5. Furco A, et al. *AIDS*. 2009;23(3):434-435.

Methods

- This is a phase IIIb, open-label trial to evaluate the PK of ETR 200 mg twice daily (bid)
  - Also assessed in the study were darunavir/ritonavir (bid and once daily [qd]) and/or rilpivirine (qd); a darunavir/cobicistat 800/150mg qd treatment arm is currently in development
- Primary objective
  - To compare ETR PK during the second and third trimesters of pregnancy and at 6 to 12 weeks postpartum
- Secondary objectives
  - To evaluate the antiviral activity, safety, and tolerability of ETR-based ARV regimens during gestation and postpartum
  - To compare ETR concentrations in maternal plasma vs cord blood samples (at delivery)
  - To assess infant outcomes

ClinicalTrials.gov Identifier: NCT00855335.

Study Population and Baseline Demographics

Subject characteristics	
Subjects, n	15
Subjects included in pharmacokinetic analysis, n	13
Subjects with data available for infants delivered, n	11
Age at screening, median (range), years	26 (20-34)
Race/ethnicity, n (%)	
White	2 (13)
Black or African American	11 (73)
Hispanic	2 (13)
BMI, median (range), kg/m^2	30 (23-47)
First pregnancy, n (%)	
Yes	3 (20)
No	12 (80)
Time since conception, median (range), days	153 (136-177)

- Five subjects discontinued treatment
  - One subject failed to meet all inclusion/exclusion criteria, 1 was noncompliant with study visits, and 3 were lost to follow-up
  - No subjects discontinued due to an adverse event (AE)

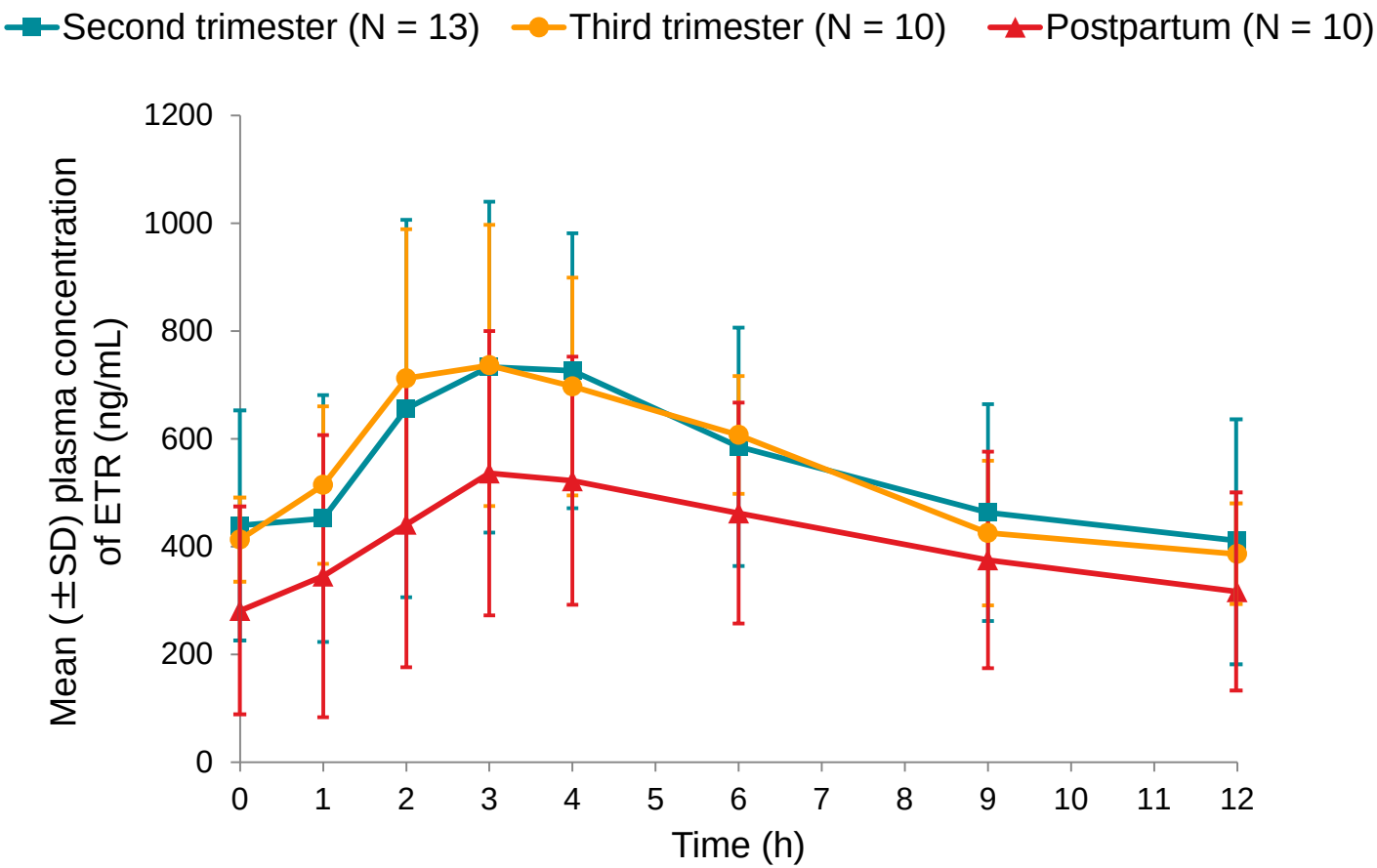
BMI, body mass index.

Baseline Disease Characteristics

Disease characteristics	
Time since HIV diagnosis, median (range), years	7 (0-20)
CD4+ count, cells/mm³, n (%)	
<50 cells/mm³	1 (7)
50 to <100 cells/mm³	1 (7)
100 to <200 cells/mm³	3 (20)
200 to <350 cells/mm³	2 (13)
≥350 cells/mm³	8 (53)
Viral load, copies/mL, n (%)	
<50 copies/mL	9 (60)
50 to <400 copies/mL	4 (27)
400 to <1000 copies/mL	1 (7)
≥1000 copies/mL	1 (7)
Previous ARV experience, n (%)	
PIs: 0	5 (33)
PIs: 1	6 (40)
PIs: ≥2	4 (27)
NNRTIs: 0	2 (13)
NNRTIs: 1	11 (73)
NNRTIs: ≥2	2 (13)
Therapies used at baseline, n (%)	
Abacavir + lamivudine	2 (13)
Emtricitabine + tenofovir	5 (33)
Lamivudine + zidovudine	8 (53)
PIs (lopinavir + low dose ritonavir)	1 (7)
Integrase inhibitor (raltegravir)	1 (7)

PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

Plasma Concentration-time Profiles of ETR After Administration of ETR 200 mg bid



- Individual cord/maternal plasma ratios of ETR ranged between 18.83% and 63.41% (median: 31.86%; n = 10)

SD, standard deviation.

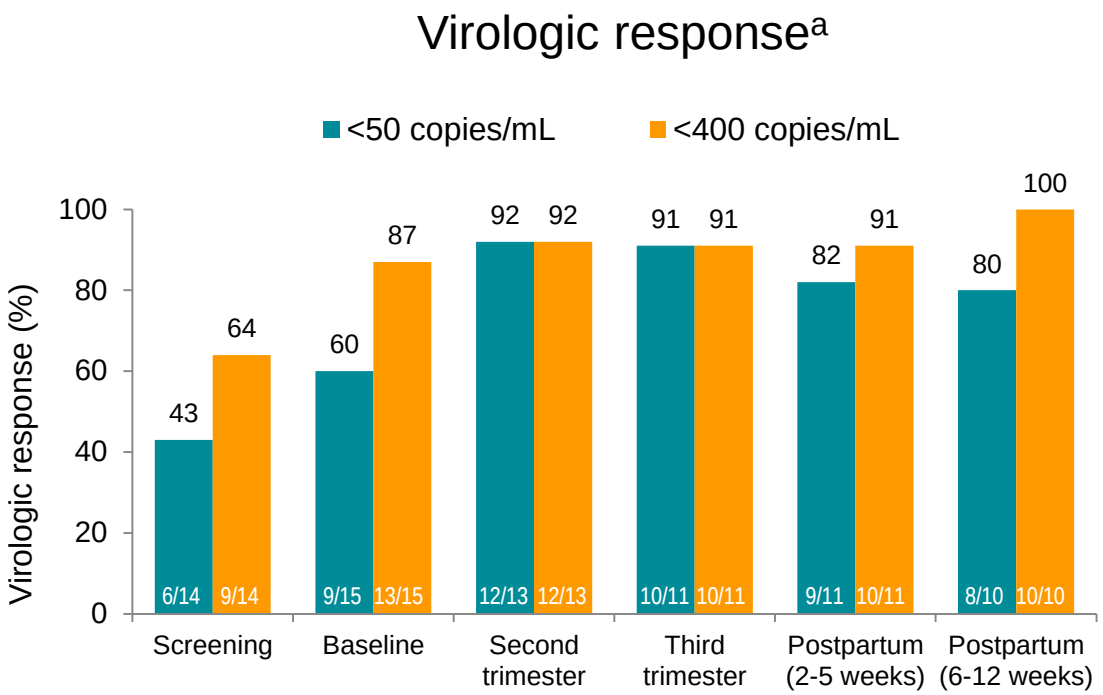
PK Parameters of ETR After Administration of ETR 200 mg bid

PK of ETR[a]	Second trimester	Third trimester	Postpartum
N	13	10	10
C_{0h}, ng/mL	439 ± 212	413 ± 78.2	281 ± 193
C_{min}, ng/mL	383 ± 210	352 ± 105	271 ± 183
C_{max}, ng/mL	774 ± 300	785 ± 238	569 ± 261
t_{max}, ng/mL[b]	3.05 (2.00-4.00)	3.00 (2.00-6.00)	4.00 (1.00-9.00)
AUC_{12h}, h•ng/mL	6616 ± 2766	6843 ± 1484	5002 ± 2520

- In general, ETR PK parameters were increased by ~1.4-fold in the second trimester vs postpartum, and by ~1.2- to 1.4-fold in the third trimester vs postpartum

C_{0h}, predose plasma concentration; C_{min}, minimum plasma concentration; C_{max}, maximum plasma concentration; t_{max}, time to reach the maximum plasma concentration; AUC_{12h}, area under the plasma concentration-time curve over 12 hours.
[a]Mean (±SD), except where indicated.
[b]Median (range).

Antiviral Response During Pregnancy and in the Postpartum Period



- CD4+ percentage increased slightly over time
- None of the 11 infants born during the study had a positive HIV test result

[a]The numbers in white font at the bottom of each bar represent n/N, where n is the number of subjects with the indicated viral load and N is the total number of subjects with data.

Safety Results

Preferred term	n (%)
Patients with ≥1 AE	12 (80)
Events occurring in ≥2 patients	
Nausea	3 (20)
Headache	3 (20)
Premature labor	3 (20)
Vomiting	2 (13)
Allergic rhinitis	2 (13)
Hypertension	2 (13)

- Four subjects experienced a serious AE; none were considered possibly related to ETR
  - One subject, premature rupture of membranes; 1 subject, hypertension; 1 subject, headache; 1 subject, pregnancy-induced hypertension (twice) and premature labor
- There were no significant laboratory abnormalities that led to discontinuation

Conclusions

- ETR exposures were higher during pregnancy vs postpartum; this increase was not considered clinically relevant
- The regimen was generally well tolerated[1]; no subjects discontinued due to an AE
- The antiviral activity of ETR during pregnancy was consistent with that observed in HIV-infected nonpregnant adults,[2] and there was no mother-to-child HIV transmission
- These data indicate that combination ARV therapy with ETR 200 mg bid may be a treatment option for HIV-infected pregnant women

- Please see poster Abst#_2 during the poster sessions

1. Katlama C, et al. *Antivir Ther*. 2010;15(7):1045-1052.
2. Clumeck N, et al. *Int J STD AIDS*. 2010;21(11):738-740.

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