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Real Life HAART Efficacy in Chronically HIV-1 Infected Children 15-Year Follow-Up

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Abstract

Background: It is now widely accepted that the antiretroviral first line-treatment basis in HIV-1 infected children is a combination of 2 nucleoside reverse transcriptase inhibitors and 1 protease inhibitor or 1 non NRTI. However, after few months or years, some patients presented with virological failure.

Objective: Using a "real life conditions" cohort, we aimed to study the median duration of Viral Controlled Replication (VCR) and the factors associated with failure in infected children.

Methods: Thirty six HIV-1 infected patients were followed between September 1996 and September 2010. Children were included starting from the date of initiation of their first successful HAART. Duration of effective VCR was defined as a length, in months, from inclusion to virological failure defined as a HIV-1 PCR-RNA higher than 400 c/ml.

Results: The overall median VCR duration was 46.2 months. Duration was significantly shorter in patients: previously exposed to mono therapies, with CD4 count lower than 350 and with PI-based HAART. After adjustment, the negative effect of PI-based HAART regimen compared to nNRTI-based HAART remained significant (HR=5.7 [95%CI=1.43-22.7]).

Conclusion: Therefore, retrospective analysis of "real life" condition data in observational cohort may contribute to a better understanding of non optimal virological care.

Keywords: Children; HIV; Real life; HAART

Abbreviations: VCR: Viral Controlled Replication; VF: Viral Failure; PI: Protease Inhibitor; nNRTI: Non Nucleoside Reverse; IQR: Inter Quartile Range

Introduction

Healthcare is well standardized in HIV-1 infected children living in industrialized countries. Most of them justify antiretroviral therapy [1,2]. It is now widely accepted that the antiretroviral first line-treatment basis is a combination of 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and 1 Protease Inhibitor (PI) or 1 non NRTI (nNRTI) [3,4]. However, after few months or years of treatment, some patients presented with Virological Failure (VF). Besides particularities in the children's pharmacokinetics, the availability of a syrup formulation for antiretroviral drugs and the (parental or self) adherence to therapy, other factors probably associated with VF are still poorly understood in real life conditions. At Nice University hospital, all HIV-infected children have been prospectively followed by the same medical team since 1996, leading to an exhaustive database with continuous and homogeneous follow up. Using this "real life conditions" cohort, we aimed to study the median duration of Viral Controlled Replication (VCR) and the factors associated with failure in HIV-1 infected children followed between September 1996 and September 2010.

Subjects and Methods

Children were included starting from the date of initiation of their first successful HAART with confirmed virological efficacy (2 PCR-RNA HIV-1 samples below 400 copies per ml (c/ml) 3 months apart). Additional inclusion criteria were: 1-materno-foetal transmission of HIV-1 infection; 2-age between 1 and 18 years old (y.o.); 3-HAART combination with 2 NRTIs and 1 PI or 2 NRTIs and 1 nNRTI. Duration of effective VCR was defined as a length, in months, from inclusion to virological failure (VF). VF was defined as a HIV-1 PCR-RNA higher than 400 c/ml. Patients without VF were censored in September 2010. Qualitative factors supposed to be associated with VCR duration were compared using Kaplan Meier curves and log-rank tests. Association of VCR duration with quantitative factors were assessed using univariable Cox proportional hazards model. All factors found associated with p-value<0.15 were analysed in multivariable Cox model.

Results

Thirty six patients (20 females) met the inclusion criteria. At baseline, median age was 9.5 y.o. (IQR: 6.7-11.1). Median follow up duration was 37.4 months (range: 3-126 months; IQR: 13.2-52.8). Nine patients were previously diagnosed with AIDS (CDC classification 1994). Eighteen patients received monotherapy (mainly azidothymidine) and

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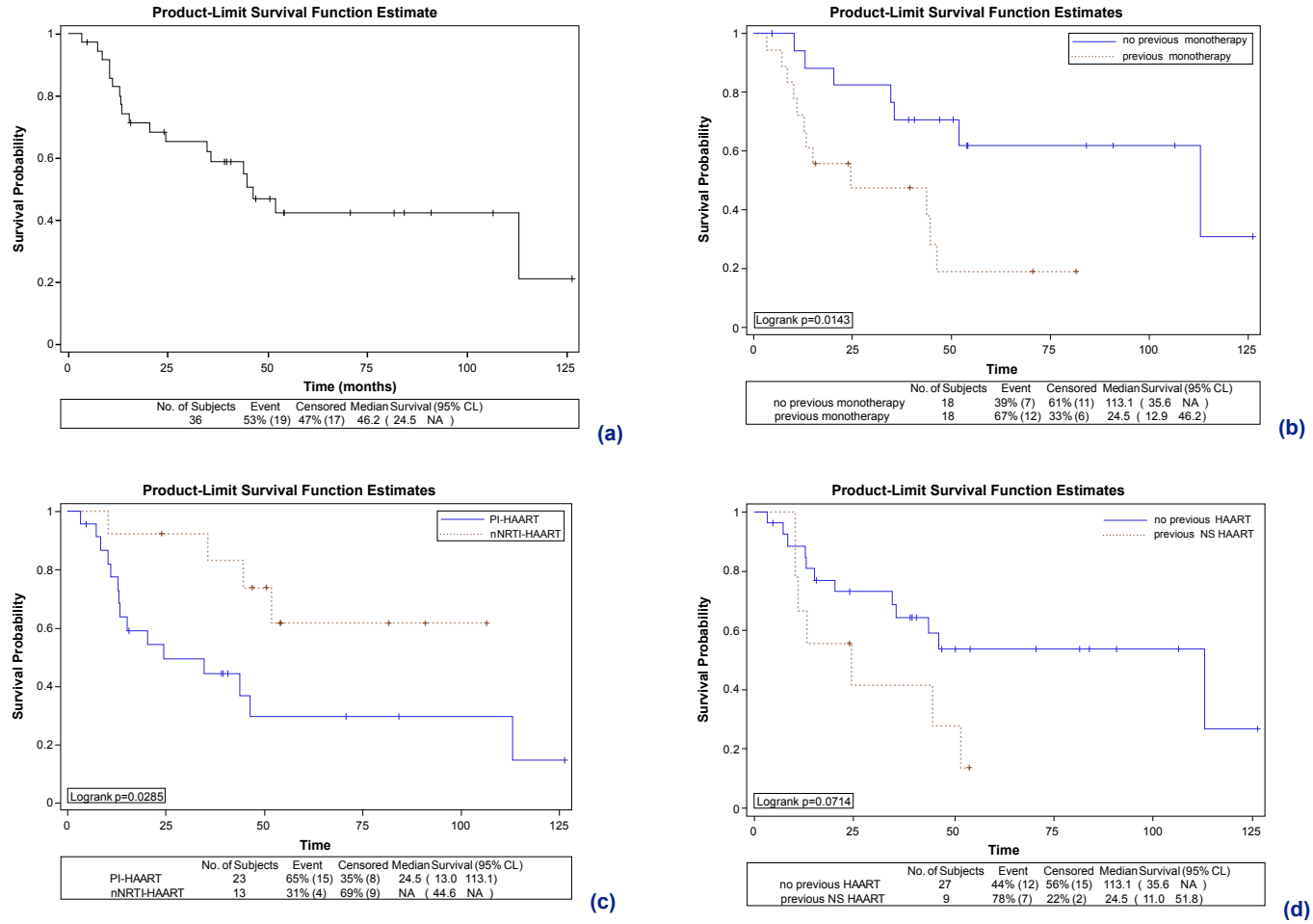

Figure 1: Kaplan Meier survival curve for the cumulative durations of viral control replication (months) (a): for all children; (b) according to previous monotherapy or not; (c): according to HAART regimen (PI versus nNRTI); (d): according to the presence of previous non successful HAART combination or not.

25 received dual therapy before inclusion. A previous non successful HAART combination (no confirmed virological efficacy in 2 samples below 400 c/ml 3 months apart) was noted in 9 patients at inclusion. Ten children underwent Structured Therapy Interruption (STI) before HAART introduction. Overall, median $\log_{10}$-transformed viral load (VL) at inclusion was 4.55 $\log_{10}$ c/ml (IQR: 3.1-4.9), median CD4 T cell count was 406 c/ml (IQR: 220-844) and median CD4 T cell percentage was 20% (IQR: 15%-32%). During the 15 years follow up period, 19 patients (53%) presented with virological failure while 17 were still on virological success at the time of analysis. Patients with previous mono or dual therapy were significantly older than those who were not previously exposed to ART (10.1 and 9.75 y.o. respectively, $p<0.05$). These patients had significant lower CD4 T cell count at inclusion (240 and 360 cell/ml respectively, $p<0.05$).

The overall median VCR duration in our cohort was 46.2 months (figure1a). Duration of VCR was significantly shorter: in patients previously exposed to mono therapies (figure 1b), patients with CD4 count lower than 350 at inclusion and patients with PI-based HAART (figure 1c) (log rank p=0.01, 0.02, 0.03 respectively). Patients with a previous non successful HAART combination were more likely to have a shorter VCR duration but not significantly so (p=0.07, figure 1d). No significant difference in VCR duration was observed according to patient's sex, previous AIDS clinical event, STI, boosted PI or CD4% immuno deficient definition. After adjustment for the described variables above associated with VCR duration and age at inclusion, the negative effect of PI-based HAART regimen compared to nNRTI-based HAART remained significant (HR=5.7 95% CI=1.43-22.7), p=0.01).

Discussion

For many reasons, randomized prospective studies, though essential, are rare in paediatric HIV infection. Experience from retrospective cohort analysis may partly compensate this scarcity. Our study reports results of HAART efficiency in children with materno-foetal HIV-1 infection over a 15-year period. Recently published retrospective data from the COHERE group suggested that after 5 years of HAART introduced in early infancy, 12% of the children presented with virological failure and up to 20.3% by the age of 8 [4]. Overall, 57% of our patients presented with virological failure 5 years after initiation of HAART. This difference may be explained by the fact that median age at entry was higher in our cohort. Indeed, even though age is not significantly associated with VCR duration in our cohort, other VCR-associated variables are related with age. Moreover, most patients in the COHERE study are anti retroviral naives, while half and two-thirds of our patients had been previously exposed to mono or dual ART respectively. Although, currently not recommended, these practices were common before the availability of HAART.

Results from the randomized open label prospective multicentric study conducted by PENTA/pACTG groups showed that first-line HAART with PI gives similar virological results as nNRTI-based HAART four years after initiation (-3.16 *versus*-3.31 $\log_{10}$ copies/ml respectively; p=0.26). At the end of the trial after 5 years of follow-up, 57% of the children had persistent VCR on first HAART regimen with no class difference (PI *versus* nNRTI) [5]. At the same endpoint, we found that more than 62% of our patients receiving nNRTI-based HAART were on controlled viral suppression and less than 30% in the PI patient group (figure 1c, p=0.03). One of the reasons that may, in part, explain this discrepancy is that when HAART became widely available, we believed that the simplest the treatment was, the better it would be taken. Meanwhile, given the low genetic barrier of the nNRTI class, once daily Efavirenz was prescribed to the presumed most adherent children, potentially introducing a selection bias whereas BID boosted-Lopinavir was used in other children in the PI based regimen. Frange et al. recently published data on a cohort of 46 naïves HIV-1 infected children treated with boosted-Lopinavir-based HAART. They showed that after 12 months of follow-up in real life conditions, 16.3% of patients presented with VF (after an initial virological success) [6]. These results are close to those found in our cohort; 23% of VF in the PI-based HAART groups at month12.

Our data reports the results of the first 15 years of HAART practice in children using a small but homogenous "real life" cohort. All the children follow up was conducted by a single practitioner and treatment strategies were adapted from the successive French national guidelines. Surprisingly we observed that nNRTI-based HAART gave better results than PI-HAART. Although, children receiving these nNRTI combinations may have been unintentionally selected, we recommend further investigations to assess PI- and nNRTI-HAART regimens virological efficacy in a paediatric setting.

In 1997 we published one of the first experiences of PI based HAART in 7 HIV-1 infected children [7]. More than ten years ago, 6 of them are still alive and in good health condition (personal data). Therefore, we still believe that, besides prospective randomised studies, retrospective analysis of "real life" condition data in observational cohort may contribute to a better understanding of non optimal virological care.

References

1. AIDS info (2011) Guidelines for the use of antiretroviral agents in pediatric HIV infection.
2. PENTA Steering Committee, Welch S, Sharland M, Lyall EG, Tudor-Williams G, et al. (2009) PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. HIV Med 10: 591-613.
3. CDC (1994) 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 43: 28.
4. Pursuing Later Treatment Options II (PLATO II) project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE), Castro H, Judd A, Gibb DM, Butler K, et al. (2011) Risk of triple-class virological failure in children with HIV: a retrospective cohort study. Lancet 377: 1580-1587.
5. PENPACT-1 (PENTA 9/PACTG 390) Study Team, Babiker A, Castro nee Green H, Compagnucci A, Fiscus S, et al. (2011) First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. Lancet Infect Dis 11: 273-283.
6. Frange P, Briand N, Avettand-fenoel V, Veber F, Moshous D, et al. (2011) Lopinavir/ritonavir-based antiretroviral therapy in human immunodeficiency virus type 1-infected naive children: rare protease inhibitor resistance mutations but high lamivudine/emtricitabine resistance at the time of virologic failure. Pediatr Infect Dis J 30: 684-688.
7. Monpoux F, Sirvent N, Cottalorda J, Mariani R, Lefbvre JC (1997) Stavudine, lamivudine and indinavir in children with advanced HIV-1 infection: preliminary experience. AIDS 11: 1523-1525.