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Poster presentation

Are recommended doses of efavirenz optimal in young children? (ANRS 12103)

Déborah Hirt*[1,2], Saïk Urien[2], Mathieu Olivier[4], Hélène Peyrière[4], Boubacar Nacro[5], Serge Diagbouga[6], Emmanuelle Zouré[5], François Rouet[6], Hervé Hien[6], Philippe Msellati[7], Philippe Van de Perre[8,9] and Jean-Marc Tréluyer[3,1]

Address: [1]Université paris-descartes, Paris, France, [2]Hôpital Tarnier, Paris, France, [3]Hôpital Cochin-Saint Vincent de Paul, Paris, France, [4]Hôpital Lapeyronie, Montpellier, France, [5]CHU Sourô Sanou, Bobo Dioulasso, Burkina Faso, [6]Centre Muraz, Bobo Dioulasso, Burkina Faso, [7]Université Paul Cézanne, Aix en Provence, France, [8]Hôpital Arnaud de Villeneuve, Montpellier, France and [9]Université Montpellier 1, Montpellier, France

* Corresponding author

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Background

Pediatric studies suggested that the actual recommended efavirenz dosage produced insufficient plasma concentrations in children. In the context of a phase II trial on once-a-day pediatric HAART, the aims of this study were to describe efavirenz concentration-time courses in treatment naïve children, to study the effect of age and bodyweight on efavirenz pharmacokinetics and to test relationships between doses, plasma concentrations and efficacy.

Methods

Efavirenz concentrations were measured in 48 children after 2 weeks of didanosine – lamivudine – efavirenz treatment, and samples were available in 9/48 children between month 2 and 5 of treatment. A total of 200 efavirenz plasma concentrations were collected and a population pharmacokinetic model was developed with NONMEM. The influence of individual characteristics was tested using a likelihood ratio test. Estimated minimal (C_{min}), maximal (C_{max}) concentrations, area under the curve (AUC) were correlated to the decrease in HIV-1 RNA levels after 3 months of treatment. The threshold C_{min} (and AUC) improving efficacy was determined. The target minimal concentration of 4 mg/L was considered for toxicity. An optimized dosing schedule was simulated in order that the higher percentage of children is in the effective and not toxic concentrations interval.

Results

Efavirenz pharmacokinetics was best described by a one-compartment model with first order absorption and elimination. Mean efavirenz apparent elimination clearance and volume of distribution were respectively 0.211 L/h/kg and 4.48 L/kg. The elimination clearance significantly decreased with age. With the recommended doses given to 46 out of the 48 children, 19 % had a minimal concentration below 1 mg/L; they were 44 % under this limit in the less than 15 kg children. A significant higher percentage of children with C_{min} > 1.1 mg/L (or AUC > 51 mg/L.h) had a viral load decrease greater than 2 $\log_{10}$ copies/mL after 3 months of treatment, compared to children below these values.

Conclusion

To optimize the percentage of children with a C_{min} between 1.1 and 4 mg/L, children should receive the following once daily efavirenz dose: 25 mg/kg from 2 to 6 years, 15 mg/kg from 6 to 10 years and 10 mg/kg from 10

to 15 years. These assumptions should be prospectively confirmed.