Comparison of Adherence Monitoring Tools and Correlation to Virologic Failure in a Pediatric HIV Clinical Trial

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Abstract

There is no consensus on a gold standard for monitoring adherence to antiretroviral therapy (ART). We compared different adherence monitoring tools in predicting virologic failure as part of a clinical trial. HIV-infected Thai and Cambodian children aged 1–12 years ($N=207$) were randomized to immediate-ART or deferred-ART until CD4% <15%. Virologic failure (VF) was defined as HIV-RNA >1000 copies/mL after ≥ 6 months of ART. Adherence monitoring tools were: (1) announced pill count, (2) PACTG adherence questionnaire (form completed by caregivers), and (3) child self-report (self-reporting from children or caregivers to direct questioning by investigators during the clinic visit) of any missed doses in the last 3 days and in the period since the last visit. The Kappa statistic was used to describe agreement between each tool. The median age at ART initiation was 7 years with median CD4% 17% and HIV-RNA 5.0 log₁₀copies/mL and 92% received zidovudine/lamivudine/nevirapine. Over 144 weeks, 13% had VF. Mean adherence by announced pill count before VF in VF children was 92% compared to 98% in children without VF ($p=0.03$). Kappa statistics indicated slight to fair agreement between tools. In multivariate analysis adjusting for gender, treatment arm ethnicity and caregiver education, significant predictors of VF were poor adherence by announced pill count (OR 4.56; 95%CI 1.78–11.69), reporting any barrier to adherence in the PACTG adherence questionnaire (OR 7.08; 95%CI 2.42–20.73), and reporting a missed dose in the 24 weeks since the last HIV-RNA assessment (OR 8.64; 95%CI 1.96–38.04). In conclusion, we recommend the child self-report of any missed doses since last visit for use in HIV research and in routine care settings, because it is easy and quick to administer and a strong association with development of VF.

Introduction

ADHERENCE IS A KEY FACTOR in successful antiretroviral therapy (ART), improving HIV treatment outcomes and also preventing HIV drug resistance.^{1,2} Low levels of

adherence to ART of $\leq 95\%$ are independently associated with viral resistance, opportunistic infections, and hospitalization.³ Adherence in perinatally HIV-infected children is challenging because lifelong treatment is needed. Multiple factors have been associated with poor adherence, including

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This abstract was presented as poster presentation at the 5th International Workshop on HIV Pediatrics (P_52) on 28–29 June 2013 and the 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention (WEPE525), on 30 June–3 July 2013 in Kuala Lumpur, Malaysia.

behavioral impairment, mental health problems, and recent stressful life events.^{4,5}

A number of adherence monitoring methods have been used to assess adherence in HIV-infected children, for example, interviewing caregivers, child or carer self-report, and pill counts, all of which are feasible in resource limited settings.⁶ An ideal adherence assessment should be reliable, valid, and practical, causing minimal inconvenience to health care providers, caregivers, and children. However, there is no gold standard for assessing ART adherence in routine practice,^{1,6} or in the context of randomized clinical trials.⁷ A number of guidelines recommend self-report.^{8,9} Farley et al. reported announced adherence by pill count, but not a 3-day recall of missed doses, was associated with HIV-RNA suppression, in HIV-infected children in the USA.¹⁰ There are limited data comparing different adherence monitoring tools in predicting virologic failure (VF) in HIV-infected Asian children.

Our team reported the treatment outcomes among ART-naïve, HIV-infected children in the Pediatric Randomized Early versus Deferred Initiation in Cambodia and Thailand study (The PREDICT study).¹¹ Three different adherence monitoring tools were used in the PREDICT study, therefore, we evaluated the association of each monitoring tool with virologic outcomes.

Methods

This is a substudy of an open label, randomized study to evaluate when to start ART in HIV-infected children; (PREDICT study, clinicaltrials.gov identification number NCT00234091).¹¹ ART-naïve HIV infected children, aged 1–12 years, Center for Disease Control and Prevention clinical (CDC) classification N (no HIV symptoms), A (mild HIV symptoms), or B (moderate HIV symptoms),^{12,13} CD4 15–24%, and no active infections were enrolled. The children were randomized to either the immediate-arm in which they were started highly active antiretroviral therapy (HAART) at week 0 or the deferred-arm in which they were started HAART when a confirmed CD4% dropped to <15%, or if the child developed symptoms of AIDS. The children were followed up every 12 weeks until 144 weeks for weight, height, clinical evaluation, CD4%, and CD4 cell count. Immediate-arm children and those in the deferred-arm who initiated and had been taking ART for ≥6 months were included in this adherence analysis. Plasma HIV-RNA was measured every 24 weeks. VF was defined as HIV-RNA ≥1000 copies/ml after ≥6 months on ART.

Adherence monitoring tools

Adherence to ART was assessed by three adherence monitoring tools every 12 weeks until 144 weeks.

Tool 1. Announced pill count: All ARTs were dispensed at the clinic by pharmacists/nurses. When children came to clinic, they returned their medication boxes from their last visit. Nurses performed a pill count with the child and caregiver present, and calculated percent adherence by pill count at each visit. This took approximately 10 min/visit. The investigator shared the results of adherence by pill count with the child and caregiver after they completed tools 2 and 3 (described below). For liquid medications, at every visit, the ART bottles were weighed to calculate volume of medica-

tion, and the percentage adherence was determined. When families failed to return the ART, the study nurse called children and caregiver for the remaining amount of ART and recorded the data. Percent adherence by pill count was calculated as [(dispensed drug – returned drug)/drug that patient should have taken in the period since the previous clinic visit] x 100. This was averaged over the scheduled clinic visits since the previous HIV-RNA measurement. Poor adherence was defined as average adherence by announced pill count <95% since the previous HIV-RNA measurement.

Tool 2. Pediatric AIDS clinical trials group (PACTG) adherence questionnaire:¹⁴ the questionnaire was translated into Thai, and validated and previously used to assess adherence in HIV-infected Thai children.¹⁵ The English version was used for the translation of the Cambodian version. A language expert reviewed and ensured that the questions conveyed the same meaning in the English and the Cambodian versions. The primary caregiver was asked to complete the questionnaire independently, which took approximately 15 min per visit. The number of missed doses in past 3 days was one of the questions, and any missed doses in the 3 days before the current visit was defined as poor adherence. The questionnaire also asked if there were any barriers to taking medicines, including for example, bad taste, child forgot to take the medicine, and caregiver was sick, or not staying with the child.

Tool 3. Child self-report: At every visit, the investigator asked children if they had missed any doses in the past 3 days, or since the last clinic visit. This took approximately 1 min/visit. For young children, the caregivers answered for this question. Poor adherence was defined as any missed dose in the 3 days before the visit, or reporting any missed dose at either of the clinic visits in the 24 weeks before the current HIV-RNA was measured.

The study was approved by national and local institutional review boards, and written informed consent was obtained from children's caregiver prior to enrollment.

Statistical analysis

Statistical analysis was carried out using Stata version 12 (StataCorp LP, College Station, TX). The agreement between each tool for good or poor adherence was assessed using a kappa statistic. Kappa agreement levels were classified as 0.01–0.20 for slight agreement, 0.21–0.40 for fair agreement, 0.41–0.60 for moderate agreement, 0.61–0.80 for substantial agreement, and 0.81–0.99 for almost perfect agreement.¹⁶

Longitudinal random effects logistic regression models were used to estimate the odds of VF, while also accounting for time on study and within and between subject variability. Subjects were censored once VF had developed or at week 144 if there was no VF. A univariate model was developed for each adherence assessment method, and other potential predictors of VF, including the potential predictors were gender, age, ethnicity, treatment arm, CDC clinical classification, non-nucleoside reverse transcriptase inhibitor-based or protease inhibitor based-regimen, %CD4, and HIV-RNA at HAART initiation, family status, school attendance, and HIV disclosure status of the child. A multivariate model for each adherence assessment method was developed adjusting for variables with *p* value ≥0.2 in univariate analysis.

TABLE 1. CHARACTERISTICS OF HIV-INFECTED CHILDREN

Characteristics	N=207
Age at antiretroviral therapy initiation (years)	7 (4–9)
% female	54%
Thai: Cambodia	58:42%
%CDC clinical classification N:A:B	1:62:37%
CD4%	17 (14–21)%
CD4 count (cells/mm ³)	506(342–772)
HIV-RNA (log ₁₀ copies/mL)	5.00(4.48–5.00)
<i>First regimen</i>	
AZT/3TC/NVP	190(92%)
AZT/3TC/LPV/r	10(5%)
AZT/3TC/EFV	3(1%)
3TC/ABC/NVP	3(1%)
AZT/3TC/ABC	1(0.5%)
<i>Family status</i>	
% living with family average to above average income: living with family low/very low income: orphanage	25:59:16%
Attending school : not yet reached school age: not attending school	67:27:6%
Primary caregiver	61:39%
Father or mother vs. the others	
Caregiver education level; high school/bachelor:elementary:no education:unknown	42:41:13:4%

Data are presented as median (IQR) or %.
 ABC, abacavir; AZT, zidovudine; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NVP, nevirapine.

Results

Among 299 HIV-infected children who were enrolled in the PREDICT study, 207 children were eligible for this substudy. The other 92 children were ineligible because they were still ART-naïve at the end of the study ($n=81$) or had been taking ART for <6 months ($n=11$). For the eligible children, 147/207 (71%) children were randomized to the immediate-arm and 60/207 (29%) were randomized to the deferred-arm. All children were perinatally-infected with

HIV. The median (IQR) age was 7 (4–9) years, 54% were female, 58% were Thai, and 92% received zidovudine/lamivudine/nevirapine as their first-line therapy. The number (%) of children who used liquid formulations in their regimens at ART initiation was 189 (91.3%), and at 144 weeks, was 52 (25.7%). The median daily pill burden was 6 (6–6) pills at ART initiation and 8 (6–10) pills at week 144. The majority of children (84%) lived with family, 64% had father or mother as primary caregiver, and 67% attended school. Other characteristics at ART initiation are presented in Table 1.

Treatment outcomes

Two hundred and two (97.6%) of 207 children completed 144 weeks of follow-up. Five children did not complete 144 weeks of follow-up because of death ($n=1$), lost to follow up ($n=1$), and referral to another hospital because the family moved to another part of the country ($n=3$). Median CD4% and CD4 count at week 144 were 32% and 938 cells/mm³, respectively. During 144 weeks, 194 (93.7%) children had CD4% $\geq 25\%$. The number (%) of children with HIV-RNA < 50 copies/mL at week 144 was 185 (91.6%).

Over 144 weeks, 27 children (13%) developed VF. Among these 27 children, the median age was 6 (4–9) years, 10 (37%) were female, and 19 (70%) were Thai. Mean (SD) adherence by announced pill count averaged over all visits before VF developed was 92 (13.5%) in children with virological failure; in children without VF, mean adherence averaged over all follow-up was 98 (2.9%) ($p=0.03$). There was no difference in mean (SD) percent adherence by pill count by antiviral drugs among children who developed VF: zidovudine 95.0 (13.3%), lamivudine 94.6 (14.9%), nevirapine 95.5 (13.0%), lopinavir/ritonavir 99.9 (0.3%) ($p=0.76$). From the PACTG adherence questionnaire, the most common reasons for poor adherence among VF children were out of supply because of delayed visits to clinic (29%), child forgot to take the medicine (21%), and the child refused to take medicine (21%). The proportion of children with good or poor adherence by each tool is shown in Table 2. Overall, more than 90% of children had good adherence by each tool. For example, 9% of children reported a missed dose in the 24 weeks since the previous HIV-RNA was performed.

TABLE 2. PROPORTION OF CHILDREN WITH GOOD AND POOR ADHERENCE BY EACH MONITORING TOOL; AND A COMPARISON OF THE AGREEMENT EACH TEST VERSUS ANNOUNCED PILL COUNT

Adherence tools	Tool1:Adherence by pill count		Kappa statistic		
	Good	Poor	Agreement	Kappa	p Value
Tool 2. Adherence by PACTG adherence questionnaire					
Never missed a dose	88.3%	8.6%	88.71%	0.03	0.18
Missed dose in previous 3 days	2.7%	0.4%			
Tool 2. Reported any barrier to adherence in the PACTG adherence questionnaire					
No	88.5%	7.3%	90.03%	0.18	<0.001
Yes	2.7%	1.5%			
Tool 3. Child self-report: having any missed dose in previous 3 days					
Never missed a dose	89.8%	8.3%	90.31%	0.07	0.002
Missed dose	1.4%	0.5%			
Tool 3. Child self-report: having any missed dose in the 24 weeks since the last clinic visit					
Never missed a dose	84.4%	6.6%	86.94%	0.21	<0.001
Missed dose	6.4%	2.6%			

Data of children were censored after having virologic failure.

TABLE 3. PREDICTORS OF VIROLOGIC FAILURE BY USING LONGITUDINAL LOGISTIC REGRESSION

Characteristic	N	Univariate			Multivariate		
		OR	95%CI	p Value	aOR	95%CI	p Value
Male vs. female	207	6.46	(1.35–30.83)	0.02			
Age (years)	207	0.9	(0.70–1.17)	0.44			
Thai vs. Cambodia	207	3.09	(0.60–15.84)	0.18			
Immediate-arm vs. deferred-arm	207	3.13	(0.91–10.76)	0.07			
CDC classification B/C vs. N/A	207	1.88	(0.45–7.75)	0.38			
NNRTI vs. PI based regimen	207	1.31	(0.17–10.35)	0.8			
%CD4 at HAART initiation $\leq 20\%$ vs. $> 20\%$	207	0.49	(0.05–4.37)	0.52			
%CD4 at baseline $\leq 20\%$ vs. $> 20\%$	207	1.11	(0.23–5.28)	0.9			
HIV-RNA log ₁₀ copies at HAART initiation: ≥ 5 vs. < 5 log ₁₀ copies/mL	207	3.39	(0.49–23.47)	0.22			
Family status	196			0.36			
Orphanage		Ref					
Living with family; low or very low income		1.5	(0.21–10.80)				
Living with family; $\geq$ average income		0.35	(0.03–4.37)				
Parent as primary caregiver (versus others)	199	0.38	(0.08–1.71)	0.21			
Caregiver education: elementary/no education vs. high school/bachelor	198	5.69	(0.44–73.17)	0.18			
Children not attending vs. attending school	199	1.25	(0.25–6.18)	0.79			
Non HIV-disclosed vs. disclosed children	207	1.93	(0.34–10.89)	0.46			
Tool 1. Percent adherence by pill count since the previous visit $< 95\%$ vs. $\geq 95\%$	205	4.93	(2.09–11.63)	< 0.001	4.56	(1.78–11.69)	0.002
Tool 2. PACTG questionnaire: Missed vs. never missed a dose in previous 3 days	204	3.66	(0.43–31.25)	0.236	3.22	(0.41–24.96)	0.264
Tool 2. Reported any barrier to adherence in the PACTG questionnaire	203	7.65	(2.75–21.26)	< 0.001	7.08	(2.42–20.73)	< 0.001
Tool 3. Child self-report missed dose vs. never missed a dose in previous 3 days	204	4.48	(0.92–21.81)	0.064	2.85	(0.52–15.76)	0.229
Tool 3. Child self-report missed dose vs. never missed a since the last clinic visit	207	6.18	(2.61–14.64)	< 0.001	8.64	(1.96–38.04)	0.004

Agreement between adherence monitoring tools

Kappa agreement between announced pill count and the PACTG adherence questionnaire was 0.03 (slight agreement); announced pill count and any reported barrier to adherence in the PACTG adherence questionnaire in the previous 24 weeks was 0.18 (slight agreement); announced pill count and the child self-report of missed doses in the previous 3 days was 0.07 (slight agreement), and announced pill count and a reported missed dose in the 24 weeks since last clinic visit was 0.21 (fair agreement) (Table 2). Agreement between the PACTG adherence questionnaire and the child self-report of missed doses in the previous 3 days was 0.47 (moderate agreement).

Predictors of virologic failure

After adjusting for gender, ethnicity, treatment arm, and caregiver education in multivariate longitudinal random effects logistic models, adherence tools which significantly predicted VF were poor adherence by announced pill count (OR 4.56; 95%CI 1.78–11.69), having reported any barrier to adherence (OR 7.08; 95%CI 2.42–20.73), and missed a dose in 24 weeks since the last clinic visit (OR 8.64; 95%CI 1.96–38.04) (Table 3). Age, CDC clinical classification, type of regimen, CD4% at ART initiation, plasma HIV-RNA at ART initiation, family status, type of caregiver, child's attending school status, HIV-disclosure, and poor adherence by missed dose in previous 3 days by PACTG adherence questionnaire and child self-report were not associated with VF (all $p > 0.20$).

Discussion

Determining which adherence monitoring tool is best for use in children is challenging. In our study, the child self-report of having any missed any dose in the previous 24 weeks since the last HIV-RNA, the parent reporting any barrier to adherence in the PACTG adherence questionnaire, and poor adherence by announced pill count were independently associated with VF in univariate models, and after adjusting for gender, ethnicity, treatment arm, and caregiver education. In contrast, adherence assessed by the PACTG adherence questionnaire, and by 3-day child self-report were not associated with VF. Based on our study results, we recommend the child self-report of any missed dose since the previous visit to measure ART adherence not only in HIV research but also in routine care,¹⁷ because it had the most significant association with VF, and is easy and fast to administer in a busy clinic setting.

Several adherence monitoring methods have been studied in HIV-infected children but there is no consensus among researchers on how best to define and measure ART adherence in this population. A systematic review of pediatric HIV care programs in low- and middle-income countries reported heterogeneous methods were used to measure ART adherence.¹⁸ A review of self-reported measures of adherence found that self-reporting with longer recall periods were more likely to yield adherence estimates that significantly correlated with HIV-RNA, compared to those using a shorter recall period.¹⁷ Similarly, self-reported missed doses in the past

month was more successful in predicting VF than a 3-day recall in a group of US children.¹⁰ These longer recall periods are consistent with the findings of our study. Asking the child whether they have missed any doses since the last clinic visit is practical and can be done in any setting. The patients' beliefs about whether their answer will have positive or negative consequences can influence the accuracy of their self-report,⁵ so the questioning a patient about their adherence should be done in a calm and nonjudgmental way. In addition, when attempting to describe overall adherence, asking simple questions about any missed doses is generally more sensitive than complex questioning about missed doses of each drug in the regimen separately.^{19,20}

Pill counts are commonly used to assess adherence in clinical practice. Adherence by pill count <95% for >3 times at any visit significantly predicted VF in a study of HIV-infected Thai children.²¹ Adherence by pill count reveals lower adherence estimates than self-reports,¹⁸ and offers comparable adherence data to Medication Event Monitoring System caps (MEMS cap) while being less costly.²² In our study, poor adherence by announced pill count was also significantly associated with VF. The child self-report of any missed doses since the last visit had a similar level of significance compared to adherence by pill count (Table 3) but was much faster to administer.

The slight to fair agreement between each adherence tool in our study (Table 2) concurs with studies in adults where poor agreement among different adherence measuring tools has also been found.²³ Although we found moderate agreement between the PACTG adherence questionnaire and child-report tools, both involved 3-day recall periods (one in the form of a caregiver questionnaire and the other as a direct question for the child and/or caregiver), and neither were associated with VF.

HIV-RNA monitoring is essential to detect treatment failure in HIV-infected children. The VF rate in this study was similar to previous reports from other resource-limited settings; 13% in Ugandan children,²⁴ 16% in Cambodian children,²⁵ and 16% in Thai children.²⁶ If HIV-RNA is not routinely available, WHO guidelines recommend clinical and immunologic monitoring.²⁷ However, immunologic failure has a low sensitivity in detecting VF.²⁸

Predictors of VF in HIV-infected children reported in other studies include physician documentation of poor adherence, lower baseline CD4%, male gender, and treatment with nevirapine versus efavirenz-based HAART, and being an orphan.^{25,26,29,30} In US children, reporting a barrier to adherence in the PACTG adherence questionnaire was significantly associated with elevated HIV-RNA.¹⁰ VF was significantly associated with reporting any barrier in the PACTG questionnaire in our study, so this tool could be useful for helping physicians to identify children at risk for VF, and address specific barriers that prevent them from adhering to their treatment regimens.

Our study had a number of limitations. First, the adherence assessments in our study were indirect methods that do not measure the presence of drug in the individual. Second, we did not record whether self-reporting data came from the caregiver or the child themselves. Self reporting by caregivers and children is subject to recall bias, and may overestimate adherence by 10–20% compared to electronic methods.³¹ Despite this limitation, self-reporting of missed

doses since the last clinic visit was significantly associated with the development of VF. Third, almost all children in this study were treated with non-nucleoside reverse transcriptase inhibitor-based HAART, so the results may not be applicable to children on boosted protease inhibitor-based HAART. The strength of our study was that the data were collected systematically in a carefully designed US NIH-funded trial over 3 years, together with frequent HIV-RNA monitoring.

Several ongoing studies will contribute more to the evidence base defining how best to assess adherence in children with HIV. The Pediatric European Network for Treatment of AIDS is conducting a Medication Event Monitoring System (MEMS cap) study in children using efavirenz-based HAART (the BREATHER Study; the clinical trials.gov NCT01641016). Moreover, ART concentration in hair as an adherence measuring tool is being evaluated in an on-going trial.³² Other strategies to help to improve ART adherence in children include using taste-masking products with ART;³³ a randomized controlled trial to evaluate a simplified once daily lopinavir–ritonavir regimen in HIV-infected children (the KONCERT study; the clinical trials.gov NCT01196195) is ongoing.

In summary, as adherence assessment should be routinely integrated into every clinic visit,⁶ we recommend the child self-report of any missed doses since the previous clinic visit to monitor ART adherence in HIV research and clinical practice, because it showed a strong association with VF, and is easy and fast to administer in HIV-infected children.

Acknowledgments

The PREDICT study is sponsored by National Institute of Allergy and Infectious Disease (NIAID), Grant number U19 AI053741, Clinical trial.gov identification number NCT00234091. Antiretroviral drugs for PREDICT are provided by GlaxoSmithKline (AZT, 3TC), Boehringer-Ingelheim (NVP), Merck (EFV), Abbott (RTV) and Roche (NFV). The study is partially funded by the National Research Council of Thailand. We are grateful to the children and their families for participating PREDICT.

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Author Disclosure Statement

No competing financial interests exist.

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