Low plasma nevirapine levels during antiretroviral treatment initiation and dose escalation in HIV-infected children: therapeutic implications

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Background: Nevirapine, a component of antiretroviral therapy (ART) in resource-limited settings is known for auto-induction of metabolism, and thus is prescribed at half therapeutic dose until day 14 (‘lead-in period’), and then escalated to full dose. However, young children have higher clearance rates, suggesting that dosing strategy based on adult studies may not be appropriate in children. We aimed to determine plasma nevirapine concentrations achieved during the first month among children initiated on nevirapine-containing ART.

Methods & Materials: ART-naïve HIV-infected children, initiating ART were included in this prospective study. Plasma nevirapine trough levels were analyzed in duplicate (with additional 10% repeats for quality control) by high performance liquid chromatography (HPLC) (lowest detection limit 0.062 mg/ml) at days 7, 14 (lead-in period) and 28 (full dose) after ART initiation. Baseline transmitted drug resistance genotyping, serial CD4 count and viral load was done.

Results: Among 28 children aged 2-12 years initiated on nevirapine-based ART between 2013-2014, six were excluded due to drug toxicity, and two were transferred out within first month. Among 20 children included in the study, 19 reported >95% adherence at all study visits. Transmitted drug resistance was seen in 5 (10%) children (V90I, K103N, K101E, E138G, Y188L, M41L, L210W, T215Y). Median trough nevirapine concentration was 4.83 µg/ml (IQR 3.48-6.06) at day 7 of ART initiation, 3.35 µg/ml (IQR 2.06-7.91) at day 14 (lead-in period), and 7.97 µg/ml (IQR 5.55-10.66) on day 28 (p = 0.018). During the lead-in period 40% (8/20; 15% at day 7, 35% at day 14) of children failed to achieve therapeutic levels of >3 µg/ml, while after dose escalation, only 5% (1/20) had low therapeutic levels. Low trough nevirapine levels was not significantly associated with age, viral load, CD4 count or transmitted drug resistance.

Conclusion: Our results showed significantly lower therapeutic concentrations of nevirapine during the lead-in period in young children initiating nevirapine-based ART in India. Given nevirapine’s low genetic barrier, sub-therapeutic levels during the early high viremic period can lead to later drug resistance development and treatment failure. Long-term drug resistance studies among viral quasispecies can determine the true effect of early subtherapeutic concentrations.