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Contribution of different antiretroviral regimens containing zidovudine, lamivudine and ritonavir boosted lopinavir on HIV viral load reduction during pregnancy

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Abstract

Background—Antiretroviral (ARV) regimens used for the prevention of mother-to-child transmission of HIV (PMTCT) have evolved overtime. We evaluated the contribution of different ARV regimens on the reduction of the plasma HIV-RNA viral load (VL) during pregnancy.

Methods—A total of 1,833 VL measurements from ARV-naïve pregnant women participating in perinatal prevention trials in Thailand were included. Women received either (1) zidovudine (ZDV) monotherapy, (2) ZDV+lopinavir/ritonavir (LPV/r) or (3) ZDV+lamivudine (3TC)+LPV/r. VL time-course during pregnancy was described as a function of pre-treatment VL and treatment duration using an Emax non-linear mixed effect model. VL reduction and median time to achieve a VL<50 copies/mL were estimated for each regimen.

Results—Among 745 women, 279 (37%), 145 (20%) and 321 (43%) received ZDV monotherapy, ZDV+LPV/r, ZDV+3TC+LPV/r, respectively. The predicted VL reduction from baseline to delivery after a median of 10 weeks of treatment were 0.5, 2.7 and 2.9 log₁₀ copies/mL

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with ZDV monotherapy, ZDV+LPV/r and ZDV+3TC+LPV/r. At delivery, 1%, 57% and 63% of women receiving ZDV monotherapy, ZDV+LPV/r or ZDV+3TC+LPV/r had a VL<50 copies/mL. The addition of 3TC to ZDV+LPV/r reduced the time to achieve a VL<50 copies/mL and the higher the pre-treatment VL, the larger the impact 3TC had on reducing the time to VL<50 copies/mL.

Conclusion—The addition of 3TC to ZDV+LPV/r was associated with a slight further VL reduction but the time to reach a VL<50 copies/mL was shorter. This beneficial effect of 3TC is critical for PMTCT in women who receive ARVs late and with high pre-treatment VL.

Introduction

Antiretroviral (ARV) therapy during pregnancy dramatically reduces mother-to-child transmission of HIV (MTCT). It is thought that ARVs reduce perinatal HIV transmission through two complementary mechanisms: 1) reducing RNA viral load (VL) and therefore decreasing fetal/infant exposure to maternal viruses during pregnancy/delivery, and 2) providing pre/post-exposure prophylaxis to the fetus/infant if the drugs cross the placenta. Zidovudine (ZDV) monotherapy modestly reduces maternal VL [1] and may primarily work as pre/post62 exposure prophylaxis as it readily crosses the placenta [2]. The combination of ZDV with lamivudine (3TC) which also crosses the placenta, produces a more rapid and substantial decline in maternal VL which may explain its higher preventive effect [3,4]. Finally, protease-inhibitors (PIs) generally poorly cross the placenta and probably prevent MTCT essentially by reducing the maternal VL [5–7]. Very low rates of transmission have been reported in women with VL <50 copies/mL at delivery [8].

In this analysis, data from pregnant women who received either ZDV monotherapy (with/without single dose nevirapine (sdNVP) at onset of labor), ZDV+LPV/r, or ZDV+3TC+LPV/r (with/without sdNVP at onset of labor) were used to evaluate the effect of the addition of LPV/r to ZDV, and of 3TC to ZDV+LPV/r, on the VL reduction during pregnancy.

Material and methods

Data were collected from ARV-naïve pregnant women who participated in the PHPT-5 study in Thailand. Pregnant women received either ZDV monotherapy, or ZDV+LPV/r in the first phase of the PHPT-5 trial (NCT00409591) [9]; or ZDV+3TC+LPV/r in the second phase of the PHPT-5 trial (NCT01511237) [10]. Plasma HIV-RNA levels were assessed at baseline and during pregnancy using the Abbott m2000 RealTime® HIV-1 assay (Lower limit of quantification (LLQ), 40 copies/mL). VL time-courses were analysed through a non-linear mixed effect modelling approach (MONOLIX software v4.3.3, <http://www.lixoft.com/>) and parameters estimated using the stochastic approximation EM algorithm (SAEM) [11]. An Emax model was applied to determine the effect of each regimen on the VL time-course during pregnancy. The model equation was

$$VL = VL_0 - \left[\frac{E_{MAX} \times T}{T_{50} + T} \right]$$

where, T: duration of treatment; VL₀: pre-treatment VL; E_{max}: maximum VL reduction (log₁₀ ceps/mL); T₅₀: duration of treatment (days) corresponding to E_{max}/2 (i.e. the shorter the T₅₀ the faster the time to reach E_{max}). The effects of adding LPV/r to ZDV, and 3TC to ZDV+LPV/r, were assessed. CD4 cell counts and gestational age (GA) at ARVs initiation were also tested on model parameters.

Population parameters including covariates were expressed as below:

$$\begin{aligned} VL_{0,POP,COV} &= VL_{0,POP,REF} + \beta_{VL0,COV} COV, \\ E_{MAX,POP,COV} &= E_{MAX,POP,REF} \times \exp(\beta_{EMAX,COV} COV), \\ T_{50,POP,COV} &= T_{50,POP,REF} \times \exp(\beta_{T50,COV} COV), \end{aligned}$$

where *COV*: the covariate and β : the covariate effect on the parameters.

Inter-individual variability was modeled with η_i being the inter-individual random effect for subject *i* with mean 0 and variance ω^2 . Individual parameters including covariates were expressed as below:

$$\begin{aligned} VL_{0,COV,i} &= VL_{0,POP,REF} + \beta_{VL0,COV} COV + \eta_{i,VL0}; \quad \eta_{i,VL0} \sim N(0, \omega_{VL0}^2) \\ E_{MAX,COV,i} &= E_{MAX,POP,REF} \times \exp(\beta_{EMAX,COV} COV) \times \exp(\eta_{i,EMAX}); \quad \eta_{i,EMAX} \sim N(0, \omega_{EMAX}^2) \\ T_{50,COV,i} &= T_{50,POP,REF} \times \exp(\beta_{T50,COV} COV) \times \exp(\eta_{i,T50}); \quad \eta_{i,T50} \sim N(0, \omega_{T50}^2) \end{aligned}$$

The distributions of VL<LLQ were estimated using the SAEM extension algorithm [12]. The effect of a covariate on a structural parameter was retained if it produced acceptable relative standard error (RSE<50%) and a decrease in the Bayesian Information Criterion (BIC) compared to the covariate-free model [13]. VL time-courses were simulated from the final population model and compared with the observed data to evaluate the predictive performance of the model using visual predictive check (VPC) [14].

Simulations were performed to determine the time to reach a VL<50 copies/mL per regimen. Using the final population model, VL time-courses during pregnancy were predicted using different treatment durations and pre-treatment VL levels (2,000 replicates).

The PHPT-5 study received ethical clearance from the Thai Ministry of Public Health, the Harvard School of Public Health, and Chiang Mai University Faculty of Medical Associated Sciences Ethics Committees. All women provided written informed consent for their participation and that of their infants.

Results

Data from 745 HIV-infected pregnant women were included: 279 (37%) received ZDV monotherapy, 145 (20%) received ZDV+LPV/r and 321 (43%) received ZDV+3TC+LPV/r during pregnancy. The median (interquartile range, IQR) maternal VL values for the women who received ZDV monotherapy, ZDV+LPV/r and ZDV+3TC+LPV/r pre-treatment were 4.03 (3.50–4.49), 4.17 (3.56–4.51) and 4.29 (3.68–4.68) log₁₀ copies/mL, respectively;

while at delivery were 3.59 (3.06–4.05), <1.60 (<1.60–2.00) and <1.60 (<1.60–1.77) log₁₀ copies/mL; baseline CD4 cell counts were 458 (366–563), 454 (371–594) and 372 (265–461) cells/mm³; GA at treatment initiation were 29 (28–31), 28 (28–30) and 26 (19–33) weeks; GA at delivery were 39 (38–40), 39 (38–39) and 39 (38–40) weeks, respectively. Finally, the median durations of ZDV monotherapy, ZDV+LPV/r and ZDV+3TC+LPV/r were 71 (60–79), 70 (60–77) and 109 (51–155) days, respectively.

A total of 1,833 VL results from 745 women were available (98% 2 measurements). The Emax model described the VL time-course during pregnancy well and produced accurate parameter estimates. CD4 at baseline was associated with pre-treatment VL and retained in the model (Table 1).

Figure 1 shows a good fit between the VL data and model predictions. Using the final model, the predicted VL reductions from baseline to delivery after a median of 10 weeks of treatment were 0.5, 2.7 and 2.9 log₁₀ copies/mL with ZDV monotherapy, ZDV+LPV/r and ZDV+3TC+LPV/r, respectively. The percentage of women with a predicted VL<50 copies/mL at delivery were 1%, 57% and 63% after receiving ZDV monotherapy, ZDV+LPV/r or ZDV+3TC+LPV/r, respectively.

Simulations showed that women receiving ZDV+LPV/r achieved VL<50 copies/mL after a median of 7 (4–14) weeks and those receiving ZDV+3TC+LPV/r achieved VL<50 copies/mL after a median 6 (4–11) weeks (based on the observed pre-treatment VL of 4.11 log₁₀ copies/mL).

Finally, the model simulation shows that the addition of 3TC to ZDV+LPV/r reduces the time to achieve VL<50 copies/mL and that this reduction is proportional to the pre-treatment VL, i.e. the higher the pre-treatment VL, the larger the reduction in time to achieve a VL<50 copies/mL (Figure 2). For example, for women with a pre-treatment VL of 4.5 log₁₀ copies/mL, the addition of 3TC to ZDV+LPV/r would reduce the time to achieve a VL<50 copies/mL by 3 weeks (i.e. from 12 to 9 weeks), while for women with pre-treatment VL of 3.5 log₁₀ copies/mL it would only reduce the time to achieve a VL<50 copies/mL by 1 week.

Discussion

We modelled the VL reduction and the time to achieve VL<50 copies/mL for three different ARV regimens during pregnancy. The maximum reduction in VL was modest with ZDV monotherapy but significantly larger with the addition of LPV/r. The addition of 3TC to ZDV+LPV/r was associated with a significant but slight additional VL reduction. Furthermore, the addition of 3TC to ZDV+LPV/r reduced the time to achieve a VL<50 copies/mL. The impact that 3TC had on reducing the time to a VL<50 copies/mL was greater when the pre-treatment VL was higher.

A study limitation is that women's adherence to ARVs was not taken into account. Adherence was measured by pill count at each visit and did not differ according to study treatments [9, 10]. Also, since women were ARV-naïve and ARVs prophylaxis was short

(median 70 days for ZDV and ZDV+LPV/r, and 109 days for ZDV+3TC+LPV/r), we assumed the absence of resistant mutations.

In the PRIMEVA trial comparing LPV/r monotherapy with ZDV+3TC+LPV/r for PMTCT, LPV/r monotherapy reduced the VL below 50 copies/mL at delivery in 78% of the women, compared to 97% with ZDV+3TC+LPV/r ($p=0.01$) [15]. Using the same VL<50 copies/mL threshold in our study, 63% of women who received ZDV+3TC+LPV/r had VL<50 copies/mL at delivery. However, the median pre-treatment VL in our study, 4.11 log₁₀ copies/mL, was higher than the 3.3 log₁₀ copies/mL in the PRIMEVA trial. Our results are consistent with those of the MONARK study in which 70% of naïve adult patients receiving ZDV+3TC+LPV/r had VL<50 copies/mL after 16 weeks of treatment [16]. For ZDV+LPV/r, our model predicts that 57% of women would have VL<50 copies/mL at delivery, consistent with the results from the PHPT-5 pharmacokinetic substudy [17].

In the ANRS-075 study [4] initiating ZDV at 23 weeks and adding 3TC at 32 weeks of gestation, VL reduction at delivery was 1.24 log₁₀ copies/mL. In our study, adding 3TC at the same time as initiating ZDV+LPV/r for a 10-week treatment duration, produced a modest but significant VL reduction (2.9 log₁₀ copies/mL vs. 2.7 without 3TC). In a study by Read *et al.* investigating the optimum timing of short-term cARV in pregnancy [18], the estimated duration to achieve VL<50 copies/mL appeared longer than in our study; however, the study analyzed various databases, with women receiving different ARV regimens (including NNRT-based) during pregnancy, a quarter of them having previously received cARV, and/or having baseline resistance mutations.

Given the time needed to reach VL<50 copies/mL, our results also support early initiation of cARV during pregnancy [19]. However, early initiation of PIs-based regimens for MTCT has been associated with preterm birth [20] therefore the risks/benefits of early PMTCT have to be considered. Although VL reduction is not the only mechanism involved in PMTCT, our results support the use of cARV including PI plus two NRTI in pregnant women with high pre-treatment VL. The addition of 3TC to ZDV+LPV/r associated with a slight further VL reduction but shortened the time to reach a VL<50 copies/mL; thus, the beneficial effect of 3TC may be critical for PMTCT in women with high pre-treatment VL and/or who start ARVs late during pregnancy.

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Figure 1.

Visual predictive check plots. The solid lines denote the median, 5th and 95th percentiles of the observed data. The grey areas represent the 95% confidence intervals of the median, 5th and 95th percentiles of the model prediction. Abbreviations: ZDV, zidovudine; LPV/r, lopinavir/ritonavir; 3TC, lamivudine.

Figure 2. Median treatment duration (weeks) to achieve viral load <50 copies/mL according to different viral load at baseline with 2000 replicates of simulations. Abbreviations: ZDV, zidovudine; LPV/r, lopinavir/ritonavir; 3TC, lamivudine. Dash and solid, lines stand for ZDV+LPV/r and ZDV+LPV/r+3TC therapies respectively.

Table 1

Population parameters of HIV time-course model for 745 HIV-infected pregnant women enrolled in PHPT-5 first and second phase studies.

Parameters	Estimate	SE	RSE (%)	P-value ^a
<i>Structural model</i>				
VL ₀ , log ₁₀ copies/mL	4.78	0.083	2	
$\beta_{VL0,CD4}$	0.519	0.055	11	<0.001
T ₅₀ , days	34	2.3	7	
E _{MAX} , ZDV+LPV/r	4.01	0.13	3	
E _{MAX,ZDV}	0.70	0.014	2	<0.001
E _{MAX,ZDV+3TC+LPV/r}	4.42	0.066	1	0.003
<i>Statistical model</i>				
$\omega_{\eta_{VL0}}$	0.588	0.024	4	
$\omega_{\eta_{T50}}$	0.745	0.055	7	
$\omega_{\eta_{EMAX}}$	0.046	0.007	15	
σ_{VL}	0.487	0.016	3	

Abbreviations: SE, standard error; RSE (%), relative standard error (standard error of estimate/estimate*100); VL₀, estimated viral load before treatment initiation; $\beta_{VL0,CD4}$, effect of CD4 to parameter VL₀, $VL_0 = 4.78 \times (CD4/100)^{-0.519}$; T₅₀, treatment duration corresponding to half of maximum effect in days; ZDV, zidovudine; LPV/r, lopinavir/ritonavir; E_{MAX}, ZDV+LPV/r, E_{MAX,ZDV}, E_{MAX,3TC+ZDV+LPV/r}, maximum treatment effects in log₁₀ copies/mL; $\omega_{\eta_{VL0}}$, $\omega_{\eta_{T50}}$ and $\omega_{\eta_{EMAX}}$, the variability corresponding to interindividual random effect of VL₀, T₅₀ and E_{max} (square roots of variances) and σ_{VL} , residual (square roots of variances)

^a Likelihood ratio test