Pediatric HIV-1-infection: perspectives on vaccination strategies and immune reconstitution during long-term antiretroviral therapy

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Chapter

Viral dynamics after starting first-line HAART in HIV-1-infected children

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Abstract

Background: After starting HAART, the plasma HIV-1 RNA (pVL) declines rapidly to undetectable levels in most treated adults and children. The viral dynamics in children are assumed to differ from those in adults. Therefore viral decay and time to reach a pVL of < 400 copies/mL during the first weeks after starting HAART were studied in a cohort of HIV-1-infected children.

Methods: Viral decay expressed as half-life and time to reach a pVL of < 400 copies/mL in 39 HIV-1-infected children starting HAART were calculated and correlated with age, pretreatment with antiretroviral mono- or duo-therapy, and baseline pVL.

Results: Baseline pVL correlated with age (r= −0.41, p=0.01). Median half-life of the virus was 2.1 days (IQR 1.8-3.0). No correlation was found between the half-life of the virus and the baseline pVL at the start of treatment, antiretroviral pretreatment or age. Eight children did not reach a pVL of < 400 copies/mL with the first allocated medication regimen. These children were significantly younger than those in whom HIV was successfully suppressed (p=0.009). The remaining 31 children reached a pVL of < 400 copies/mL in a median of 8.1 weeks after the start of therapy; time to reach a pVL of < 400 copies/mL was only correlated with baseline pVL.

Conclusions: These results suggest that pVL at baseline correlated with age. HAART was able to suppress pVL below the lower limit of detection in children with a viral decay rate of 2.1 days, similar to adults and irrespective of baseline pVL.
Introduction

HIV-1 infection in children progresses more rapidly compared to adults [1]. This is thought to be caused by the high plasma HIV-1 RNA load (pVL) found in children and their immature immune system. The high pVLs in the very young (10⁶ copies per ml and more) are assumed to be reminiscent of those determined in primary HIV infection in adults [2]. However, the spontaneous decline in children is slower than in adults with primary HIV-1-infection [3-6]. These high pVLs are assumed to be a cause of a poorer response to HAART in children compared to adults [7,8].

The pVL is a predictor of disease progression in HIV-1-infected children before starting therapy [5,9,10]. The pVL is also one of the most important outcome measures during treatment with HAART in HIV-1-infected patients.

Modeling changes in pVL after initiation of antiretroviral therapy has provided substantial insight in the dynamics of HIV-1 in adults [11,12]. The decline of pVL after the start of HAART can be best described by a two-phase model. An initial fast decline of more than 99% of pVL in the first weeks after start of therapy represents the decline in free viral particles. After the first few weeks, this is followed by a slower decline, representing the elimination of long-lived HIV-infected cells [13].

Very little is known about the dynamics of HIV-1 in children. A small study with 16 children aged < 2 years showed that infants under the age of 3 months have a slower decline in pVL than children aged between 3 months and 2 years at the start of HAART [14]. The impact of age on HIV RNA response during HAART has been supported by the results of a large UK/Irish collaborative study in 265 children [15]. However, viral decay rates were not defined and a proper explanation for the altered HIV dynamics at young age still remains to be given. When these findings are indeed explained by an inherently reduced viral decay rate at young age, the clinical implications may be very important. It could mean that the moment to start HAART in young children should be reconsidered, if not strictly restricted to those in whom combination therapy is life saving. As a consequence of such unfavorable viral dynamics, HAART may result in the early development of antiretroviral drug resistance in a group of children for whom not that many drugs are as yet registered or available in a palatable drug formulation.

To test whether the early viral dynamics after the start of first-line HAART indeed depend on age, we analyzed the first weeks after the start of HAART in a cohort of HIV-1-infected children. Baseline pVL, early viral half-life, and time to reach a pVL of < 400 copies/mL were studied in our prospective studies in HIV-1-infected children starting HAART at our center.
Methods

Study design and subjects
Data were obtained from the pediatric Amsterdam cohort on HIV-infection (PEACH). This is an ongoing prospective cohort of all children and young adolescents under the age of 18, infected with HIV-1 who are treated and followed at our institute. For the present study we selected 39 children who started HAART between 1997 and 2003 of whom we could calculate viral dynamics, having at least two pVL measurements in the first 3 weeks after starting HAART. First-line HAART in children consists of a combination of two nucleoside-reverse transcriptase inhibitors (NRTI), with one non-nucleoside-reverse transcriptase inhibitors (NNRTI) or a protease inhibitor (PI) [16] as in adults.

The doses of the individual drugs given to the patients (Table 1) were as follows; the twice-daily regimen commonly used, consisted of: stavudine 1 mg/kg, lamivudine 4 mg/kg, nelfinavir 45 mg/kg, each twice daily. In some cases, indinavir 800 mg/m²/day, zidovudine 240 mg/m²/day, or lopinavir/ritonavir 800/200 mg were prescribed in two doses daily. In case of nevirapine we started with 4 mg/kg once daily escalating to 7 mg/kg twice daily after 14 days; in children older than 8 years we started with 4 mg/kg once daily escalating to 4 mg/kg twice daily.

Our once-daily regimen consisted of: abacavir 16 mg/kg, max 1 x 600 mg, lamivudine 8 mg/kg, didanosine 200- 240 mg/m², and efavirenz 14 mg/kg (max 600 mg/day), in one dose each day.

Dose adjustments were performed according to the weight of the children and, in case of nelfinavir [17] and of efavirenz (KML Crommentuijn, HJ Scherpbier, ADR Huitema, TW Kuijpers, JH Beijne; unpublished data), on consecutive plasma levels.

Day curve drug evaluation of PI and efavirenz was done at day 1 of the regimen. Subsequent evaluations of the drug levels were done with random samples at each visit. None of the children needed dose adjustment based on plasma concentrations below the threshold during the first 3 weeks. Adherence support was intensified when problems with compliance were encountered either by drug levels or by interview.

The Medical Ethical Committee approved the study. All caregivers gave written informed consent. For the present analyses only the first HAART regimen of each child was considered.

pVL determination
pVL was determined either using Nuclisens HIV-1 RNA QT (Biomérieux, Boxtel, the Netherlands) or Versant HIV-1 RNA 3.0 (Bayer, Tarrytown, NY, USA). All tests were performed according to the instructions of the manufacturers. Due to a different lower limit of detection in the two assays, all pVL below 400 copies/mL were considered as undetectable.
Mathematical model
All pVL measurements available from the first 3 weeks after start of HAART were included in the model. When a pVL was higher than the previous viral load, all further measurements were excluded in order to include only the patients that showed a viral decrease. When pVL dropped below the lower limit of detection, only the first measurement below the lower limit of detection was imputed as the lower limit of detection.

The kinetics of plasma HIV-1 RNA during the first 3 weeks after the start of therapy were analyzed by a simple one-exponential model [18]: \( V(t) = V(0) \cdot e^{-kT} \)
Where \( V = \text{pVL} \), \( k = \text{virus decay rate constant} \), and \( T \) is time (days) since start HAART. For data fitting to the model the least-squared method was used [19]. The half-life elimination of pVL was calculated as follows: \( T_{1/2} = \ln 2/k \).

Statistical analyses
Continuous data were analyzed using a Mann-Whitney U test. Categorical data were compared with a Fisher’s exact test. Analysis of time to reach undetectable pVL was performed using Kaplan-Meier survival estimates and differences between groups were tested using the log-rank test. The independent effects of age and baseline pVL were analyzed in a multivariate Cox proportional hazards model. All p-values were two-tailed. P-values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS for Windows version 11.5 (SPSS, Chicago, Illinois, USA).

Results
Patient population
Baseline characteristics of the patients are shown in Table 1. The median age was 4.4 years, 19 (49%) were female, 14 (36%) presented with a Centers for Disease Control and Prevention (CDC) category C event [20], and 13 had been pretreated with mono- or duo-NRTI therapy before 1997.

Table 1. Patient baseline characteristics (n=39).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (IQR)</td>
<td>4.4 (1.4-8.5)</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>19/20</td>
</tr>
<tr>
<td>Mode of transmission (vertically/sexually)</td>
<td>37/2</td>
</tr>
<tr>
<td>Prior treatment</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>26</td>
</tr>
<tr>
<td>Mono/duo-therapy</td>
<td>13</td>
</tr>
<tr>
<td>HAART Nelfinavir, 3TC, d4T</td>
<td>25</td>
</tr>
<tr>
<td>Nelfinavir, ZDV, 3TC</td>
<td>1</td>
</tr>
<tr>
<td>Indinavir, ZDV, 3TC</td>
<td>2</td>
</tr>
<tr>
<td>Lopinavir/ritonavir, 3TC, d4T</td>
<td>1</td>
</tr>
<tr>
<td>Efavirenz, abacavir, ddi, 3TC</td>
<td>9</td>
</tr>
<tr>
<td>Nelfinavir + nevirapine, 3TC, d4T</td>
<td>1</td>
</tr>
<tr>
<td>Baseline plasma HIV-1 RNA, median log copies/mL (IQR)</td>
<td>4.9 (4.6-6.0)</td>
</tr>
</tbody>
</table>
Until 2002, first-line treatment was a nelfinavir-containing regimen. Thereafter a single-day efavirenz-containing regimen was implemented as first choice. In sum, 26 children were treated with nelfinavir, two with indinavir, one with the combination lopinavir/ritonavir, and nine with efavirenz, all combined with at least two NRTI's.

**Baseline pVL**
Median pVL was 4.9 log copies/mL (interquartile range (IQR), 4.6-6.0 log copies/mL) at the start of HAART. Children pretreated with mono- or duo-NRTI before the start of HAART had a lower baseline pVL than those who were treatment-naive at start (5.4 vs. 4.8 log copies/mL, p=0.07).

Baseline pVL correlated negatively with age in the total cohort (r=−0.41, n=39; p=0.01) (Figure 1A), or when only the naive patients were taken into account (r=−0.54; p=0.004) (Figure 1B), indicating that younger children had higher pVL.

**Viral dynamics**
Individual viral decay and half-life of pVL in the first 3 weeks after the start of therapy could be calculated by the least-squared mean method [19]. The time between the first and the last measurement during this period was 2.0 weeks (IQR, 1.1-2.1 weeks). The median viral decay constant was 0.33 (IQR, 0.23-0.39). Median half-life of the pVL was 2.1 days (IQR, 1.8-3.0). NRTI pretreatment did not influence the half-life of virus during subsequent HAART treatment (pretreated vs. naive; 2.2 vs. 2.1 days; p=0.9). Most importantly, there was no correlation
between the half-life of the virus and age at start of HAART \( (r = -0.05; p = 0.8) \) (Figure 2A) or with the baseline pVL at the start of treatment \( (r = -0.2; p = 0.2) \) (Figure 2B). No significant difference in viral half-life between a single-day efavirenz containing regimen \( (n = 9) \) and nelfinavir containing regimen \( (n = 26) \) was found in our cohort \( (2.1 \pm 2.3; p = 0.67) \).

One of the patients had a viral decay constant that was different from the other patients. This 9-year old patient had been pretreated with single NRTI for 173 weeks until the start of HAART. This patient started with a very low pVL (620 copies/mL) and already reached an undetectable viral load at the next visit. Therefore the decay constant is an underestimation of the real situation. However, analyses of the data excluding this patient revealed no substantial differences to our conclusions.

**Viral suppression**

Of the 39 patients, eight \( (21\%) \) did not reach a pVL of < 400 copies/mL during the first 48 weeks or had stopped their first prescribed regimen for other reasons. Although clinically and immunologically improved, five children did not reach a pVL of < 400 copies/mL during 48 weeks continuous use of first-line HAART. The reason for ending medication in the other three was inconvenience of therapy. The eight children who failed to reach a pVL of < 400 copies/mL after the start of their first regimen were significantly younger than those who reached a pVL of < 400 copies/mL \( (\text{median } 1.7 \text{ vs. } 5.3 \text{ years, } p = 0.009) \). Children who failed to reach a pVL of < 400 copies/mL after the start of their first HAART regimen had a viral half-life during the first 3 weeks comparable with those who did reach a pVL of < 400 copies/mL \( (\text{median } 2.3 \text{ days (IQR, } 1.8-3.3; \ n = 8) \text{ vs. } 2.1 \text{ days (IQR, } 1.8-2.9; \ n = 31); p = 0.2) \). Sex, CDC-classification and the number of children that were pretreated with single NRTI before initiation of HAART did not differ between the groups.

The children responding successfully to HAART reached a pVL of < 400 copies/mL in a median of 8.1 weeks after the start of therapy. Kaplan-Meier analyses showed that the
time to reach a pVL of < 400 copies/mL was longer in children with a baseline pVL above the median of 4.9 log copies/mL than in children with a pVL below the median (log-rank 8.7; p=0.003) (Figure 3A). Pretreatment (log-rank 0.6; p=0.4) did not result in a prolongation of the time to reach a pVL of < 400 copies/mL (Figure 3B). Age under the median of 4.4 years was associated with a non-significant longer time to reach a pVL of < 400 copies/mL (log-rank 2.1; p=0.15) (Figure 3C).

Because age and baseline pVL are correlated and a non-significant difference is found in time to reach a pVL of < 400 copies/mL in younger vs. older children (median 12.0 vs. 7.8 weeks) we included both variables in a Cox regression analysis. The analysis revealed that baseline pVL (odds ratio (OR), 0.4 [95% CI, 0.2-0.7]; p<0.001) and not age (OR, 1.03 [95% CI, 0.96-1.12]) was correlated with the time to reach a pVL of < 400 copies/mL. No interaction was found.

Figure 3. Time to virologic response. Kaplan-Meier analyses of the time to reach a pVL of < 400 copies/mL. In A, pVL above (straight line) or under (dotted line) the median (4.9 log10 copies/mL) at baseline (log-rank, 8.7; p=0.003). In B, children pretreated with NRTI therapy (dotted line) or treatment-naive (straight line) at the start of HAART (log-rank, 0.6; p=0.4). In C, age above (dotted line) or under (straight line) the median (4.4 years) at the start of HAART (log-rank 2.1; p=0.15).

Discussion

We analyzed the HIV-1 dynamics in the first weeks after the start of HAART in a cohort of HIV-1-infected children in relation to age, antiretroviral pretreatment and baseline pVL. In this prospective study all children who had at least 2 measurements in the first 3 weeks after the start with HAART were selected in order to reduce the change of selection bias. A median viral half life of 2.1 days was calculated, similar to that established in adults on a three-drug regimen [19].
The viral decay constant and viral half-life were independent of baseline pVL, age at start of HAART or NRTI pretreatment. Hence, the time needed to reach a pVL of < 400 copies/mL in these children was significantly longer in children with a baseline above the median compared to children with a pVL under the median of the group at baseline.

Baseline pVL and the viral decay rate are a reflection of viral turnover. Without treatment, production and degradation of the virus determines the turnover, where the amount of susceptible cells and the fitness of the virus define production and the immunologic host response to the virus the degradation of the virus. When the viral turnover is high, the early decay rate after start of effective therapy will be fast, and, vice versa when low, viral decay will be slow.

Young children tend to have higher pVL than adults. This may be defined by the stage of the infection being acute or subacute in children, whereas most adults present with chronic HIV-infection [4-6]. Although limited to very young children, it is often used to explain the relatively low success rate of treatment of HIV-1 in children, apart from the problems with adherence in this group of patients [7,8] and the need for higher weight adjusted dosage in the very young [21]. None of the children needed dose adjustment based on plasma concentrations below the threshold during the first 3 weeks. The initial intake of medication of these children seemed to be good.

The magnitude of the viral half-life in our cohort was similar to the half-life reported for adults [19,22,23]. Therefore, our data do not support the hypothesis that the decline in pVL is different in children compared to adults. An equal viral decay between sexual infected adolescents and young adults was found in a previously reported study by Wu et al. on 115 HIV-1-infected patients [24]. One third of the patients in our cohort was treated with efavirenz in a single-day treatment regimen. No significant difference in viral half-life between the regimens was found in our cohort. In contrast, a more rapid decay of pVL in efavirenz-containing drug regimen when compared to a nelfinavir-containing HAART was seen in the study by Wu et al. This difference may relate to the fact that in their study a non-linear mixed-effects biphasic model for the first 6 weeks was used. Instead, we used a linear regression model for the first 3 weeks after the start with HAART, as was previously used by Ho et al. [11] and Wei et al. [12]. Taking the first 3 weeks together seemed legitimate according to the data presented by van Leth et al. for adults [23].

In a previous report, early viral dynamics were described for 12 children under the age of 2 years [14]. It was found that children less than 3 months of age had lower viral decay rates than children between 3 and 24 months of age (0.66 vs 1.03 days, respectively). Children under 3 months of age are likely to have an increasing pVL as a result of the primary HIV-1 infection rather than the steady state observed later during the chronic stage of infection. This is a possible explanation for the relationship between pVL at baseline and age in our study also. Adult patients with primary infection are known to have lower decay rates than chronically infected patients [25]. In our cohort 11 children
were under the age of 2 at the start of HAART of whom only one child started at 2 months of age. We found that all children responded similarly to HAART with respect to pVL. We cannot exclude any difference in viral decay rate below the age of 3 months.

In our cohort a correlation between baseline pVL and time to reach a pVL of < 400 copies/mL was found. In a Cox proportional hazards model we found that this was not confounded by age. In sharp contrast to our findings, age (and not baseline pVL) was recently reported to correlate with the time to reach an undetectable pVL in a large pediatric cohort study [15]. However, the authors used categorical data and the exact relation between age and baseline pVL was not further substantiated. This non-linear dataset of the study may explain that children with a high pVL became undetectable in the same period of time as children with a low pVL.

Instead, we found that the decay rate was comparable irrespective of baseline pVL, suggesting that more time is needed to become undetectable when the pVL is higher at start of HAART. The time needed to suppress pVL below 400 copies/mL was correlated with baseline pVL. If a regimen of antiretrovirals is sufficiently robust, treatment continues to suppress viral replication. To eliminate higher pVL, more time is needed, which would be in line with the finding that age per se does not influence the success of HAART when determined after 48 weeks [26]. In line with this is the finding that in adults initial viral decay is not correlated with success after 48 weeks on treatment [23].

On the other hand, the initial decay rate may differ from the HIV suppression in the period after the first weeks. Success of HAART in the longer-term suppression of HIV is dependent on additional factors such as adherence, parental support, drug formulation, drug metabolism, as well as viral mutations that may render the medication less effective. In our cohort, a considerable number of children starting with first-line HAART did not reach undetectable pVL. These children were significantly younger, which may well be related to the aforementioned factors of long-term success. Retrospectively, mutation analysis of the virus before the start with HAART was performed. No mutations associated with the components of the regimen were detected in these children prior to the start of HAART.

Time to reach undetectable pVL was analyzed in adults, comparing a three-drug with a five-drug regimen. It was shown that a five-drug regimen suppressed the pVL below the lower limit of detection faster than a three-drug regimen [19]. However, the viral half-life during the first weeks on therapy was comparable between the two treatment groups. Unless adherence or preexistent drug resistance may impact this early stage of treatment, we may believe that the initial viral decay rate during chronic infection would not be different among various HAART regimens.

In conclusion, initial HIV decay after starting HAART was not correlated with age and expressed as viral half-life of 2.1 days- was similar to the decay rates calculated for adults. Even though baseline pVL correlated with age, the early decay rate did neither correlate with the age of the child nor with the baseline pVL at the start of HAART.
Thus, the hypothesis that pVL turnover in children is different from adults cannot be substantiated by our findings.

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References


