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Variable and suboptimal nevirapine levels in infants given single-dose nevirapine at birth without maternal prophylaxis

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Poor access of HIV-1 infected women to prenatal care results in infants receiving single-dose (sd) nevirapine (NVP) to prevent mother-to-child-transmission (pMTCT) of HIV-1 without maternal treatment. When the maternal dose was missed and only the infant received sdNVP, we observed a reduced rate of NVP-resistance compared with the combined maternal–infant regimen [1], indicating lower selective pressure by NVP. We reasoned that incomplete oesophageal peristalsis [2] could expel sdNVP from the mouth with drooling and/or regurgitation of amniotic fluid. We hypothesized that sdNVP absorption would increase with infants' age at the time of drug administration and measured NVP concentrations in infants first given sdNVP at various times within the first 2 days of life.

Infants treated with sdNVP were enrolled in an observational cohort study conducted in Beira, Mozambique, from June 2005 to July 2008 [1], under the approval of Institutional Review Boards in Seattle and Beira. Specimens for this analysis were selected from infants whose mothers did not take antenatal sdNVP, whose time of birth and administration of 2 mg/kg of sdNVP were recorded, and whose blood was collected 8–40 h after sdNVP ingestion, to reflect the period of absorption but not metabolism of sdNVP [3]. Whole blood specimens collected as dried blood spots (DBS) were used to determine NVP concentrations by liquid chromatography mass spectrometry, with a lower limit of detection of 5 ng/ml, in the University of California at San Diego Antiviral Assay Laboratory.

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Conflicts of interest

There are no conflicts of interest.

NVP concentrations were compared by the dose administered relative to body mass, the time interval between ingestion of NVP and collection of blood, and by infant's age when sdNVP was administered using Spearman's rank correlation coefficients. The estimated NVP concentration at 7 days of age was determined by modelling the decay of the measured NVP concentrations using a population newborn estimate of the elimination rate constant λ_z , 0.0228 h^{-1} (corresponding half-life, 30.4 h) [4].

Among 870 infants enrolled, the mothers of 236 (27%) did not take sdNVP. Specimens from 83 with recorded date and time of sdNVP and DBS were selected for this study. sdNVP was administered to these infants at a median of 20 min (range 0–330) of age. Blood was collected a median of 21 h (range 8–40) after sdNVP. The infants' median birth weight was 2.8 kg (range 2.00–3.85), and NVP oral suspension was administered at a median dose of 2.0 mg/kg (range 1.4–3.2). These parameters did not differ significantly from those of the entire study population.

The median NVP concentration in the 83 infants' whole blood was 1649 ng/ml (range <5–4508). The NVP dose-to-infant-weight ratio did not correlate with the infants' NVP blood concentrations ($\rho = +0.13$, $P=0.24$, Spearman rank correlation). The time interval between sdNVP administration and DBS collection did not correlate with infants' blood NVP concentrations ($\rho = -0.15$, $P=0.18$; Spearman rank correlation).

Infants' NVP blood concentrations varied widely within the age strata examined (Fig. 1a). A comparison of NVP concentrations across infants' age quartile at sdNVP administration (<10, 11–20, 21–30 or >30 min of age) did not detect a relationship between age at sdNVP administration and NVP concentration less than 100 ng/ml. Notably, a small proportion of infants ($n=6/83$; 7.2%) did not reach the minimum NVP target concentration of 100 ng/ml (10 times the median half maximal inhibitory concentration, or $10 \times \text{IC}_{50}$). All of these infants were dosed at 30 min of age or less; thus, 9.2% of infants administered sdNVP at 30 min of age or less did not achieve the target.

The estimated NVP concentration in infants at 7 days of age suggests that 78% ($N=51/65$) of infants dosed at 30 min of age or less and 83% ($n=15/18$) of infants dosed more than 30 min of age would have NVP concentrations less than 100 ng/ml (Fig. 1b).

The administration of infant-only sdNVP to newborns within minutes of birth resulted in extremely variable NVP concentrations, with very low concentrations observed in nearly 10% dosed between 0 and 30 min of age. Variable NVP concentrations in infants dosed immediately after birth could result from immature swallowing peristalsis early in life [2]. As NVP concentrations were projected below the 100 ng/ml target at 7 days of age in 80% of infants, our findings combined with other studies [4] suggest that multiple doses of NVP may be needed to achieve protective NVP concentrations.

In summary, the variable and low NVP concentrations observed in infants administered sdNVP in the first minutes of life suggest unreliable adsorption and that infant-only sdNVP may be insufficient for effective prophylaxis. Rather, HIV-exposed infants born to untreated mothers should receive a combination of antiretrovirals, as recommended by Department of Health and Human Services [5].

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Fig. 1. Infant-only single-dose (sd) nevirapine (NVP) resulted in highly variable concentrations
 Eighty-three infants, whose mothers did not take sdNVP, were administered sdNVP at a median of 20 min (range 0–330) of age. NVP concentrations (assay lower limit of detection of 5 ng/ml) measured at a median of 21 h (range 8 to 40) – predicted to be near peak blood concentrations – were highly variable. (a) Notably, 7.2% did not achieve the minimum target concentrations of 100 ng/ml (10 times the in-vitro median inhibitory concentration, or $10 \times IC_{50}$). (b) Modelling predicts that 80% would fall to <100 ng/ml before 7 days of age.