Virologic Response to Potent Antiretroviral Therapy and Modeling of HIV Dynamics in Early Pediatric Infection

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Background. Human immunodeficiency virus (HIV) infection in infancy features a persistently high viral load and elevated antiretroviral drug clearance rates, which pose significant therapeutic challenges to the clinician. Viral and cellular kinetic analyses performed in HIV-infected adults have yielded significant insights into the dynamic setting of this viral infection. Similar studies are needed in pediatric populations, in whom differing dynamics might translate into age-specific treatment approaches.

Methods. Viral and cellular kinetic analyses were performed using a nonlinear mixed-effects model in a cohort of 48 infants 1–24 months of age enrolled in a trial of ritonavir-based highly active antiretroviral therapy (HAART).

Results. Infected cell compartment kinetics were comparable with reported adult values, with no age-specific differences demonstrated—suggesting the ability to suppress viral replication in infants receiving HAART. Comparisons between 2 ritonavir dosing schedules revealed significant improvement in phase 1/2 decay constants in favor of the higher dose. A negative correlation was established between plasma RNA levels and phase 1 decay rates, which has worrisome implications for infant therapeutics given high infant pretreatment plasma virus levels.

Conclusions. Ritonavir-based HAART regimens in infancy result in HIV decay constants comparable to those reported in adults, without age-specific variability. Despite higher plasma HIV levels and CD4 lymphocyte counts in infancy, HAART can result in timely, effective control of viral replication.

HIV infection in the first few years of life possesses some unique features and poses significant therapeutic challenges to the clinician. It has been well documented in natural history studies of HIV infection that, although peak plasma virus levels during acute infection among adults and infants are similar, subsequent declines in plasma virus levels require considerably longer time in infancy, resulting in higher systemic viral exposure during the first 2 years of life [1, 2]. These sustained high virus levels are temporally related to observed increased rates of disease progression in early infancy and are likely to be a causative factor. This phenomenon occurs in the context of multiple variables that may impact virus-cell homeostasis during infancy: proportionately higher numbers of CD4 lymphocytes relative to body size, a developing and relatively immature immune system, significant somatic cell prolif-
eration, and pervasive immune system activation through natural and iatrogenic antigen exposure.

Viral and cellular kinetic analyses performed in HIV-infected adults have yielded significant insights into the dynamic setting of this viral infection [3, 4]. Implications of these findings include remarkably high levels of viral production and cell turnover (supporting the need for early, aggressive therapeutic intervention) and the risk of rapid emergence of viral resistance to antiretroviral agents [5–7]. Similar studies are needed in pediatric populations, especially among young infants whose unique features suggest the possibility of different cellular and viral dynamics in comparison with adults. In fact, preliminary data from a small number of infants receiving a potent, non–protease inhibitor–containing antiretroviral regimen suggest age-specific viral turnover rates [8].

The analyses reported here were performed on a cohort of 48 infants <2 years of age who were enrolled in Pediatric AIDS Clinical Trials Group (PACTG) 345, a phase 1/2 trial of the safety and antiviral effects of a potent 3-drug regimen (zidovudine [AZT], lamivudine [3TC], and ritonavir [RTV]) [9]. Key questions addressed here include the following: (1) Will HIV-infected infants experience “adultlike” responses to highly active therapy? (2) Are viral/cellular production and turnover rates similar when comparing infants with adults? (3) What are the relative viral and cellular kinetics of 2 dosing regimens?

METHODS

Study population. Forty-eight HIV-infected infants between the ages of 1 and 24 months were enrolled and stratified into 3 age groups: 1–3 months, 3–6 months, and 6–24 months (table 1) [9]. All infants were naive to 3TC and protease inhibitor antiretroviral therapy. On enrollment, all infants were treated with the following antiretroviral regimen: AZT at 160 mg/m² 3 times a day; 3TC at 4 mg/m² every 12 h; and RTV at 350 mg/m² every 12 h in cohort 1 and at 450 mg/m² every 12 h in cohort 2. At the inception of this trial, pediatric dosing for children >2 years of age was 350–400 mg/m² every 12 h. For cohort 1, RTV monotherapy was administered for 7 days, after which triple therapy with the addition of AZT and 3TC was instituted. Infants in cohort 2 received triple therapy from the outset. Infants were enrolled into cohort 1 between July 1997 and March 1998, and cohort 2 infants were enrolled between February 1998 and March 2001. This clinical trial was conducted with the approval of the institutional review boards at each participating clinical trial site, and informed consent was obtained from the parent or guardian of each infant.

Monitoring. Intensive blood sampling for determining plasma RNA levels was performed before entry; at baseline; at days 1, 3, 7, 14, and 28; monthly from 1 to 18 months; and every 2 months thereafter. The NucliSens assay (Organon Teknika) was used to determine quantitative plasma RNA levels, with a lower limit of quantitation of 400 RNA copies/mL [10]. All assays were performed in a single laboratory certified by the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases, and incorporated quantitative standards supplied by the Viral Quality Assurance Laboratory of DAIDS [11]. Plasma samples were stored at −70°C until the assay was performed. Samples from the first 28 days of the study were assayed in batch format to avoid interassay variability, whereas subsequent samples were assayed in real time. Virologic failure was defined as (1) failure to achieve at least a 1 log₁₀ decrease in plasma RNA level by 28 days of therapy; (2) failure to achieve a nondetectable plasma RNA level (<400 copies/mL) by 3 months of therapy; or (3) rebound to detectable plasma RNA levels after achieving nondetectable status. All virologic failures were based on repeat plasma RNA testing for confirmation of initial failure values.

Model of viral/cellular dynamics and statistical analyses. Biphase plasma RNA data from baseline through 100 days of treatment were fitted into 2 viral dynamic models developed by Wu and Ding [12, 13]. These comprised a nonlinear mixed-effects (NLME) model with and without a cohort covariate. The model accommodates missing values and ignores data on the shoulder during the first day of treatment [5, 14] in an attempt to reduce possible estimation bias. Specifically, the NLME model estimates viral decay rates with the viral RNA data at baseline and day 1 removed. This model also does not require the assumption of pretreatment steady state, which may not be valid during early pediatric HIV infection and does not assume complete control of viral replication at the initiation of treatment (see Wu and Ding [13] for more details). The biphase viral dynamic model can be written as

\[ V(t) = P_1 e^{-d_1 t} + P_2 e^{-d_2 t}, \quad t > t_0, \]

where \( d_1 \) and \( d_2 \) are the first- and second-phase decay rates and

Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th>Age group, RTV dosing cohort</th>
<th>Age, days</th>
<th>Plasma HIV RNA level, log₁₀ copies/mL</th>
<th>CD4 lymphocyte count, cells/mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (6–24 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg/m² (n = 6)</td>
<td>464</td>
<td>4.72</td>
<td>2261</td>
</tr>
<tr>
<td>450 mg/m² (n = 8)</td>
<td>377</td>
<td>5.10</td>
<td>1541</td>
</tr>
<tr>
<td>2 (3–6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg/m² (n = 5)</td>
<td>111</td>
<td>5.47</td>
<td>1768</td>
</tr>
<tr>
<td>450 mg/m² (n = 9)</td>
<td>145</td>
<td>5.46</td>
<td>1473</td>
</tr>
<tr>
<td>3 (1–3 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg/m² (n = 6)</td>
<td>57</td>
<td>5.62</td>
<td>2223</td>
</tr>
<tr>
<td>450 mg/m² (n = 14)</td>
<td>61</td>
<td>5.35</td>
<td>1717</td>
</tr>
</tbody>
</table>

NOTE. Data are mean values. RTV, ritonavir.
Figure 1. Plasma HIV RNA levels over the initial 6-month treatment period, comparing the 2 ritonavir dosing cohorts for each of the 3 enrollment age groups—6–24 months (A), 3–6 months (B), and 1–3 months (C). The X-axis represents the infant age at which samples were obtained, in months. Each line represents an individual infant.

$P_1$ and $P_2$ are macroparameters (see Ding and Wu [15] and Wu and Ding [13] for more details).

For plasma RNA values below the limit of quantitation (400 copies/mL), a value of 200 copies/mL was imputed. Only the first in any series of values below quantitation was included in the model. Phase 1 decay rates ($d_1$) for productively infected cells, phase 2 decay rates ($d_2$) for long-lived cells, and the respective compartment half-lives ($H_1$ and $H_2$) were calculated. Assuming complete suppression of viral replication by the treatment regimen, the decay rates $d_1$ and $d_2$ are equivalent to the death rates of productively infected cells and long-lived/latently infected cells, respectively [6]. If this assumption is invalid,
Table 2. Phase 1 kinetics of productively infected cells.

<table>
<thead>
<tr>
<th>Age group, RTV dosing cohort</th>
<th>(d_1)</th>
<th>(H_{1i})</th>
<th>(R_i)</th>
<th>(t_0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (6–24 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg/m² (n = 6)</td>
<td>0.405</td>
<td>1.71</td>
<td>.989</td>
<td>11.4</td>
</tr>
<tr>
<td>450 mg/m² (n = 8)</td>
<td>0.566</td>
<td>1.23</td>
<td>.982</td>
<td>7.2</td>
</tr>
<tr>
<td>2 (3–6 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg/m² (n = 5)</td>
<td>0.353</td>
<td>1.96</td>
<td>.990</td>
<td>14.5</td>
</tr>
<tr>
<td>450 mg/m² (n = 9)</td>
<td>0.593</td>
<td>1.17</td>
<td>.981</td>
<td>7.4</td>
</tr>
<tr>
<td>3 (1–3 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg/m² (n = 6)</td>
<td>0.362</td>
<td>1.95</td>
<td>.991</td>
<td>14.3</td>
</tr>
<tr>
<td>450 mg/m² (n = 14)</td>
<td>0.578</td>
<td>1.20</td>
<td>.975</td>
<td>7.1</td>
</tr>
</tbody>
</table>

**NOTE.** \(d_1\), phase 1 viral decline; \(H_{1i}\), phase 1 half-life; \(R_i\), phase 1 proportion of plasma virus; RTV, ritonavir; \(t_0\), phase transition time.

interpretation of the decay rates becomes more complicated [12]. The half-life of the 2 decay phases can be calculated as \(H_i = \log(2)/d_i\) and \(H_{1i} = \log(2)/d_1\). The proportion of plasma virus originating from the 2 compartments can be approximated by \(R_i = P_i/(P_1 + P_i)\) and \(R_{1i} = P_{1i}/(P_{1i} + P_i)\). The transition time between the 2 phases is defined as \(t_1 = (\log R - \log P_1)/(d_1 - d_2)\).

The nonlinear least squares method was used to fit individual plasma RNA data. The Wilcoxon 2-sided test was used for 2-sample comparisons (P values were not adjusted for multiple comparisons in this exploratory analysis). Comparisons of this method with other methodologies have been published [15, 16].

**RESULTS**

**Cohort characteristics and virologic response.** Seventeen infants were enrolled into cohort 1, who received RTV at a dose of 350 mg/m² every 12 h, and 31 were enrolled into cohort 2, who received RTV at 450 mg/m² every 12 h (table 1). The mean baseline log₁₀ plasma RNA level ranged from 4.7 to 5.6, whereas the mean baseline CD4 lymphocyte count was in the low normal range for age, from 1473 to 2261 cells/mm³.

Figure 1A–1C shows plasma RNA levels over the initial 6-month treatment period, comparing the 2 RTV dosing cohorts for each of the 3 enrollment age groups. All infants experienced a dramatic early (or phase 1) decline in plasma RNA level over the first 7–14 days of therapy. This was observed regardless of ultimate virologic success or failure. Declines in plasma RNA levels of 2–3 orders of magnitude were common. Subsequent to the acute phase 1 decline in plasma RNA level, a much slower phase 2 decline over several months was observed in those with sustained virologic suppression. The majority of such infants reached nondetectability by 2–4 months of age.

**Viral and cellular dynamics.** Viral decay curves were fit to the data (NLME model), resulting in biphasic patterns. Analyses using a viral dynamic model that does not assume steady state at baseline allowed the calculation of first- and second-phase decay constants representing the death rate of productively infected (phase 1) and long-lived/latently infected (phase 2) cells. Tables 2 and 3 list a series of calculated variables by age group for phases 1 and 2, respectively. Data were sufficient to allow phase 1 analyses for all 48 infants. Although the NLME model allowed phase 2 calculations for all infants, 13 of 48 had limited data due to early events such as plasma RNA rebound, reaching nondetectability before 100 days, or study dropout. Some analyses of phase 2 kinetics were performed both with and without data on these 13 infants.

Phase 1 decay constants ranged from 0.353 to 0.405 among those receiving the lower RTV dose, with no statistically significant difference between the age groups (table 2). The half-life of productively infected cells was short, calculated as being between 1.7 and 2.0. Almost all plasma virus at baseline, estimated at 98%–99%, originated from this compartment (i.e., productively infected cells). A consistent trend of a higher phase 1 decline (range, 0.566–0.593) and a shorter half-life of productively infected cells (1.2 days) was observed for the higher-dose RTV cohort; the trend was statistically significant when all age groups were combined (\(P = .0397\) for the entire cohort \([n = 48]\); \(P = .0202\) for the subcohort \([n = 35]\) after the exclusion of the 13 subjects with limited longitudinal data). The time to achieve the transition between phases 1 and 2 was ~7 days, decreased from 11–14 days for cohort 1.

Phase 2 decay constants for the lower-dose RTV cohort ranged from 0.012 to 0.018, with relatively prolonged half-lives (range, 38–47 days) for this long-lived/latently infected cell compartment (table 3). As with phase 1 decay constants, no age-specific differences were observed. When compared with the lower-dose RTV cohort, there was a consistent trend toward higher phase 2 decay rates (range, 0.045–0.053) and shorter half-lives (range, 13–15.6 days) for the higher-dose RTV cohort; this trend was statistically significant when all age groups were combined (\(P = .0202\) for \(n = 35\); \(P = .077\) for \(n = 48\)).

Table 3. Phase 2 kinetics of long-lived/latently infected cells.

<table>
<thead>
<tr>
<th>Age group, RTV dosing cohort</th>
<th>(d_2)</th>
<th>(H_{2i})</th>
<th>(R_{2i})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (6–24 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg/m² (n = 6)</td>
<td>0.012</td>
<td>47.3</td>
<td>.011</td>
</tr>
<tr>
<td>450 mg/m² (n = 8)</td>
<td>0.045</td>
<td>15.6</td>
<td>.018</td>
</tr>
<tr>
<td>2 (3–6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg/m² (n = 5)</td>
<td>0.016</td>
<td>42.6</td>
<td>.010</td>
</tr>
<tr>
<td>450 mg/m² (n = 9)</td>
<td>0.053</td>
<td>13.0</td>
<td>.019</td>
</tr>
<tr>
<td>3 (1–3 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg/m² (n = 6)</td>
<td>0.018</td>
<td>38.0</td>
<td>.009</td>
</tr>
<tr>
<td>450 mg/m² (n = 14)</td>
<td>0.052</td>
<td>13.3</td>
<td>.025</td>
</tr>
</tbody>
</table>

**NOTE.** \(d_2\), phase 2 viral decline; \(H_{2i}\), phase 2 half-life; \(R_{2i}\), phase 2 proportion of plasma virus; RTV, ritonavir.
remained the only covariate with a significant correlation with
incorporated an adjustment for treatment, baseline plasma RNA level
was demonstrated for the decay rate for either phase. When
short (P < 0.001). Once again, no age-specific effect
hort 1, and P = 0.237 for cohort 2, and
significant (negative) correlation with phase 1 decay rates (for co-
plasma RNA level, CD4 and CD8 lymphocyte counts, weight,
rates (NLME model 1) and the following baseline variables:
Correlation between viral decay rates and baseline covariates.
The Spearman correlation rank test was used to test for sig-
ificant correlations between individual cohort 1 and 2 decay
rates (NLME model 1) and the following baseline variables:
plasma RNA level, CD4 and CD8 lymphocyte counts, weight,
and age. Only baseline plasma RNA level demonstrated a sig-
nificant (negative) correlation with phase 1 decay rates (for co-
hort 1, r = −0.534 and P = 0.032; for cohort 2, r = −0.605 and
P = 0.0009). A significant correlation between the cohort 1
phase 2 decay constant and plasma RNA was also demonstrated
(r = 0.882; P = 0.0004), but not for the higher-dose RTV co-
hort (r = 0.237; P = 0.195). Once again, no age-specific effect
was demonstrated for the decay rate for either phase. When
both cohorts were combined in NLME model 2, which incor-
porated an adjustment for treatment, baseline plasma RNA level
remained the only covariate with a significant correlation with
the decay rates (for phase 1, r = −0.411 and P = 0.0048; for
phase 2, r = 0.455 and P = 0.0018).

DISCUSSION
The triple antiretroviral drug combination of AZT, 3TC, and
RTV was well tolerated, safe, and highly active when admin-
istered to infants enrolled in PACTG 345 between 1 and 24
months of age [9]. This trial, with its intensive early monitoring,
allowed for comprehensive analyses of infected cell compart-
ment kinetics through the marker of plasma virus decay in
response to this highly active antiretroviral regimen.

The kinetic parameters of viral decay (or the kinetics of in-
fected cell compartment decay) in this study appear to be similar
to values reported in adults and recently in infants [3–6, 8, 17].
This observation suggests that the ability to suppress viral rep-
lication in infants with potent antiretroviral regimens is com-
parable to that in adults. In fact, the 43% rate of durable viral
suppression (defined as <400 copies/mL at 96 weeks) demon-
strated in this study [9] is comparable to that in many early
adult trials with protease inhibitor–containing regimens, not-
withstanding the higher plateau plasma virus levels observed in
infancy. The success rate of durable viral suppression and the
calculation of half-lives of the long-lived cell population of 2
weeks and 3–4 weeks for the higher- and lower-dose RTV co-
horts, respectively, have to be tempered by the concept of a truly
latent viral reservoir. Several groups have demonstrated the per-
sistence of replication-competent viral genomes within an
additional cell compartment—quiescent memory cell popula-
tions—which makes complete viral eradication all but unattain-
able and will require unique therapeutic approaches [18–22].

No significant age-specific differences in viral or infected cell
dynamics/clearance were detected in this cohort. This is in
contrast to a previous report of an age-specific decline in viral
(or infected cell compartment) clearance [8]. There are several
possible explanations for these divergent results: (1) both stud-
ies enrolled a relatively small number of infants for kinetic
analyses; (2) potential pharmacokinetic and pharmacodynamic
interpatient variability may directly affect these initial analyses;
(3) somewhat different models were used in the 2 studies; and
(4) the present study used a protease inhibitor–containing reg-
imen, compared with a non–protease inhibitor regimen in the
previous study. In support of the last hypothesis, pharma-
cokinetic data from this study (Rodman et al., unpublished data)
also suggested that the RTV dose of 350 mg/m² twice daily may
be suboptimal for infants with an observed increase in drug
clearance with decreasing age, leading to the enrollment of
cohort 2 with a RTV dose of 450 mg/m². Although phase 1
plasma virus decay of 3 orders of magnitude in the first 7–14
days was universally observed, regardless of ultimate outcome,
up to 4 months was required to achieve undetectable plasma
virus, suggesting the need for more intensive therapy (i.e.,
higher doses and/or additional antiretroviral agents) to accel-
erate the process. Several studies in adults have demonstrated
that optimal long-term outcome is inversely related to the rate
of achieving complete suppression of viral replication. In ad-
dition, the slower phase 2 decay in children receiving the lower
dose of RTV (350 mg/m² twice daily) is probably due to the
lower drug levels found in those children with good adherence,
suggesting that periodic evaluation of drug levels may improve
the virologic outcome.

Analyses comparing viral and infected cell dynamics between
the 2 RTV dose cohorts demonstrated a significant improve-
ment in rates of decline for both phases 1 and 2 in favor of
the higher dose. Specifically, the transition time between the 2 phases was reduced by >50%—from 14 to 7 days—and the half-life of phase 2 was reduced from a range of 38 to 47 days to 13 to 16 days. Recent studies in adults have documented increasingly potent highly active antiretroviral therapy regimens that result in “better” decay rates and predict that even the most aggressive antiretroviral regimens may yet be less than “ideal” [23, 24]. Long-term follow-up and evaluation of potential low-level viral replication is indicated to determine whether the predicted benefit of more-rapid clearance of infected cell compartments translates into clinical benefit.

An intriguing study result was the negative correlation between baseline plasma RNA levels and phase 1 decay rates. This has also been demonstrated in adult cohorts and has particular significance for HIV-infected infants with high plasma RNA levels persisting through the first 1–2 years of life. The potential effect of even a small decrease in phase 1 decay for infants with high plasma virus levels is depicted in figure 2. The solid lines represent optimal (or “best case”) decay parameters for 2 individuals with high and low plasma RNA starting points. The phase 1 half-life is 1 day, with a transition to phase 2 at 7 days. The dashed line represents a 20% slower phase 1 decay constant, consistent with the negative correlation between baseline plasma RNA level and phase 1 decay. Phase 2 decay constants were assumed to be identical in all cases, with a half-life of 14 days. A likely mechanism underlying the negative correlation between baseline RNA and the phase 1 decay constant is suboptimal therapeutics—either less than maximum dosing or difficulty with adherence, or both—which may be particularly problematic in the presence of high baseline plasma RNA levels.

The higher value for $R_1$ (and related lower $R_2$) for the higher-dose versus lower-dose cohort is intriguing but remains unexplained (tables 2 and 3). Note that $R_1 = P/(P + P')$ and $R_2 = P'/P + P'$; thus, $R_1 = 1 - R_2$. One possible reason is that the more-potent higher-dose treatment may result not only in faster decay rates (i.e., higher $d_1$ and $d_2$) but also in the conversion of some productively infected cells into long-lived infected cells that are slowly producing virus (i.e., higher $R_1$ and lower $R_2$).

Further intensive efforts are needed to elucidate the virus-cell-drug interactions in young infants. Despite some daunting challenges (e.g., high plasma virus levels and a developing immune system), these early treatment results and kinetic analyses suggest a hopeful environment for the control of viral replication in HIV-infected infants.

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**References**


