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High nevirapine levels in breast milk and consequences in HIV-infected child when initiated on antiretroviral therapy

Nevirapine remains used in resource-limited areas for both the prevention of mother-to-child transmission and maternal antiretroviral therapy (ART). As breastfeeding practice is prolonged in Africa [1], breastfed infants HIV-infected while their mother is receiving ART may have high risk of drug resistance, which may limit their future treatment options. We evaluate the intake of nevirapine through breastmilk and its consequences for their breastfed HIV-infected children while their mother was receiving a nevirapine-based ART.

The MONOD-ANRS-12206 randomized clinical trial was conducted, from May 2011 to June 2015, in Ouagadougou, Burkina-Faso and Côte d'Ivoire, Abidjan (ClinicalTrials.gov registry number: NCT01127204). Confirmed HIV-1 infected children less than 24 months of age received a lopinavir/ritonavir-based ART twice daily as first-line ART for 12 months. Those virologically suppressed (HIV-1 RNA <500 copies/ml) at 12 months were randomized in two arms from 13 to 25 months: remain on lopinavir-based ART, or switch to an EFV-based ART once daily. This nested sub-study assessing the pharmacokinetics of the transfer of nevirapine into breast milk was carried out in the breastfeeding mother-child pairs in Burkina Faso where mothers were receiving 200 mg of nevirapine per day as part of their ART. Using milk concentrations and assuming that the mean volume of milk ingested by a 2-year-child is around 500 ml per day, doses ingested via breast-feeding were estimated. Nevirapine child plasma concentrations resulting from the estimated milk doses were simulated using a previously population pharmacokinetic model [2] and compared with the half maximal inhibitory concentration (IC₅₀) against laboratory and clinical isolates of HIV-1 (10–100 ng/ml) (viramune accessdata.fda.gov) and to the minimal expected trough concentrations in adults (C_{min}) [3]. Children's HIV-RNA viral loads were monitored before ART initiation (W-4), then quarterly up to until 25 months of follow-up. Drugs resistance mutations were sought retrospectively.

Among the 57 infants enrolled in the MONOD trial in Burkina Faso [4], six were still breastfed 6 months after their inclusion while their mother was receiving a nevirapine-based ART. Five out six (83%) mother-infant pairs with available data regarding the timing of maternal ART were enrolled in this pharmacokinetics sub-study: maternal median age of 30 years (range: 24–39 years), children median age of 17.5 months (range: 14–22 months), after being ART-initiated at a median age of

11.5 months (range: 8–16 months). The median maternal plasma nevirapine concentrations measured 3h30 [interquartile range (IQR): 2h30–4h30] after intake were 5157.5 ng/ml (IQR: 5054.7–6023.8). Median breast-milk nevirapine concentrations were 425.2 ng/ml (IQR: 410.1–591.0). Median doses ingested via breast-feeding by a child aged of 1.46 years (1.19–1.65), weighing 7.4 kg (7.2–8.4) would be 1.0 mg (0.7–1.1) per day. Plasma concentrations profiles in children varied between 300 and 500 ng/ml, thus three to five times the highest IC₅₀ (half maximal inhibitory concentration) (Fig. 1).

Among the five breastfeeding-ART-exposed infants enrolled, two children had a detectable HIV-RNA at 12 months despite a LPV/r-based ART and were not randomized. At their 25-month follow-up, one was virologically suppressed and one failed, with a HIV-RNA of 261 914 copies/ml and drug resistance mutations (K103N, Y181C to NNRTI) detected that already existed before their ART initiation. The remaining three children were virologically suppressed at 25-month follow-up, including one child randomized into the EFV-based ART arm.

This is to our knowledge the first study on nevirapine transfer through breast milk in children older than 12 months. Data were already reported before 6 months of age in a large cohort of mother-child pairs [4–8]. Our

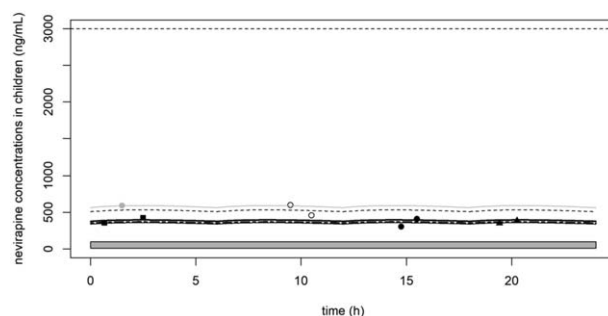


Fig. 1. Nevirapine observed concentrations (points) and corresponding individual concentration-time course (curve) in children following maternal breastfeeding (gray point corresponds to the gray curve/white circle corresponds to the dotted curve/black squares correspond to the solid curve/black triangles correspond to the bold dotted curve/black circles correspond to the thin black curve). Grey rectangle corresponds to nevirapine IC₅₀ against laboratory and clinical isolates of HIV-1, (from 10 to 100 ng/ml) and dashed line to the curative target of 3000 ng/ml.

results documented high concentrations of antiretroviral drugs excreted into breastmilk, and transferred to breastfed children, as their simulated concentrations were between the IC₅₀ and the minimal expected trough concentrations in adults. These HIV-infected children were diagnosed very late at a median age of 11 months with a HIV virus already resistant to NNRTI drugs.

In an era of therapeutic saving strategies, our study documents that plasma nevirapine levels obtained in breastfed infants are high. They have a substantial risk of getting an HIV virus with NNRTI-drug resistance mutations already archived before their treatment initiation if they are exposed to a breastfeeding mother on NNRTI-based therapy. Our results strengthen the needs to particularly avoid NNRTI-based regimen as first-line in those breastfed children, as their future treatment options are compromised.

Our data support the use of antiretroviral drugs not transferring into breastmilk for maternal therapy to not compromise the potential future options for their children, if they get HIV-infected. With this aim, the added value of integrase inhibitor used for maternal ART needs to be further explored [9].

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V.L., C.S.D. designed the MONOD trial; D.H., J.M.T., C.P., V.L. designed the pk-study design. D.D., C.Y. performed the trial in Ouagadougou. C.S.D., T.T. were in charge of virological analysis. C.P., D.H. did the pk analysis. K.M. did the trial analysis. C.P., D.H., V.L. wrote the first draft of the report. All authors critically revised the manuscript, and read and approved the final version.

Clinical Trial Number: ClinicalTrial.gov registry no. NCT01127204

Conflicts of interest

There are no conflicts of interest.

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