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Five-year trends in antiretroviral usage and drug costs in HIV-infected children in Thailand

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Abstract

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Background—As antiretroviral treatment (ART) programmes mature, data on drug utilization and costs are needed to assess durability of treatments and inform programme planning.

Methods—Children initiating ART were followed in an observational cohort in Thailand. Treatment histories from 1999–2009 were reviewed. Treatment changes were categorized as: drug substitution (within class), switch across drug class (non-nucleoside reverse-transcriptase inhibitors (NNRTIs) and protease-inhibitor (PI), and to salvage therapy (dual PI or PI and NNRTI). Antiretroviral drug costs were calculated in six-month cycles (US$ 2009 prices). Predictors of high drug cost including characteristics at start of ART (baseline), initial regimen, treatment change and duration on ART were assessed using mixed-effects regression models.

Results—507 children initiated ART with a median 54 (IQR, 36–72) months of follow-up. Fifty-two percent had a drug substitution, 21% switched across class and 2% to salvage therapy. When allowing for drug substitution, 78% remained on their initial regimen. Mean drug cost increased from $251 to $428 per child per year in the first and fifth year of therapy, respectively. PI-based and salvage regimens accounted for 16% and 2% of treatments prescribed and 33% and 5% of total costs, respectively. Predictors of high cost include: baseline age ≥8 years, non nevirapine-based initial regimen; switch across drug class and to salvage regimen ($p<0.005$).

Conclusion—At 5 years, 21% of children switched across drug class and 2% received salvage therapy. The mean drug cost increased by 70%. Access to affordable second and third-line drugs is essential for the sustainability of treatment programmes.

Keywords

Children; HIV; antiretroviral therapy; cost; Thailand

Introduction

In 2011, an estimated 562,000 HIV-infected children were on antiretroviral therapy (ART) globally. Coverage of ART is estimated at 28% of children eligible for treatment as compared to 57% among adults [1]. As part of the UNAIDS Global Plan to eliminate paediatric AIDS by 2015, there are calls to expand access to early infant HIV diagnosis and timely provision of ART for HIV-infected children [1]. As countries and donors consider scale-up of paediatric treatment programmes, there is a need for data on the cost of ART from the healthcare provider's perspective, to inform programme planning and decision analytic models for optimal allocation of resources.

Antiretroviral drugs constitute a major expenditure for HIV treatment programmes, accounting for 30% to over 50% of total annual costs in low- and middle-income countries[2–6]. A recent modelling study based on data from the Global Fund recipient countries, projected dramatic increases in expenditures on antiretrovirals as increasing number of patients inevitably require more costly second and third line regimens [5]. Cross-sectional studies estimated that 2% to 10% of paediatric cohorts in Africa and Asia are receiving second line therapy, while estimates in South America are much higher at 13% to 40%, due to varying levels of programme maturity and patient monitoring strategies [7,8]. There are scarce data on drug utilization in children and cost implications at the programmeme level, particularly in in low- and middle-income countries.

In this study we analysed data from a large prospective observational cohort of children initiating ART in Thailand (NCT00433030 www.clinicaltrials.gov). The objectives were to describe the long-term trends in drug utilization, costs from the healthcare provider perspective and to assess predictors of high drug costs.

Methods

Study population

HIV-infected children received ART as part of an open observational cohort study in a network of 28 public hospitals throughout Thailand, as described elsewhere [9,10]. In brief, the study began in 1999 and is ongoing. All visits, ART and laboratory monitoring were provided free of charge. Parents/guardians provided written informed consent at study entry and from December 2006, assent was requested from children ≥8-years-old. The study was approved by the Thai Ministry of Public Health and local Ethics Committees.

Inclusion Criteria

Antiretroviral naïve children (<18 years old) who initiated ART (defined as ≥3 drugs including ≥2 drug class) between 1st January 1999 and 31st January 2009; and were on follow-up for >1 day were included in this analysis, with follow-up data included through 30th September 2009.

Antiretroviral treatment

Children initiated ART based upon clinical and immunological criteria: US Centers of Disease Control and Prevention (CDC) HIV clinical disease stage B or C or CD4 T cell percentage <20% if under 2 years old, and CD4<15% if 2 years old or above [11,12]. Protease inhibitor (PI) based regimens were first available in 1999, mainly unboosted nelfinavir, and from 2006 ritonavir boosted lopinavir. Non-nucleoside reverse transcriptase inhibitors (NNRTI) based regimens were available from 2002, including an adult generic fixed dose combination of stavudine, lamivudine and nevirapine (GPOvir-S©) and from 2008 zidovudine, lamivudine and nevirapine (GPOvir-Z©) produced in Thailand. These fixed dose combinations were widely used in older children who could swallow, with tablets divided into half or quarters according to the child's body weight[13]. From 2006, there was a gradual phase out of the use of stavudine to avoid long-term toxicity [14]. Children received alternative regimens as needed for toxicity/intolerance or treatment failure as defined by the physician at site.

Follow up

Children attended the clinic monthly for a basic physical exam, drug refills and adherence counseling by a nurse. They saw a physician every month during the first 3 months of treatment and every 3 months thereafter. Laboratory monitoring including CD4 and viral load assessments were conducted every 6 months.

Deaths were reported by the sites. Loss to follow-up was defined as missed scheduled visit and no contact for over six months.

Treatment history

Data on individual treatment history was prospectively collected with start and end dates of all drugs disbursed, including dates of treatment interruptions (defined as stopping all drugs for any duration).

Treatment changes were reviewed and categorised as: (i) drug substitution: change of ≥1 drug within the same drug class; (ii) switch: change of ≥1 drug including change across drug class, from NNRTI to PI-based regimen or vice versa and (iii) change to salvage therapy defined as dual PI or PI plus NNRTI based regimen. All treatment switches were reviewed and reason for change was categorised as: treatment failure (immunologic, virologic or clinical), toxicity/intolerance, treatment simplification (to reduce pill burden) or other

reasons. Use of salvage therapy was assumed to be due to treatment failure. Two children participated in a clinical trial after entry into the observational cohort. Since their subsequent treatment did not reflect standard of care, these children were censored on entry to the trial.

Drug cost

The outcome of interest was drug cost which refers only to cost of antiretrovirals and does not include cost of other medications or other related services. Costs were calculated per 6-month cycle based on individual treatment history and dosage, incorporating all treatment changes and interruptions during the cycle. Drug dosage was based on the closest weight available at start of each cycle using the WHO weight/dosage categories (<10kg, 10–14kg, 15–19kg, 20–29kg, ≥30kg)[15]. Missing weight data (5%) was imputed using the carry-forward method from the previous recorded month, except for missing baseline weight (2%), where backward imputation was used based on the next available weight. Costs were calculated up to date of death or last visit, not including the cost of prescription at last visit. Children who did not complete a 6-month cycle were censored at date of last visit or death, and drug costs were calculated up to that date. Periods of treatment interruption were assigned a cost of zero. Some drug combinations used during the initial years of the study are no longer recommended. As the aim of this analysis was not to document historical costs, but rather to estimate likely costs of similar cohorts receiving treatment today, we applied the cost of the most comparable drugs or treatment combination (same drug class) widely used in Thailand today. For example, cost of unboosted nelfinavir was replaced by the cost of ritonavir-boosted lopinavir which is the preferred PI.

Drug costs were standardised at 2009 government prices based on bulk purchasing and reported in Thai baht. Where government prices were not available non-governmental organisation prices paid by the programme were used. Costs were converted to US dollar (US$) using the 2009 average market exchange rate of 34.3 bath per dollar [16].

Statistical Analyses

First, Kaplan Meier probability of treatment change for failure (defined as switch across drug class for documented reason of failure or to salvage therapy) was assessed; children were at risk from date of ART initiation to first switch for failure or last follow up visit. In addition, we assessed the probability of virological failure defined as: non suppression (viral load (VL) ≥400 copies) after one year of ART in infants or after 6 months in older children; or virological rebound with confirmed VL ≥400 copies after previous suppression as per Thai guidelines [17]. We used the 400 copies/mL over the recommended 50 copies/mL threshold as this was the lower limit of detection of the virological assays during the earlier years of the programme. Children were censored at date of first virological failure or last follow up.

Second, we assessed predictors of drug cost using the outcome of log transformed cost per 6-month cycle. Where drug cost was zero (due to extended treatment interruption) the value of one was applied to allow inclusion in the analysis. Explanatory variables considered were baseline characteristics at start of ART: sex, age, CD4%, viral load, CDC stage, anthropometric measures (weight-for-age z-score (WAZ), height-for-age z-score (HAZ) and weight-for-height for age z-score (WHZ) based on the Thai reference curves [18,19]), calendar year and initial regimen. In addition, we considered duration on follow-up and type of treatment change: drug substitution, switch across class and to salvage treatment (as separate binary variables). All explanatory variables had <10% missing values except for viral load with 17% missing data.

As the outcome was repeat measures of cost over follow-up time, a multilevel regression model was used with subject level clusters [20]. A random coefficient model with a random slope for follow-up time was chosen over a fixed-effect model of time as this was a better fit to the observed data ($p<0.05$). Variables associated with higher drug cost in univariable and multivariable analyses with $p<0.2$ were included in the final model based on a complete case analysis. The predicted log costs were retransformed using Duan's method, the mean predicted value was calculated and compared to the mean actual cycle cost and the distribution of cluster level standardised residuals checked [21]. Results were compared with a generalized estimation equation (GEE) model with an autoregressive correlation structure, using predicted individual intercepts [22]. In sensitivity analyses, missing baseline explanatory variables were imputed using multiple imputation using chained equations (MICE) [23]. All statistical analyses were performed using STATA 11 (Stata Corporation, College Station, TX).

Results

A total of 507 children were included in this analysis. At start of ART, the median age was 7 years (15% ≤2 years) and the median CD4% was 7% (Table 1). Fifty-five percent of children initiated on nevirapine (NVP) based regimen, 40% on efavirenz (EFV) based, and 5% on PI-based regimens. As of September 2009, there were 36 deaths (7.1%), 25 loss to follow up (4.9%), and 52 (10.1%) withdrew from the study, mostly due to relocation. The median duration of follow-up was 54 months (IQR, 36–72), 207 (41%) children reached 5 years of ART.

Treatment changes

Overall, 311 (61%) children experienced treatment change (Table 2): 187 (60%) had one, 68 (22%) had two, and 56(18%) had three or more changes. Seventy-three percent of changes were drug substitutions. Two-thirds of these were changes in NRTI backbone, of which 73% was stavudine replacement. If we ignored drug substitutions, 397 (78%) children would be considered to be on their initial regimen.

One hundred and six children (21%) had treatment changes across drug class: 93% switched from NNRTI to PI and 7% from PI to NNRTI-based regimens. The reasons for switch were: 93 (88%) treatment failure, 5 (5%) intolerance/toxicity, 3 (3%) treatment simplification and 5 (5%) for other reasons (3 Tuberculosis concomitant treatment, 1 pregnancy, and 1 by error). Among children who switched due to treatment failure, the median time to switch was 23 (IQR 17–33) months after start of ART. Overall, ten children (2%) received salvage regimen at a median of 27 (IQR, 20–51) months after start of ART. The Kaplan Meier probability of treatment change for failure was 1.5% (95% CI, 0.6–2.9) at 1 years, 17.8% (95% CI, 14.5–21.7) at 3 years and 21.4% (95% CI, 17.6–25.8) at 5 years of therapy (Figure 1).

The probability of virological failure was 18.1% (95% CI, 14.9–21.9); 23.4% (95% CI, 19.7–27.6) and 27.8% (95% CI, 23.5–32.5) at 1, 3 and 5 years, respectively. Among the 120 children experiencing virological failure, 82 (68%) had a treatment change across drug class or to salvage therapy. The median duration between first virological failure and treatment change was 9.6 months (IQR, 7.8–14.0).

Trends in antiretroviral drugs prescribed and costs

When we take into account all treatments disbursed, 79% was NNRTI-based. However, the proportion of children on NNRTI-based regimens declined from 95% at baseline to 69% at 5 years, while the proportion on PI-based regimens increased from 5% to 23, respectively

(Supp. Figure 1). A small proportion of children received NRTI-only regimens in the process of treatment change or to address adherence issues. In addition, 44 children experienced 52 episodes of treatment interruptions, which represented 2% of total treatment time.

The mean cost of antiretrovirals varied significantly by drug class and weight category. NNRTI-based regimens were the least costly from $255 to $748 per child per year depending on weight/dosage (Table 3). PI-based regimens ranged from $582 to $1,626, while the most costly were dual PI salvage regimens from $1,047 to $2,386. In this cohort, the mean cost of ARV drugs increased from $251 to $428 per child per year in the first and fifth year, respectively, an increase of 70% (Supp. Figure 2). This corresponds with the rising number of children on PI-based and to a lesser extent to salvage regimens, which accounted for 16% and 2% of all treatments disbursed and 33% and 5% of total drug costs, respectively. By year 5, PI-based and salvage regimens accounted for half of the annual drug costs (Supp. Figure 3).

Predictors of high drug cost

In univariable analysis, all variables were associated with the mean cycle cost except for sex, baseline viral load, WAZ, WHZ and drug substitution (Table 4). In multivariable analyses, key independent predictors of high cost were older age at start of ART, non-NVP initial regimen, switch across drug class and receipt of salvage therapy.

Children aged ≥8 years at start of ART had 26% higher drug cost per cycle as compared to 2–7 year olds ($p<0.0001$). EFV-based and PI-based initial regimen was associated with significantly higher cycle cost as compared to NVP-based regimen ($p<0.0001$). Children with a treatment switch across drug class had 45% higher cost as compared to no switch ($p<0.0001$), while receipt of salvage regimen was associated with an 89% increase in mean drug cost as compared to children without salvage therapy ($p=0.002$). In addition, high baseline HAZ and longer duration on follow-up were associated with a small increase in mean costs ($p\leq0.006$). After adjusting for these factors, baseline CD4% and CDC stage were no longer associated. These results were consistent with those obtained when using the GEE model and the MICE dataset (data not shown). The findings were comparable when the model included only baseline characteristics and duration on ART (exclude type of treatment change), with no effect of CD4% or CDC stage and the strongest predictor of high cost remained initial regimen (data not shown).

Discussion

In this large Thai pediatric cohort, approximately two-thirds of children experienced a treatment change. However the large majority of these changes were drug substitutions within the same drug class, in response to updated treatment guidelines, namely replacement of stavudine to avoid long-term toxicities [24]. The Thai national pediatric treatment programme with over 3,400 children with a shorter median duration of follow-up of 1.7 years reported that 17.3% had a treatment change for any cause up to 2007 [25]. This is consistent with our observation of 61% treatment change over a median 4.5 years of follow-up, taking into account the large phase out of stavudine from 2006 which may not have been fully captured in the national programme.

If we ignored drug substitutions then 78% of children would be considered to be on their initial regimen. This is comparable to results from the US and Europe, where 65–71% of children remained on their initial regimen at 5-years of follow up, when allowing for drug substitutions[26,27]

In this cohort, one in five children had a treatment switch across drug class, 88% of which had documented treatment failure. The probability of treatment change for failure was 21% at 5 years. This is higher than previous estimates from cross sectional surveys which reported only 10% of children on second therapy in Asia[7]. However, the median duration on treatment in that study was unclear and it included sites with limited access to second line therapies and may underestimate actual need.

Furthermore, this study had routine access to viral load monitoring every 6 months. Early detection of viremia allows for a more rapid switch to avoid accumulation of resistance mutations as compared to clinical or immunological only monitoring used in other settings[7]. The probability of virological failure was 23% at 3 years and 28% at 5 years of therapy. This is comparable to previous reports of virological failure in children in Thailand[28]. Among the children with virological failure, 68% subsequently switched treatments, highlighting how some children may remained on failing regimens despite virological monitoring, particularly if presenting with adherence issues as reported elsewhere [29]. Only two percent of children in our cohort received salvage regimen This is lower than reports from the recent PENPACT-1 trial in the US/Europe where 7% of children needed salvage therapy at 5-years but this was based on stringent switching criteria [30].

The mean annual cost of ARV regimen per child increased by 70% from $251 to $428 over 5 years. As expected, second and third line regimens were key drivers of higher cost as our cohort matured. In the fifth year, one-quarter of children received PI-based or salvage regimen, which accounted for half of the annual drug cost (Supp. Figure 3). Similar trends has been observed in adult studies [31,32]. However, these higher costs of advanced regimens must be considered in the wider context. Most children respond well to second and third line therapy [33–35], which reduces the risk of mortality, disease progression and AIDS defining events and potentially offsetting the cost of inpatient care in part.

It is also important to note that the highest estimated cost of drugs in children in our cohort at year 5 remains lower than the reported mean annual costs of drugs in adults in Thailand[36]. A large pooled analyses of data from low and middle income countries estimated mean drug costs of $549 per adult per year[37], an increased from previous years due to the transition from stavudine to more costly tenofovir containing first line regimens.

These findings have important implications, first is the importance of adherence support for children and their caregivers to maximize durability of first line treatments. Second, improved access to affordable second and third line regimens is critical for the long-term sustainability of treatment programmes, particularly for pediatrics programmes due to the limited drug options available in child-friendly formulations.

In terms of patient level predictors of high drug cost, there was no effect of baseline CD4% or CDC disease stage, suggesting that children initiating therapy at advanced disease stage did not incur greater costs. However it is important to note that this refers only to cost of antiretroviral drugs and does not include cost of hospitalizations or treatment of opportunistic infections which are known to be considerably higher in those with advanced disease stage [3,10,38]. The strongest predictor of high drug cost was initiation on efavirenz or PI-based initial regimens. As expected, treatment switch across drug class and to salvage regimen were also associated with higher cost. The effect of older age was most likely due to higher dosage requirement. The association between higher height-for-age z-score and not weight for age z-score with higher drug cost was unexpected, further analyses using time-updated growth parameters may provide further insight.

There are several study limitations to consider. Firstly, the study was based on drugs available in Thailand and prices quoted in 2009. The antiretroviral drug market is rapidly

evolving with price reductions and introduction of new drugs that may alter some of our cost estimates. For example, there has been two price reductions of over 5% as of 30th May 2012: lopinavir/ritonavir (100mg/25mg by 6.5%), saquinavir (500mg by 12%), and the introduction of tenofovir, tenofovir/emtricitabine and darunavir for third line treatment. Nonetheless, our costs are still comparable with recent estimates by the WHO for low and middle income countries [8,39].

Second, we only examined baseline prognostic variables associated with high drug cost rather than time updated variables such as current CD4, viral load or adherence which have been reported as predictive of cost of HIV care in adults[4]. Third, we did not have patient-level data on drug formulation of regimens used which may affect the cost, although we did base our estimates on the most commonly used formulation within the weight category. Fourth, we used actual cost as paid by the healthcare provider rather than market costs. While the latter is often considered to best reflect opportunity cost of resources used [40], it would have provided an inflated estimate of cost of drugs in the Thai setting and therefore have limited application in informing national policies.

The development of a low-cost EFV based fixed dose combination which is expected to be available in Thailand at under $200 per person per year is likely to nullify the higher cost associated with EFV based first line regimen [41]. However, we consider the other main findings to stand, particularly the higher cost associated with PI-based first line regimen. This may have important implications as recent studies suggest that infants have superior response to PI-based initial therapy as compared to NVP based therapy, irrespective of prior NVP exposure[42]. Indeed PI-based regimens are already the preferred starting regimen for young children in resource-rich countries[26]. As PI drugs are also the basis of most second line and salvage regimens, they are an essential component of any treatment programme. Improved access to child-friendly second and third line drugs at affordable prices through market incentivisation, price negotiations or pooled purchasing will be critical for the long term sustainability of national treatment programmes [43,44].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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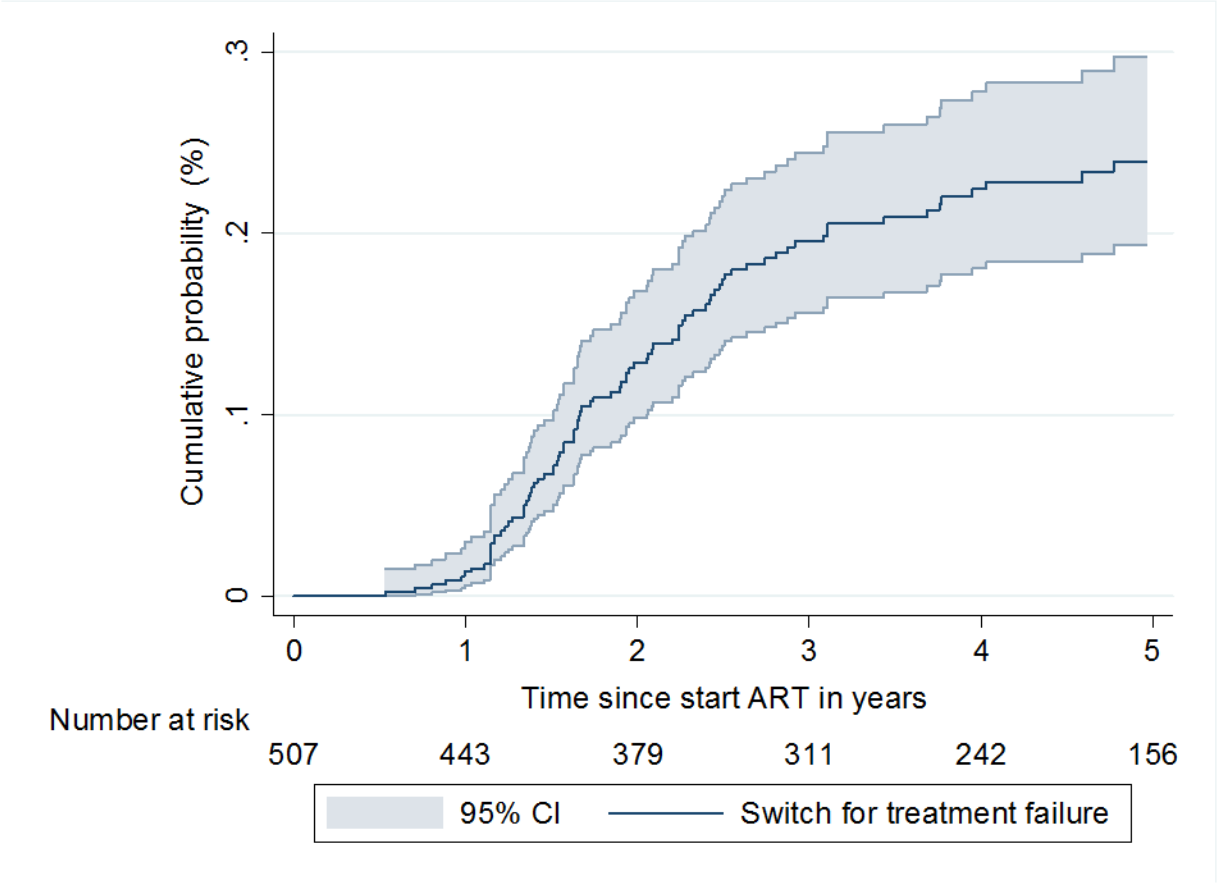

Figure 1.
Cumulative probability of switch for treatment failure

Table 1

Characteristics of children at start of ART (N=507)

	n (%)
Characteristic at ART initiation	
Sex, female	272 (54)
Age, median (years) (IQR)	7.2 (3.9 to 10.0)
<2 years	78 (15)
CDC HIV Classification (n=490)	
N or A	231 (47)
B	121 (25)
C	138 (28)
CD4%, median (IQR) (n=499)	7% (2 to 14%)
Viral load, median (IQR) (n=422)	5.1 (4.7 to 5.6)
Weight in kg, median (IQR) (n=498)	17 (12–21)
Weight for age z-score, median (IQR) (n =498)	−1.2 (−1.7 to −0.7)
≤-2 z-score	84 (17)
Height for age z-score, median (IQR) (n =467)	−2.2 (−3.1 to −1.3)
≤-2 z-score	265 (57)
Weight for height z-score, median (IQR) (n=467)	−0.5 (−1.1 to 0.1)
≤-2 z-score	39 (8)
Initial regimen	
NVP-based	272 (55)
EFV -based	199 (40)
PI-based	25 (5)
Calendar year at initiation	
<2003	50 (10)
2003–2004	233 (46)
≥2005	223 (44)

Note: Data are no. (%) unless otherwise indicated; IQR, inter quartile range.

Table 2

Summary of treatment changes and interruptions

	n	%*	Median time to first event in months after start of ART (IQR)
No treatment change	196	39	-
One or more treatment change	311	61	-
Drug substitution (within class)	266	52	31 (11–41)
Switch across drug class (NNRTI to PI or vice versa)	106	21	22 (17–33)
To salvage regimen (dual PI or PI & NNRTI)	10	2	27 (20–51)
Treatment interruption	44	9	18 (3–37)

Note:

*Denominator is total cohort (N=507), one child can contribute to more than one type of treatment change.

Table 3

Mean annual cost of antiretroviral drugs per patient by weight and drug class (USD)

	Weight category (kg)				
	<10	**10–14**	**15–19**	**20–29**	**≥30**
NNRTI based	$260	$255	$278	$465	$749
Single PI based	$583	$908	$850	$1,225	$1,626
Dual PI based	-	$1,037	$1,172	$1,633	$2,386
PI & NNRTI	-	$997	$1,009	$1,305	$1,316

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Table 4

Predictors of 6-monthly treatment cost using random coefficient model

		Univariable analysis				Multivariable analysis			
		Coef	**Exp(Coef)***	**SE**	**P**	**Coef**	**Exp (Coef)***	**SE**	**P**
Sex	Female	0.00	1.00	0.07	0.97	-	-		
Age (years)	<2 yrs	−0.17	0.84	0.11	0.12	−0.39	0.67	0.11	**<0.0001**
	2–7 yrs	−0.24	0.79	0.08	**0.002**	−0.30	0.74	0.06	**<0.0001**
	≥8 yrs	Referent	Referent			Referent	Referent		
CD4% (n=563)	per 5% increase	−0.05	0.95	0.02	**0.038**	0.01	1.00	0.02	0.78
Viral load (n=484)	per log increase	0.03	1.03	0.05	0.51	-			
CDC stage (n=561)	N or A	Referent	Referent				Referent		
	B or C	0.14	1.15	0.07	**0.06**	−0.02	0.98	0.06	0.75
WAZ (n=564)	per z-score increase	0.03	1.03	0.04	0.43	-	-		
HAZ (n=523)	per z-score increase	0.07	1.07	0.03	**0.009**	0.06	1.06	0.02	**0.006**
WHZ (n=523)	per z-score increase	0.03	1.03	0.03	0.32	-	-		
First line regimen	NVP based	Referent	Referent			Referent	Referent		
	EFV based	0.70	2.00	0.07	**<0.0001**	0.63	1.88	0.06	**<0.0001**
	PI-based	1.03	2.79	0.13	**<0.0001**	1.0	2.72	0.14	**<0.0001**
Calendar year	<2003	Referent	Referent			Referent	Referent		
	2003–4	−0.36	0.70	0.13	**0.004**	−0.18	0.83	0.11	0.10
	≥2005	0.03	1.03	0.13	0.82	0.03	1.03	0.11	0.78
Drug substitution (within class)		0.00	1.00	0.07	0.96	-			
Switch across class		0.38	1.46	0.09	**<0.0001**	0.37	1.45	0.07	**<0.0001**
To salvage therapy		0.73	2.06	0.25	**0.005**	0.64	1.89	0.20	**0.002**
Follow-up time	per 6-month increase	0.01	1.00	0.00	**<0.0001**	0.01	1.01	0.001	**<0.0001**

Note: WAZ: weight for age z-score; HAZ height for age z-score; WHZ weight for height for age z-score; NVP nevirapine; EFV efavirenz; PI protease inhibitor.

Exp(Coef) exponential of coefficient.