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Effect of 7 days of phenytoin on the pharmacokinetics of and the development of resistance to single-dose nevirapine for perinatal HIV prevention: a randomized pilot trial

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Objectives: To confirm whether 7 days of phenytoin, an enzyme inducer, would decrease the elimination half-life of single-dose nevirapine and to investigate its effect on the development of nevirapine resistance in pregnant, HIV-infected women.

Methods: In a pharmacokinetic pilot trial (NCT01187719), HIV-infected, antiretroviral (ARV)-naive pregnant women ≥ 18 years old from Zambia and Tanzania and with CD4 cell counts >350 cells/mm³ were randomized 1:1 to a control (zidovudine pre-delivery, single-dose nevirapine/zidovudine/lamivudine at delivery and zidovudine/lamivudine for 7 days post-delivery) or an intervention (control plus 184 mg of phenytoin once daily for 7 days post-delivery) group. Primary endpoints were the pharmacokinetics of and resistance to nevirapine.

Results: Thirty-five and 37 women were allocated to the control and intervention groups, with median (IQR) ages of 27 (23–31) and 27 (23–33) years, respectively. Twenty-three and 23 women had detectable nevirapine levels at delivery and subsequent samples in the control and the intervention groups, respectively. Geometric mean (GM) (95% CI) plasma levels of nevirapine at delivery were 1.02 (0.58–1.78) mg/L and 1.14 (0.70–1.86) mg/L in the control and intervention groups, respectively ($P=0.76$). One week after delivery, 0/23 (0%) and 15/22 (68%) control and intervention mothers, respectively, had undetectable levels of nevirapine (<0.05 mg/L; $P<0.001$). One week later, the figures were 10/21 (48%) and 18/19 (95%) mothers, respectively ($P=0.002$). The GM (95% CI) half-life of nevirapine was 63.2 (52.8–75.7) versus 25.5 (21.6–30.1) h in the control group versus the intervention group ($P<0.001$). New nevirapine mutations were found in 0/20 (0%) intervention-group mothers versus 1/21 (5%) control-group mothers. Overall, there was no difference in adverse events reported between the control and intervention arms ($P>0.28$).

Conclusions: Adding 7 days of an enzyme inducer to single-dose nevirapine to prevent mother-to-child transmission of HIV significantly reduced subtherapeutic nevirapine levels by shortening the half-life of nevirapine. As prolonged subtherapeutic nevirapine dosage leads to the emergence of resistance, single-dose nevirapine could be used with phenytoin as an alternative if other ARVs were unavailable.

Keywords: prevention of mother-to-child transmission of HIV, Africa, PK, nevirapine

Introduction

While the risk of HIV mother-to-child transmission (MTCT) is 20%–40% without treatment,^{1,2} a simple cheap intervention—single-dose nevirapine at the onset of labour—reduces MTCT by

~50%.^{1,3} Its major disadvantage is the development of nevirapine resistance in both mothers (1%–69%) and infants,⁴ most probably due to its long elimination half-life (61 h),^{5–7} which leads to several days to weeks of subtherapeutic plasma concentrations, coupled with its low genetic barrier to resistance.⁸ Newly emergent

resistant HIV may be transmitted to the infant or to others, limiting their treatment options, and may also reduce the efficacy of future combination antiretroviral therapy (cART) in the mother.⁹

Given its simplicity and efficacy, single-dose nevirapine is nevertheless still endorsed by the WHO as part of the regimen for prevention of MTCT (pMTCT) in resource-limited settings, when cART (WHO Option B/B+) is not feasible or not available. To cover the prolonged presence of subtherapeutic plasma concentrations of nevirapine after single-dose nevirapine at the onset of labour, Option A of the WHO (2012) guidelines recommend adding zidovudine/lamivudine for 7 days post-partum.^{10,11} This approach reduces the development of resistance to 4%–16%,⁴ but does not fully eliminate it.

Nevirapine is extensively metabolized in the liver by cytochrome P450 (CYP) isoenzymes 3A4 and 2B6.¹² A pharmacological, rather than antiretroviral (ARV), approach of adding a CYP3A4 enzyme inducer has been shown to decrease the elimination half-life of nevirapine in healthy women,¹³ the greatest reductions being seen with carbamazepine and phenytoin. In our previous trial (VITA-1), the addition of single-dose carbamazepine to single-dose nevirapine at the onset of labour also significantly reduced plasma concentrations of nevirapine 1 week after delivery in HIV-infected women, with a trend towards fewer resistance mutations.¹⁴

The CYP3A4 enzyme inducer phenytoin is a low-cost, widely available anticonvulsant and antiarrhythmic drug, which is not secreted into breast milk in clinically important amounts (in contrast to carbamazepine) and can therefore be safely given to breastfeeding mothers.¹⁵ In this pilot study, we investigated the impact of 7 days of phenytoin on the pharmacokinetics of and development of resistance to nevirapine after single-dose nevirapine as a component of ARV prophylaxis for pMTCT (the VITA-2 trial). The hypothesis was that 7 days of phenytoin would reduce the elimination half-life of nevirapine and hence the emergence of nevirapine resistance mutations.

Methods

Study participants

Participants were recruited from the Pasua and Majengo antenatal clinics in Moshi, Tanzania, and the University Teaching Hospital in Lusaka, Zambia. Eligible HIV-infected pregnant women were aged ≥ 18 years, ARV-naive, starting ARV prophylaxis for pMTCT, not intending to relocate during study participation and willing to attend follow-up visits. Exclusion criteria were serious illness requiring systemic treatment or hospitalization, the use of concomitant medication that might interfere with ARVs or phenytoin, or a CD4 cell count < 350 cells/mm³ (making the women eligible for cART). All the women gave written informed consent; illiterate patients gave oral consent documented by their own thumbprint and a witness. The study was approved by the institutional review boards of the Kilimanjaro Christian Medical University College, Moshi, Tanzania, the National Institute of Medical Research in Dar es Salaam, Tanzania, and the University Teaching Hospital, Lusaka, Zambia. The study is registered with <http://ClinicalTrials.gov> (NCT01187719).

Eligible women received pMTCT ARV prophylaxis as recommended by national Tanzanian or Zambian guidelines. Subjects started 300 mg of zidovudine twice daily from 28 and 14 weeks of gestation in Tanzania and Zambia, respectively, or as soon as possible thereafter pre-delivery. At the onset of labour, women received 200 mg of single-dose nevirapine plus 300 mg of oral zidovudine every 3 h and 150 mg of lamivudine every 12 h until delivery (Tanzania), or 600 mg of oral zidovudine and 300 mg of lamivudine every 12 h until delivery (Zambia). Post-delivery, 300 mg of zidovudine and 150 mg of lamivudine were taken twice daily for 7 days.

Newborns were given 2 mg/kg single-dose nevirapine suspension within 24–72 h after birth and then 4 mg/kg zidovudine syrup (Tanzania) or 2 mg/kg nevirapine suspension (Zambia) twice daily for 7 days. All the women in the trial breastfed their children for 6 months and then weaned them rapidly.

Women were randomized 1:1 in a parallel group design to either the national standard of care or the national standard of care plus 184 mg of phenytoin (2 \times 92 mg tablets) once daily from the onset of labour for 7 days. The randomization sequence was generated by a trial statistician from the MRC using simple randomization blocks. Participant codes and allocations were held in secure envelopes stored by the project manager at each site. At enrolment (pre-delivery), women were randomized by the study doctor at the clinic by opening the next envelope. When the woman presented in labour at the clinic, a study nurse confirmed and recorded the time of ingestion of the study drug(s) by direct observation of intake or by asking the woman if she had already taken the study drug(s) at home.

Objectives, outcomes and follow-up

The primary objectives of the pilot study were to determine the effect of 7 days of phenytoin administration on the elimination half-life of nevirapine and the development of nevirapine resistance in HIV-infected, pregnant women receiving single-dose nevirapine as part of perinatal HIV prevention. The primary outcomes were the pharmacokinetic parameters of nevirapine (elimination half-life and time to achieve an undetectable plasma concentration) and nevirapine resistance (primary nevirapine mutations L100I, K101P, K103N/S, V106A/M, V108I, Y181C/I, Y188C/L/H and G190A)¹⁶ at week 4–6. Secondary outcomes were all adverse events (AEs) possibly or probably related to pMTCT ARV prophylaxis or phenytoin, and HIV infection of the infant.

Haematology and biochemistry tests were performed at enrolment and 1 week post-partum. CD4 cell counts and viral load (VL) were assayed at delivery. Infants were tested just after birth (< 30 min) and at week 4–6 by DNA PCR assays. Blood was taken from the women and stored at delivery and days 1, 3, 5, 7 and 14 post-partum, and from the children at delivery and on day 7 post-delivery for the retrospective determination of plasma concentrations of nevirapine (and phenytoin) at the Department of Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. The nevirapine assay used HPLC with a lower limit of quantification (LLOQ) of 0.05 mg/L,¹⁷ and phenytoin was determined by a validated immunoassay with an LLOQ of 0.4 mg/L. Nevirapine resistance was assayed in plasma stored from samples at baseline and at week 4 in Tanzania and week 6 in Zambia at the Department of Virology of the University Medical Centre Utrecht, Utrecht, The Netherlands. Pharmacokinetic and resistance assays were performed blinded to randomized allocation.

The sample size of 50 subjects (25 per arm) delivering in the study clinic provided $> 80\%$ power to detect a decrease of at least 27% in the elimination half-life of nevirapine associated with 7 days of phenytoin, allowing a 20% drop-out rate (lack of follow-up samples, based on experience from the VITA-1 trial).¹⁴

Safety analyses included all women who were observed or reported taking study medication (the safety population). Analyses of pharmacokinetics and resistance included the safety population who did not receive a second dose of nevirapine, who delivered vaginally [rather than by caesarean section (C/S)] and who had pharmacokinetic evidence (a detectable plasma concentration 1 day post-delivery) of taking nevirapine, and phenytoin if this had been allocated (the protocol-specified primary pharmacokinetic population). Analyses were also carried out that included mothers who delivered by C/S, as no difference in pharmacokinetic parameters had been observed between C/S and vaginal deliveries in the VITA-1 trial. Women in the control group with phenytoin detected in any sample were excluded from the pharmacokinetic and resistance analyses. Pharmacokinetic analysis was performed using Phoenix 64 WinNonlin 6.3 (Pharsight

Corporation, CA, USA) and statistical analysis using SPSS version 18.0 (SPSS Inc.). Randomized groups were compared using *t*-tests for continuous pharmacokinetic variables [after transformation to the log scale, i.e. comparing geometric means (GMs)], rank-sum tests for all other continuous variables and exact tests for categorical variables.

Results

Study participants

We screened 335 HIV-infected, pregnant women from July 2010 to June 2011; most of the 262 women not randomized were already

on cART (*n* = 94), had a CD4 cell count <350 cells/mm³ (*n* = 82) or did not return after screening (*n* = 56) (Figure 1). Seventy-three (22%) women were randomized: 35 and 37 were allocated to the control and intervention groups, respectively. One woman had been randomized twice, so the second randomization was excluded and the woman followed the first randomization. The demographic characteristics at enrolment and delivery were generally reasonably balanced between the two groups [Table 1 and Table S1 (available as Supplementary data at JAC Online)], the main difference being the significantly shorter time from nevirapine ingestion to delivery in the intervention group, which must

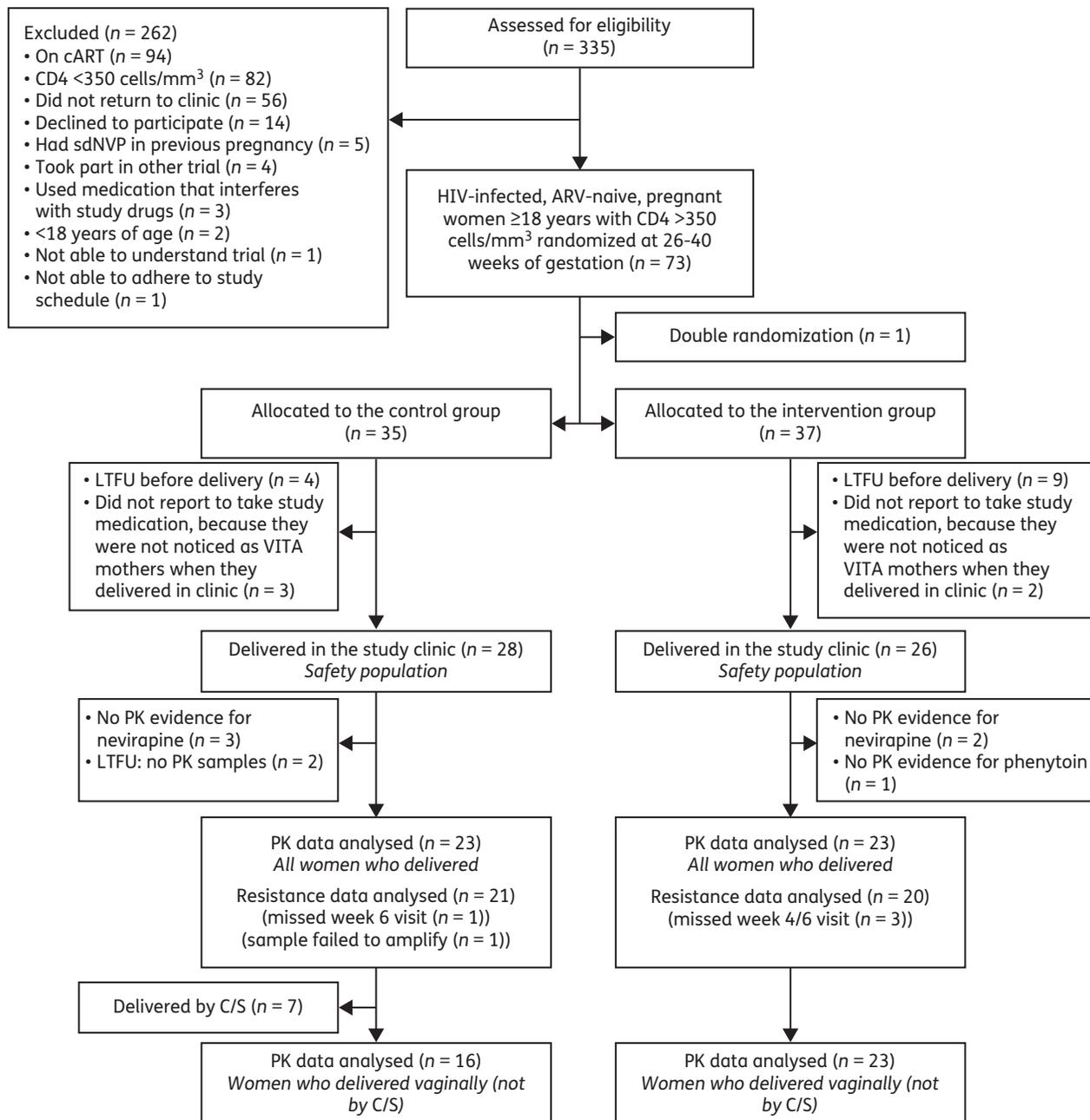


Figure 1. Profile of the VITA-2 trial (CONSORT diagram). sdNVP, single-dose nevirapine; LTFU, lost to follow-up; PK, pharmacokinetic.

Table 1. Demographic characteristics of the women and infants in the VITA-2 trial

	Control (n=28)	Intervention (7 days of phenytoin; n=26)	P value
At enrolment			
age (years)	27 (23–31)	27 (23–33)	0.74
weight (kg)	62 (55–73)	66 (56–81)	0.11
BMI (kg/m ²)	24.1 (21.7–27.9)	26.2 (23.3–30.9)	0.10
At delivery			
gestational age at delivery (weeks)	39 (38–42)	39 (38–41)	0.78
CD4 cell count (cells/mm ³)	366 (318–522)	412 (317–518)	0.76
HIV-1 RNA (copies/mL)	2832 (1000–26518)	2420 (1542–11261)	0.99
birth weight (kg)	3.0 (2.7–3.2)	3.0 (2.7–3.4)	0.87
time from nevirapine ingestion to delivery (h)	9.1 (2.5–12.6)	2.1 (1.0–4.9)	0.003

Data are presented as median (IQR) and were tested using rank-sum.

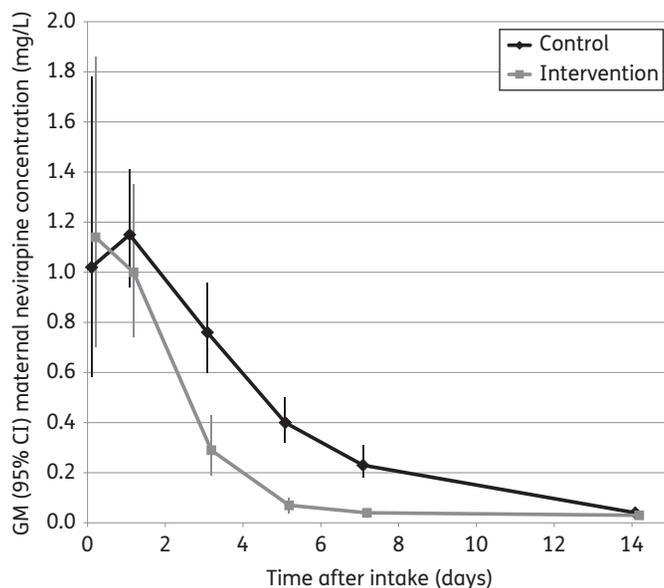


Figure 2. GM plasma concentrations of nevirapine over time post-delivery (all women who delivered including those who delivered by C/S).

have occurred by chance. This difference is, however, not expected to have had an impact on our pharmacokinetic data, as the elimination half-life of nevirapine is long. In addition, no differences were observed between the laboratory values at enrolment and delivery within either group (Table S1). The study finished once the recruitment target had been met.

Pharmacokinetics

At delivery, considering only the women who delivered vaginally (and not by C/S), there was no significant difference in plasma concentration of nevirapine between the two groups [GM (95% CI) was 1.08 (0.63–1.84) mg/L in the control patients versus 1.14 (0.70–1.86) mg/L in the intervention patients; GM ratio (GMR) (90% CI) 1.05 (0.58–1.92), $P=0.82$; t -test] (see Table S2, available as Supplementary data at JAC Online). Plasma concentrations of nevirapine subsequently decreased significantly more quickly

(Figure 2), and undetectable levels were reached significantly earlier (Table 2), in the intervention group compared with the control group. All results were similar, including women who delivered by C/S, so results from the (larger) group including women who delivered by C/S are subsequently presented.

One week post-delivery, plasma concentrations of nevirapine were reduced in both groups, but to a significantly lesser extent in the control group [GMR (1 week:delivery) (90% CI) 0.22 (0.18–0.28), 20 matched pairs] than the intervention group [GMR (1 week:delivery) (90% CI) 0.031 (0.026–0.038), 22 matched pairs]. Overall, levels were 85% lower in the intervention than the control group [GMR (intervention:control) (90% CI) 0.15 (0.11–0.20), $P<0.001$; t -test]. The GM (95% CI) elimination half-life of nevirapine was 63.2 (52.8–75.7) versus 25.5 (21.6–30.1) h in the control and the intervention group, respectively ($P<0.001$; t -test), representing a 60% reduction [GMR (90% CI) 0.40 (0.33–0.49)]. The GM (95% CI) time to achieve an undetectable nevirapine plasma concentration was 16.3 (13.8–19.3) versus 6.7 (5.7–7.8) days in the control versus the intervention group ($P<0.001$; t -test). Consequently, a significantly greater proportion of control group women had detectable plasma levels of nevirapine at 1 week and 2 weeks post-delivery (Table 2). All 23 (100%) women in the control group versus 7/22 (32%) women in the intervention group had a detectable plasma concentration of nevirapine at 1 week post-delivery ($P<0.001$; exact test) as did 11/21 (52%) women in the control group versus 1/19 (5%) women in the intervention group at 2 weeks post-delivery ($P=0.002$; exact test).

The median (range) plasma concentration of phenytoin in all the samples taken from delivery to 1 week post-delivery in the intervention group was 1.5 (<0.4–24.7) mg/L. Twenty-one of 22 (95%) mothers had only subtherapeutic phenytoin levels (the therapeutic range being defined as 10–20 mg/L).¹⁸ One (5%) mother had an undetectable plasma concentration at delivery, but her plasma level was detectable on day 1 and increased to 24.7 mg/L 1 week post-delivery. The median plasma level of phenytoin in the infants was <0.4 (range <0.4–1.9) mg/L.

Resistance

Samples taken 4–6 weeks post-delivery were available from 21 control women (as one missed the week 6 visit, and for one

Table 2. Maternal nevirapine plasma concentrations at delivery, week 1 and week 2 for women in the VITA-2 trial, including women who delivered by C/S

	Women who delivered, including women who delivered by C/S			
	control	intervention	P value	GMR (90% CI)
At delivery				
samples taken, <i>n</i>	20	22		
nevirapine plasma concentration (mg/L), GM (95% CI)	1.02 (0.58–1.78)	1.14 (0.70–1.86)	0.76 ^a	1.12 (0.61–2.03)
<0.05 mg/L nevirapine, <i>n</i> (%)	1 (5)	1 (5)		
1 week after delivery				
samples taken, <i>n</i>	23	22		
nevirapine plasma concentration (mg/L), GM (95% CI)	0.23 (0.18–0.31)	0.035 (0.027–0.046)	<0.001 ^a	0.15 (0.11–0.20)
<0.05 mg/L nevirapine, <i>n</i> (%)	0 (0)	15 (68)	<0.001 ^b	
women with 1 week and delivery samples, <i>n</i>	20	22		
nevirapine plasma concentration 1 week:delivery, GMR (90% CI)	0.22 (0.18–0.28)	0.031 (0.026–0.038)		
2 weeks after delivery				
samples taken, <i>n</i>	21	19		
nevirapine plasma concentration (mg/L), GM (95% CI)	0.044 (0.031–0.062)	0.026 (0.024–0.029)	0.006 ^a	0.59 (0.44–0.80)
<0.05 mg/L nevirapine, <i>n</i> (%)	10 (48)	18 (95)	0.002 ^b	
women with week 2 and delivery samples, <i>n</i>	18	18		
nevirapine plasma concentration 2 weeks:delivery, GMR (90% CI)	0.030 (0.026–0.034)	0.022 (0.015–0.031)		

Median nevirapine plasma concentrations are similar to the GM and are therefore not shown in Table 2.

^at-test.

^bExact test.

woman sample amplification failed due to a low VL) and 20 intervention women (as three missed the week 4–6 visit). One (5%) of the 21 women in the control group had one nevirapine-associated resistance mutation (elimination half-life 123.5 h) that had not been present at baseline, versus 1/20 (5%) with one nevirapine-associated resistance mutation in the intervention group. However, the mutation in the patient from the intervention group was already present in a sample stored at delivery. Both mutations were detected as mixtures with the wild-type nucleotide sequence (V106MV in the control group, and K103KN in the intervention group).

Safety

The 28 control and 26 intervention mothers gave birth to 30 (two pairs of twins) and 28 (two pairs of twins) babies, respectively. Twenty-one (one pair of twins) and 19 (one pair of twins) infants, respectively, were tested just after birth and at week 4–6 post-delivery. The overall transmission rate was 0/21 (0%) in the control group and 1/19 (5%) in the intervention group. However, the infected child tested positive at birth and must therefore have been infected during the intrauterine period. In the infants, 10 clinical AEs were reported: four in the control group (*n*=1 grade 1, *n*=1 grade 2 and *n*=2 grade 4) and six in the intervention group (*n*=1 grade 1, *n*=1 grade 2, *n*=1 grade 3 and *n*=3 grade 4). The grade 4 AEs were a hospitalization for overweight after birth and a death just after birth due to congenital malformation in the control group, and three stillbirths (two fresh and one macerated) in the intervention group.

Both platelet (*P*<0.001) and alanine transaminase (*P*<0.001) levels increased significantly between enrolment and 1 week post-delivery in each randomized group, but there was no difference between randomized groups in any laboratory safety parameter 1 week post-delivery (*P*>0.05). In total, 29 laboratory AEs were reported: *n*=14 in the control group versus *n*=15 in the intervention group (*P*=1.0; exact test). Most were grade 1 (*n*=11 in each group), but four (*n*=2 in each group) were grade 2, one was grade 3 (intervention) and two were grade 4 (haemoglobin <6.5 g/dL; one in each group). Eight clinical AEs were reported: three in the control group [*n*=1 grade 2, *n*=1 grade 3 and *n*=1 grade 4 (an emergency C/S)] and five in the intervention group (*n*=1 grade 1, *n*=3 grade 2 and *n*=1 grade 3). None of the laboratory and clinical AEs in the mothers or infants was judged possibly or probably related to the study medication.

Discussion

Here we demonstrate that adding a 7 day course of phenytoin, as an enzyme inducer, from the onset of labour produces a large and significant reduction in the elimination half-life of nevirapine in HIV-infected, pregnant women using single-dose nevirapine as part of their pMTCT ARV prophylaxis. Seven days of phenytoin administration was safe and effective, with no new nevirapine resistance mutations observed.

Importantly, plasma concentrations of nevirapine at delivery were similar in those receiving and not receiving phenytoin, and also comparable to those in reported previous studies,^{5,13} similar to our previous study evaluating a single dose of carbamazepine as an enzyme inducer.¹⁴ The time lag in enzyme inducer effect

reflects the time required for transcription of CYP enzymes and protein synthesis. The delay in enzyme induction and the fact that phenytoin minimally penetrates into breast milk therefore ensures that the protective perinatal effect of single-dose nevirapine is maintained. The absence of HIV transmission during the post-partum period, similar to or even lower than rates in previous studies,¹⁰ also confirms the efficacy of the pMTCT regimen.

Post-delivery, the pharmacokinetic parameters of nevirapine were substantially affected by enzyme induction. Adding phenytoin to single-dose nevirapine reduced plasma levels of nevirapine by 85% and produced a significantly larger proportion of women with undetectable nevirapine levels 1 week and 2 weeks post-delivery. Both effects are a consequence of the 60% reduction in the elimination half-life of nevirapine, an absolute difference of 35.8 h. This is the largest decline in elimination half-life of nevirapine ever reported, especially in the target population of HIV-infected, pregnant women. For example, the pilot study of L'Homme *et al.*¹³ found a median elimination half-life reduction of 38% (−19.4 h) in four healthy Dutch women receiving single-dose nevirapine with 7 days of phenytoin administration, and a single-dose of carbamazepine reduced nevirapine levels by 36% in HIV-infected, pregnant women receiving single-dose nevirapine.¹⁴ Not surprisingly, a 7 day course of an enzyme inducer has a greater effect than a single dose alone on the elimination half-life of nevirapine in HIV-infected, pregnant women.

The mechanisms by which the CYP enzymes are induced involves the transcription factors pregnane X receptor and the constitutive androstane receptor. The enzyme inducer binds to these receptors, thereby stimulating activation of the CYP enzyme.¹⁹ Studies have shown that CYP enzyme induction is correlated with dose and drug level,²⁰ with higher doses and a higher plasma level of the enzyme inducer resulting in lower serum levels of the test drug. This probably explains why induction of the CYP enzyme has a greater effect with a long course of an enzyme inducer than with only the single dose used in our previous study.

Although current guidelines, including zidovudine monotherapy pre-delivery and 7 days of zidovudine/lamivudine post-delivery, are complex, they have substantially reduced the emergence of nevirapine resistance by protecting the subtherapeutic nevirapine 'tail', since the lengthy duration of low and subtherapeutic levels of nevirapine in the blood is plausibly associated with increases in nevirapine resistance. A meta-analysis estimated that 4.5% of women using single-dose nevirapine and additional ARVs post-partum showed nevirapine resistance 4–8 weeks post-partum.⁴ In our study, the overall prevalence of new nevirapine resistance was 2.4% (1 out of 41 samples); although we observed no nevirapine resistance mutations after single-dose nevirapine in combination with 7 days of phenytoin, the numbers are clearly too low to make any conclusions about nevirapine resistance on the basis of this study alone. However, it raises the prospect that full elimination of nevirapine resistance could be possible. In the VITA-1 trial, we found that women with undetectable nevirapine plasma concentrations 1 week post-delivery were less likely to develop nevirapine resistance mutations, and that the elimination half-life in women with new nevirapine mutation(s) was almost two and five times longer than the median half-lives in the control and intervention groups, respectively. Thus, it is plausible that adding a 7 day course of phenytoin at the onset of labour might have significant

additional benefits in reducing the selection of nevirapine resistance mutations, even on top of the current ARV prophylaxis 'tail'.

The main limitation of the study was its relatively small size. The trial was designed as a pilot powered to detect a difference between the intervention and control groups in the elimination half-life of nevirapine. A much larger sample size (~200; 100 per arm) would be needed to detect significant differences in the development of nevirapine resistance between the two groups. However, this group of women is extremely challenging to recruit and retain (see Figure 1): only 22% of those assessed for eligibility pre-delivery were randomized, a further 26% of those randomized dropped out before delivery, and a further 24% of those who delivered in the study clinic did not provide samples 4–6 weeks post-delivery. We would therefore have needed to screen ~1600 women to achieve 200 women with week 4–6 samples. Although a larger Phase III trial should ideally confirm the efficacy of 7 days of phenytoin treatment on resistance as a primary outcome, the substantial significant reductions in nevirapine half-life, coupled with previous clinical and sophisticated modelling studies^{6,7} demonstrating a causal association between the half-life of nevirapine and the emergence of resistance, suggests that it is highly likely to be effective. Another limitation was the standard HIV genotyping assay used, which only detects mutations present in >20% of the viral population and not subpopulations of mutants. Deep sequencing of these samples is planned.

It is estimated that 18%–64% of the women living in sub-Saharan Africa with HIV are receiving cART for pMTCT, as now recommended by the WHO (Option B+). However, this means that thousands of women are still receiving single-dose nevirapine²¹ and demonstrates the challenge of widespread implementation of the current guidelines. Phenytoin can be used safely during pregnancy and breastfeeding²² and side effects are expected to be infrequent using such a low dose for only a short period. Where it is not possible to provide cART, phenytoin is cheap and available in almost every clinic. Phenytoin may also be a useful intervention when women stop nevirapine at the end of breastfeeding within Option B+. We have demonstrated that the implementation of this intervention would substantially and significantly reduce the half-life of nevirapine; previous data demonstrating a causal relationship between nevirapine half-life and emergence of resistance^{6,7,14} suggest that implementation would not only facilitate the reduction of nevirapine resistance, but also enable further increases in coverage for pregnant women in need of perinatal HIV prophylaxis, while probably retaining the benefits of single-dose nevirapine in reducing transmission. This strategy might therefore support the overarching goal of the technical consultation of the WHO to reduce the overall HIV transmission rate from pMTCT to <5% at the population level by the end of 2015.

In summary, the addition of an enzyme inducer for 7 days to single-dose nevirapine for pMTCT greatly reduced the presence of subtherapeutic nevirapine levels by significantly shortening the elimination half-life of nevirapine, with no new nevirapine resistance mutations observed. Since prolonged subtherapeutic nevirapine exposure is known to lead to the emergence of nevirapine resistance,^{6,7,14} and since phenytoin is safely and widely used in women¹⁵ to minimize HIV transmission from mother to child, single-dose nevirapine could be used with phenytoin as an alternative if other ARV drugs were unavailable.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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