

**Antiretroviral Medication Prescription Errors and Associated Factors among HIV Infected
Children in Selected Health Facilities in Nairobi, Kenya**

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Abstract

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Background: Access to life saving antiretroviral therapy (ART) in many resource-limited settings has increased, yet more than 30% of children on ART do not achieve viral suppression. Multiple factors contribute to viral suppression including patient, drug and health system factors. Infants and children require continuous medication dose adjustments in response to changing pharmacodynamics and inappropriate dosing may contribute to viral non-suppression. This study sought to determine the magnitude of prescription dosing errors and associated factors.

Methods: We conducted a cross sectional study among HIV Infected children aged ≤ 11 years receiving ART in four public health facilities. Demographic, clinical and prescription data were abstracted from the medical charts of children receiving ART for the last clinical visit. Descriptive statistics were used to summarize participant characteristics. Logistic regression was conducted to determine factors associated with prescription dosing errors.

Results: A total of 196 children were included in the study; among these, 52.6% were male and the median age was 7.9 years (IQR 4.8, 10.0). The most commonly used ART regimen was abacavir/lamivudine/lopinavir/ritonavir taken by 31.1% (61/196) of children. Overall, 43.6% (85/196), 45.9% (90/196) and 46.9% (92/196) of children lacked data on specific ARV formulation, dosage and frequency of dosing, respectively. Among 104 children with complete prescription information, the dosing error rate was 36.5% (38/104). In a multivariable model, being on non-nucleoside reverse transcriptase inhibitors was independently associated with prescription dosing errors (adjusted odds ratio 8.8; 95% confidence interval 2.1-36.3).

Conclusion: Half of children receiving antiretroviral therapy had inadequate prescription information and among those with adequate information, one third had prescription dosing errors. These findings call for urgent measures to address health care prescribing practices and knowledge. In addition, further evaluation should be conducted to determine associations with viral suppression.

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ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-retroviral Therapy
ARV	Antiretroviral medications
HIV	Human Immunodeficiency Virus
HMO	Health Management Organization
IQR	Interquartile range
KGs	Kilograms
MLs	Milliliters
MOH	Ministry of Health
NASCOP	National AIDS and STI Control Program
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitors
OI	Opportunistic Infection
PI	Protease Inhibitor
PDD	Prescribed Daily Dose
RNA	Ribonucleic Acid
TB	Tuberculosis
VL	Viral Load
WHO	World Health Organization
UNAIDS	Joint United Nations Programme on HIV/AIDS
UW	University of Washington

ARV DRUG ABBREVIATIONS

ABC	Abacavir
AZT	Zidovudine
3TC	Lamivudine
NVP	Nevirapine
EFV	Efavirenz
LPV/r	Lopinavir/ritonavir
TDF	Tenofovir

INTRODUCTION

Pediatric HIV infection remains a major challenge globally, particularly in Sub-Saharan Africa where more than 80% of the 2.1 million HIV infected children reside¹. Without antiretroviral therapy (ART), one-third of HIV-infected children will die by one year of age and 50% will not survive into their second year². While increased access to antiretroviral therapy (ART) has led to declines in morbidity and mortality²⁻⁴, only 43% of children living with HIV were on ART in 2016 globally¹. Furthermore, studies show suboptimal viral suppression among children and adolescents on ART, particularly in low and middle-income countries where the proportion ranges between 40-70%. This falls far short of the global target to have 90% of persons on ART achieve viral suppression^{1,4-7}. In Kenya, of the 83,255 children on ART as at December 2017, only 66% were virally suppressed^{8,9}.

Poor viral suppression is associated with increased risk of opportunistic infections, development of drug resistance and the subsequent need to transition to less available, more expensive regimens^{3,10,11}. Additionally, for sexually active HIV-infected adolescents, failure to achieve viral suppression results in higher risk of transmitting HIV¹⁰. Achieving optimal viral suppression among children is complex and multifactorial^{10,12}. Multiple studies have documented predictors and factors associated with virologic suppression among children. These include patient related factors such as age, degree of immunosuppression at ART initiation, adherence to ART; system related factors such as supply of medicines, support systems for adherence and retention; and drug related factors such as drug to drug interactions, drug

efficacy, toxicity, and dosing^{5,11,13-17}. Children experience physiologic changes and changes in weight as they grow¹⁸. Consequently, they will experience age-related pharmacokinetic changes that influence drug absorption: changes in body fat and water composition, and changes in renal and hepatic function that influence metabolism and excretion of medicines. These necessitate medication dose adjustments as they grow¹⁸⁻²².

The World Health Organization (WHO) provides weight based dosing recommendations for antiretroviral (ARV) medicines for children weighing less than 35 kilograms²³. These recommendations require that health care providers regularly review weight and conduct appropriate ARV medication dose adjustment as weight changes²⁴. Failure to adjust medication dosage in response to weight changes may lead to overdosing or under dosing. Suboptimal levels of ARV medicines below the desired therapeutic levels are predictive of virologic failure^{25,26}. On the other hand, overdosing has the potential to cause side effects and toxicity that may have detrimental consequences^{18,21}.

Errors in dosing of medications are common and form a significant proportion of overall medication errors²⁷⁻³¹. Dosing errors occur when a patient receives the wrong or inappropriate medication dose for his or her weight, age or body surface area and can occur at prescription, transcribing, dispensing, administration and monitoring³². Children are particularly vulnerable to increased risk of errors owing to number of factors. Weight or body surface area based dosing requires that accurate weight and height measurements are taken in order to calculate or determine appropriate dose^{33,34}. In addition, health system factors such as worker fatigue, understaffing and drug related factors such as route of administration, multidrug therapy and

individual factors such as age and weight among others have been associated with prescription errors in children^{27,34–40}. Specific to ARV medicines, data from the Collaborative HIV Pediatric study found poor documentation of weight and high ARV dosing error rates of up to 60%²⁹. In Africa, studies conducted in South Africa, Tanzania and Ethiopia assessing ARV medication errors have found rates ranging between 12 – 26%^{41,42,35}.

Africa carries 80% of the burden of HIV among children globally, yet studies focusing on antiretroviral therapy medication errors and associated factors in resource-limited settings are few. Understanding the magnitude of pediatric ARV dosing errors and associated factors may contribute to the observed poor treatment outcomes in children. In addition, understanding prescribing practices, service provider and facility characteristics can provide insights on implementable interventions at the facility.

The primary objective of this study was to determine the prevalence of pediatric ARV dosing errors and associated factors among children taking antiretroviral therapy in selected health facilities in Nairobi County. The study will contribute to existing data on pediatric ARV dosing errors and identify areas for quality improvement in the care of HIV infected children. In addition, the study may inform future larger scale studies on HIV pediatric treatment.

METHODS

Overall study design

This cross sectional study was conducted among HIV-infected children in HIV care and receiving antiretroviral therapy in four public health facilities within Nairobi County, Kenya.

Study Setting

Nairobi County hosts the capital city of Kenya and had over 150 public health facilities that provide antiretroviral therapy to both adults and children as at December 2016. The sampling frame included public health facilities providing pediatric ART that reported to the Ministry of health database as at December 2016. The facilities were selected using probability proportional to size sampling such that facilities with larger number of children on ART had higher probabilities of selection. Of the four health facilities selected, one was a tertiary referral facility (tier 4); one a secondary referral facility (tier 3) and two facilities were primary care facilities (tier 2) providing pediatric HIV treatment.

Study participants

The study population was children on antiretroviral therapy. The inclusion criteria included being active on follow up as at the time of the study, age 11 years and below and having been on ART for at least 6 months prior to the study. The age cut-off of 11 years was used to maximize on the population where weight based dosing would be expected. To identify the eligible children, the facility ART registers (electronic or manual) were used to develop the patient sampling frame based on the eligibility criteria. All eligible study participants were assigned a

study ID number and randomly ordered. Data was then abstracted from sequential medical records until all eligible participants in the selected study facilities were included.

Data collection

Data collection took place between April and May 2018. Data for eligible children was obtained from individual medical charts and entered into an electronic study tool. For each medical record, demographic, clinical and prescription data were obtained from the clinical notes and prescriptions for the most recent clinical visit prior to the study. Prescription data collected included weight, ART regimen, ARV drug formulation type, formulation strength, dosage and frequency of dosing. For each health facility, data on human resources availability, availability of equipment and medicines was obtained through interviews with facility management staff and entered into a facility study electronic tool. At the end of each day, completed study records were submitted electronically into a password protected study database.

Measures

The primary measure of interest was the prescription dosing errors. An error was defined as any deviation from the recommended dosing for the weight band for the particular ARV medication formulation. Kenya follows the WHO pediatric ARV dosing guidance. This dosing guidance categorizes children weighing below 35 kilograms into 6 weight bands (3–5.9 kgs, 6–9.9 kg, 10–13.9 kg, 14–19.9 kg, 20–24.9 kg, and 24–34.9kgs) and recommends standard dosing for each weight bands^{23,43}. Weight-band dosing amounts to some form of above or below the target dosing from that recommended by the manufacturer but tries to ensure that a child does not

receive more than 25% above the maximum target dose or more than 5% below the minimum target dose⁴⁴. Based on this consideration, in this study, any deviation was considered a prescription dosing error. To determine dosing accuracy, study participants were categorized into the 6 defined dosing weight bands. A binary variable of dosing error [No error versus error] was created. Individual factors evaluated for association with errors included ARV drug class, WHO stage, current age, sex and weight band category and WHO stage at ART initiation.

Data analysis

Descriptive analysis of study participants' socio-demographic and clinical characteristics was conducted and data were reported in tables as frequencies and proportions. For the primary outcome measure, study participants were categorized by the prescribed ARV drug formulations and within each formulation categorized by the defined dosing weight bands (3–5.9 kgs, 6–9.9 kg, 10–13.9 kg, 14–19.9 kg, 20–24.9 kg, and 24–34.9kgs). Subsequently, the dosage and frequency of dosing were assessed to determine correctness of dosing when compared to the national recommendations for pediatric ARV dosing. Only formulations that had complete dosage and frequency data were analyzed for dosing accuracy and data presented in row frequencies and proportions. In the analysis for dosing errors, ARV formulations that had a frequency of 5 or less were excluded from analysis. Dosing was only deemed correct if both the dosage (i.e. number of tablets or mls) and frequency of dosing (i.e. once or twice a day) were in line with national recommendations. Dosing error analysis was then conducted per child to determine the proportion of children with any dosing errors. To determine factors associated with prescription

dosing errors, a multivariate logistic regression model was fitted. Univariate analyses of predictor variables for the primary measure of interest were conducted and then variables included in the multivariable analyses performed selected based on a significance level of < 0.2 in the univariate analyses. Statistical analysis was conducted using STATA 14.0

Ethical approval

The University of Nairobi/Kenyatta National Hospital Ethical Review Committee and the Institutional review board of University of Washington, Seattle, Washington approved the study. A waiver of informed consent for medical record abstraction in accordance with 45CFR 46.116 (d) was obtained. The waiver was provided given that no personal identifiers were collected and the study did not involve interaction with children participating in the study.

RESULTS

In total, 196 HIV infected children on antiretroviral therapy were included in the study (table 1). Of these, 52.6% were male, median age was 7.9 years (Interquartile range [IQR] 4.8, 10.0). The three most commonly used ARV regimens were abacavir + lamivudine + lopinavir/ritonavir at 31.1% (61 /196), zidovudine + lamivudine + nevirapine at 21.9% (43/196) and abacavir + lamivudine + nevirapine at 18.4% (36/196).

Table 1: Sociodemographic and clinical characteristics of HIV infected children receiving ART in selected health facilities in Nairobi County

Characteristic	N (196)	%
Sex		
Female	93	47.4
Male	103	52.6
Median age at ART initiation, years (IQR¹)	1.6	(0.6,3.6)
Median current Age, years (IQR¹)	7.9	(4.8,10.0)
Current weight		
6-9.9	11	5.6
10-13.9	13	6.6
14-19.9	44	22.5
20-24.9	52	26.5
25-34.9	71	36.2
=>35	5	2.6
WHO stage at ART Initiation		
I	76	38.8
II	42	21.4
III	32	16.3
IV	5	2.6
Not documented	41	20.9
CD4 value at ART initiation		
CD4 count	53	27.0
CD4 percentage	7	3.6
not documented	136	69.4
Current TB		
No	179	91.3
Yes	17	8.7

Child Orphan		
No	66	33.7
Yes	15	7.7
not documented	115	58.7
Transfer in to the facility		
No	149	76.0
Yes	47	24.0
Current ART Regimen*		
abc_3tc_azt	1	0.5
abc_3tc_efv	26	13.3
abc_3tc_lpv	61	31.1
abc_3tc_nvp	36	18.4
azt_3tc_efv	3	1.5
azt_3tc_lpv	17	8.7
azt_3tc_nvp	43	21.9
tdf_3tc_efv	1	0.5
Other	8	4.1
Current ARV Formulation Type		
Liquid	1	0.5
Tablet	88	44.9
Tablet & capsules	12	6.1
Tablet & liquid	19	9.7
not documented	76	38.8
Health facility		
01 (tier 2)	55	28.1
02 (tier 4)	70	35.7
03 (tier 3)	54	27.6
04 (tier 2)	17	8.7

* *Abc- Abacavir, Azt - Zidovudine, 3TC -Lamudivine , Nvp -Nevirapine , Efv-Efavirenz , Lpv/r -Lopinavir/ritonavir ,TDF -Tenofovir*

¹ *IQR- Interquartile range*

Among the 196 children included in the study, 56.6% (111/196) had documentation of at least one ARV formulation that formed their treatment regimen. Of these 111 children with ARV formulations documented, 95.5% (106/111) had dosage (i.e. number of tablets or milliliters) documented, and of these 98.1% (104/106) had frequency of dosing (once or twice a day) documented (figure 1). Overall, out of the 196 children, 43.6% (85/196) of children had no documentation of the ARV formulations, 45.9% (90/196) had no documentation of dosage and 46.9% (92/196) lacked documentation of frequency of dosing (figure 1).

Dosing error analysis was conducted among 104 children with 176 ARV formulation prescriptions after excluding formulations that had a frequency of five or fewer prescriptions. Among the 104 of children, 36.5% (38/104) had at least one dosing error (table 2a). High frequency of prescription dosing errors were observed among children in weight category 20-24.9kgs at 54.5% (18/33) and children who had been transferred into the study facilities; 46.2% (12/26) compared to those who had not (33.3%; 26/78). When grouped by drug class, 61.9% (13/21) of children on non-nucleoside reverse transcriptase inhibitors (NNRTI) based regimens had at least one dosing error compared to other drug classes; protease inhibitors at 18.8% (3/16) and nucleoside reverse transcriptase inhibitors at 34.3 % (23/67) % (table 2a). Of the 176 ARV formulation prescriptions included in the analysis, 30.1% (53/176) had dosing errors, with abc/3tc 60/30mg (66.7% ;6/9) and nvp/200mg (54.2% ; 13/24) formulations having the highest errors rates (table 2b).

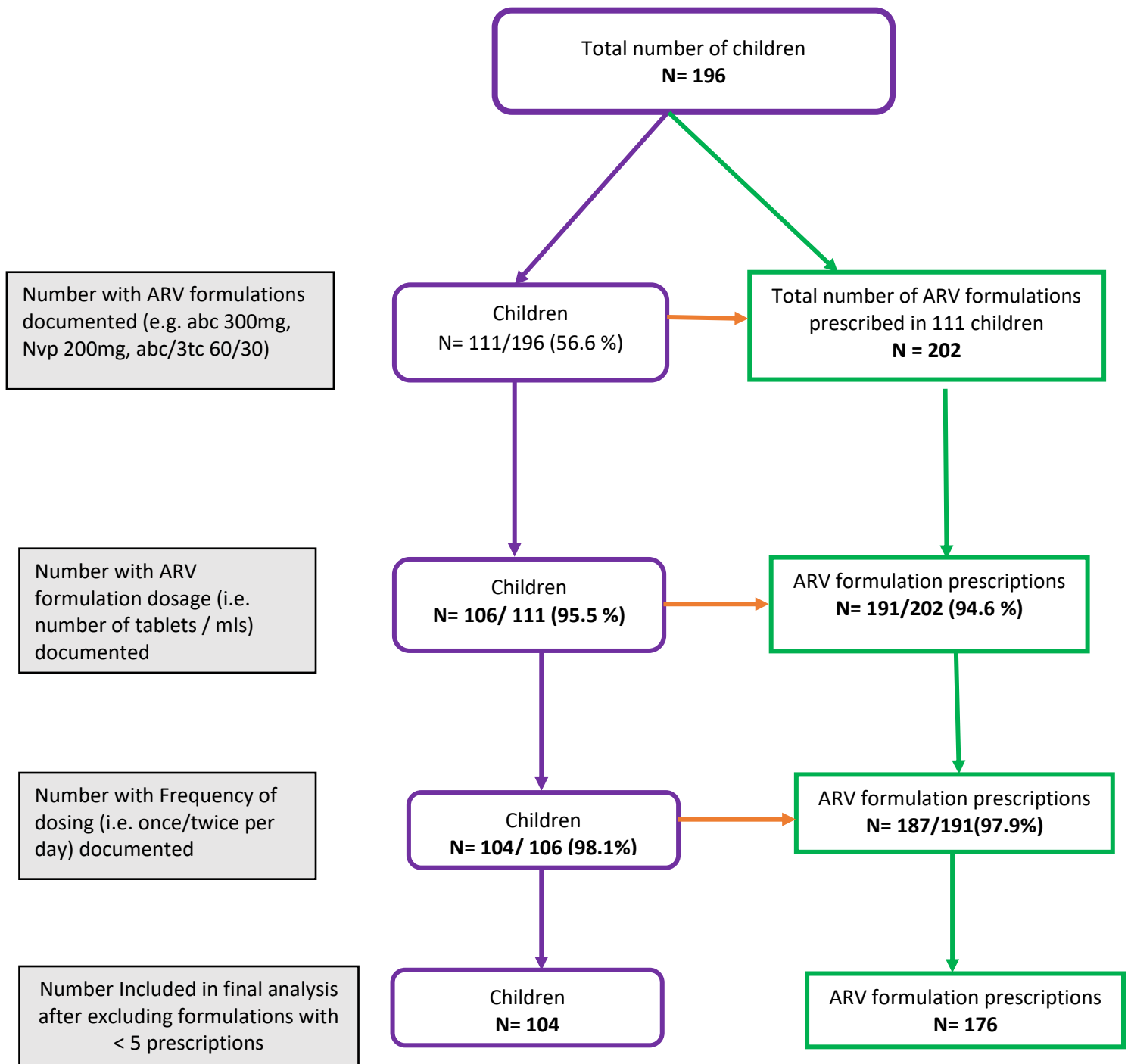


Figure 1: Flow chart of documented prescription information among children on ART and by Antiretroviral drugs formulations

Table 2a: Antiretroviral medication prescribing dosing error rates among children by select characteristics

Variable	Total N	Dosing Error		P value
		N	%	
Total children	104	38	36.5	
Sex				0.909
Female	47	17	36.2	
Male	57	20	35.1	
Current age (years)				0.983
1- <2 years	9	3	33.3	
2 - <5 years	23	8	34.8	
>=5	72	26	36.1	
Current weight(kgs)				0.630
6-9.9	6	1	16.7	
10-13.9	8	2	25.0	
14-19.9	19	7	36.8	
20-24.9	33	15	45.5	
25-34.9	37	12	32.4	
=>35	1	0	0.0	
Had the child lost any parent(s)?				0.188
No	48	14	29.2	
not documented	50	22	44.0	
Yes	6	1	16.7	
WHO stage at ART Initiation				0.224
I	43	15	34.9	
II	20	5	25.0	
III	13	3	23.1	
IV	4	1	25.0	
not documented	24	13	54.2	
Transferred from other facility				0.408
No	78	26	33.3	
Yes	26	11	42.3	
ARV drug class*				0.002
NRTI	67	23	34.3	
NNRTI	21	13	61.9	
PI	16	3	18.8	
Health facility **				0.004
01 (tier 2)	26	4	15.4	
02 (tier 4)	32	19	59.4	
03 (tier 3)	36	11	30.6	
04 (tier 2)	10	3	30.0	

*NRTI- nucleoside reverse transcriptase inhibitors, NNRTI-non nucleoside reverse transcriptase inhibitors, PI-protease inhibitor

** Tier 4-Tertiary referral hospitals; tier 3 -Secondary referral or county referral hospitals; tier 2 -primary care facilities i.e. health centers and dispensaries

Table 2b: Antiretroviral medication prescribing dosing error rates by ARV formulations

Variable	Total	N	%
Total formulations	176	53	30.1
ARV Formulation Strength*			
3TC/150	13	5	38.5
ABC/300	14	6	42.9
ABC/3TC/120/60	46	13	28.3
ABC/3TC/60/30	9	6	66.7
AZT/3TC/300/150	8	0	0.0
AZT/3TC/60/30/50	8	2	25.0
AZT/3TC/NVP/150/200/300	12	0	0.0
EFV/200	14	2	14.3
LPVR/200/50	14	4	28.6
LPVR/LIQUID/80/20ML	14	2	14.3
NVP/200	24	13	54.2
Current weight(kgs)			
6-9.9	7	1	14.3
10-13.9	11	2	18.2
14-19.9	32	10	31.3
20-24.9	60	27	45.0
25-34.9	65	13	20.0
=>35	1	0	0.0

* *Abc*- Abacavir, *Azt* - Zidovudine, *3TC* -Lamudivine , *Nvp* -Nevirapine , *Efv*-Efavirenz , *Lpv/r* - Lopinavir/ritonavir ,*TDF* -Tenofovir

In univariate logistic regression, only current sex and ARV drug class and health facility met the criteria for inclusion in the multivariate logistic regression. After controlling for these variables, children on non-nucleoside reverse transcriptase inhibitors had 8-times the odds of having a dosing error compared to children receiving nucleoside reverse transcriptase inhibitors (AOR 8.8; 95% CI 2.1-36.3) (Table 3). In addition receiving antiretroviral therapy in health facility 02 (a tier 4 facility) was associated with higher odds of dosing errors; AOR 6.1 (95% CI: 1.6 -23.7) compared to health facility 01 (tier 2). We found no significant association with sex.

Table 3: Factors associated with pediatric prescription dosing errors among HIV infected children in selected health facilities in Nairobi County

Variable	Adjusted Ratio	95% CI	p-value
Sex			
female*	1		
Male	1.411	(0.544-3.661)	0.479
Facility**			
01 (tier 2)*	1		
02 (tier 4)	6.113	(1.580-23.653)	0.009
03 (tier 3)	1.745	(0.442-6.883)	0.427
04 (tier 2)	4.234	(0.728-24.633)	0.108
ARV drug class***			
NRTI*	1		
NNRTI	8.815	(2.140-36.313)	0.003
PI	0.712	(0.164-3.089)	0.65

* Reference category

** Tier 4-Tertiary referral hospitals; tier 3 -Secondary referral or county referral hospitals; tier 2 - primary care facilities i.e. health centers and dispensaries

*NRTI- nucleoside reverse transcriptase inhibitors, NNRTI-non nucleoside reverse transcriptase inhibitors, PI-protease inhibitor

DISCUSSION

This Kenyan study found that about half of children receiving antiretroviral therapy had no documentation of drug formulations, dosage and frequency of dosing at prescription. The study also found that among the half that had adequate prescription information, one third had at least one prescription dosing error. Dosing errors were more likely to occur if children were receiving non-nucleoside reverse transcriptase inhibitors compared to other antiretroviral drug classes.

There are limited published data on pediatric antiretroviral medication errors in Kenya and other resource-limited settings. The studies that have been conducted within and outside Africa that focused on antiretroviral medicines found variable rates of medication errors. The Collaborative HIV pediatric study that analyzed cohort data over a period of 8 years among children aged 2-12 years on antiretroviral therapy found prescription dosing error rates varying between 6% and 62% for the various ARV drugs and drug classes²⁹. In Tanzania, a study conducted in a large pediatric HIV treatment center among children on antiretroviral therapy and anti-TB medications found that among 50 children aged 9 months to 18 years with 755 prescriptions made over a period of one year, 22% of the patients had at least one dosing error³⁵.

Other studies that have not specifically focused on antiretroviral medications have found high dosing error rates among children. A study in the United States (US) in 3 health maintenance organizations(HMO) found that among children weighing <35 kilograms, only 67% of doses of medications were in accordance with recommended dosing ranges⁴⁵. This rate is similar to that found in our study where a third of children with complete data had dosing errors. A systematic

review of studies in United Kingdom (UK) and US found errors ranging from 3–37% for prescribing, 5–58% for dispensing, 72–75% for administering, and documentation or transcribing errors ranging between 17–21% , supporting not only our findings of the prescription dosing errors but also documentation errors ⁴⁶. Within Kenya, a study conducted in a large referral hospital found 1023 errors among 405 non-HIV infected patient records, 73.9% of which were documentation errors, followed by dosing errors at 8.8%³⁶. This proportion of documentation errors while higher than that found in our study highlights the challenge of documentation in contributing to medication errors.

Our study found that non-nucleoside reverse transcriptase inhibitors were significantly associated with prescription dosing errors. This finding is supported by findings from the Collaborative HIV pediatric study that found that non-nucleoside reverse transcriptase inhibitors had more frequent errors than nucleoside reverse transcriptase inhibitors²⁹.

This study was not without limitations. Data were abstracted from medical charts and about 50% of children had missing data on formulation type, strength, dosage and frequency, which may bias the results. However, there was nothing in the study to suggest that those with missing data were systematically different from those with adequate information. Due to the small numbers in some of the variable categories that had complete data for analysis, only major correlates were likely to be significantly associated with prescribing dosing errors. Lastly, the study was cross sectional in nature and the results may not reflect consistent prescription dosing status among children on ART.

Despite these limitations, this study presents data that largely remains unavailable locally and globally. A review of literature revealed limited published data on antiretroviral dosing errors among children. This study therefore is critical in adding to the available data on pediatric dosing. Kenya has among the highest ART treatment coverage for HIV infected children with 83,255 children on ART representing a treatment coverage of 77%⁴⁷. However, viral suppression remains low at an average of 65% among children⁹. Dosing errors have the potential to contribute to poor viral suppression if children are under dosed and indirectly if overdosed and they experience toxicity and hence discontinue treatment. Although the study did not assess the association with viral suppression, the results of this study provide insight into potential factors contributing to suboptimal viral suppression. Data from this study may also inform large-scale antiretroviral medication error studies and assessment of the association with viral suppression. Lastly, this study revealed concerning levels of prescription information gaps. Clinicians who prescribe antiretroviral medications are the front line determinants of what and how much medications a child receives. Pharmacists rely on clinician prescriptions and lack of information on what formulation, dosage should be provided could lead to gross dispensing errors particularly among children whose dosage should change as weight changes. Moreover, for children, the same antiretroviral drugs can have different strengths and hence the need for clear dosing instructions. While the country has put in place multiple quality measures including use of electronic prescription systems in some centers and other quality improvement measures such as use of dosing checklists, more needs to be done to address poor prescription practices and accurate dosing.

REFERENCES

1. Global HIV Statistics UNAIDS_FactSheet_en.pdf. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. Accessed June 23, 2018.
2. Newell M-L, Coovadia H, Cortina-Borja M, et al. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet Lond Engl*. 2004;364(9441):1236-1243. doi:10.1016/S0140-6736(04)17140-7
3. Nesheim SR, Kapogiannis BG, Soe MM, et al. Trends in opportunistic infections in the pre- and post-highly active antiretroviral therapy eras among HIV-infected children in the Perinatal AIDS Collaborative Transmission Study, 1986-2004. *Pediatrics*. 2007;120(1):100-109. doi:10.1542/peds.2006-2052
4. Ciaranello AL, Chang Y, Margulis AV, et al. Effectiveness of pediatric antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2009;49(12):1915-1927. doi:10.1086/648079
5. Adjé-Touré C, Hanson DL, Talla-Nzussouo N, et al. Virologic and immunologic response to antiretroviral therapy and predictors of HIV type 1 drug resistance in children receiving treatment in Abidjan, Côte d'Ivoire. *AIDS Res Hum Retroviruses*. 2008;24(7):911-917. doi:10.1089/aid.2007.0264
6. Bunupuradah T, Sricharoenchai S, Hansudewechakul R, et al. Risk of first-line antiretroviral therapy failure in HIV-infected Thai children and adolescents. *Pediatr Infect Dis J*. 2015;34(3):e58-62. doi:10.1097/INF.0000000000000584
7. Wamalwa DC, Lehman DA, Benki-Nugent S, et al. Long-term virologic response and genotypic resistance mutations in HIV-1 infected Kenyan children on combination antiretroviral therapy. *J Acquir Immune Defic Syndr 1999*. 2013;62(3):267-274. doi:10.1097/QAI.0b013e31827b4ac8
8. ART | Dashboard. <http://commodities.nascop.org/#>! Accessed November 18, 2017.
9. Dashboard. <https://viralload.nascop.org/>. Accessed January 14, 2018.
10. Kahana SY, Fernandez MI, Wilson PA, et al. Rates and correlates of antiretroviral therapy use and virologic suppression among perinatally and behaviorally HIV-infected youth linked to care in the United States. *J Acquir Immune Defic Syndr 1999*. 2015;68(2):169-177. doi:10.1097/QAI.0000000000000408
11. Kekitiinwa A, Lee KJ, Walker AS, et al. Differences in factors associated with initial growth, CD4, and viral load responses to ART in HIV-infected children in Kampala, Uganda, and the

- United Kingdom/Ireland. *J Acquir Immune Defic Syndr* 1999. 2008;49(4):384-392. doi:10.1097/QAI.0b013e31818cdef5
12. Cruz MLS, Cardoso CAA, Darmont MQ, et al. Viral suppression and adherence among HIV-infected children and adolescents on antiretroviral therapy: results of a multicenter study. *J Pediatr (Rio J)*. 2014;90(6):563-571. doi:10.1016/j.jpmed.2014.04.007
 13. Lindsey JC, Hughes MD, Violari A, et al. Predictors of virologic and clinical response to nevirapine versus lopinavir/ritonavir-based antiretroviral therapy in young children with and without prior nevirapine exposure for the prevention of mother-to-child HIV transmission. *Pediatr Infect Dis J*. 2014;33(8):846-854. doi:10.1097/INF.0000000000000337
 14. Muller AD, Bode S, Myer L, Stahl J, von Steinbuchel N. Predictors of adherence to antiretroviral treatment and therapeutic success among children in South Africa. *AIDS Care*. 2011;23(2):129-138. doi:10.1080/09540121003758523
 15. Puga D, Cerutti B, Molisana C, et al. Still Far From 90-90-90: Virologic Outcomes of Children on Antiretroviral Therapy in Nurse-led Clinics in Rural Lesotho. *Pediatr Infect Dis J*. 2016;35(1):78-80. doi:10.1097/INF.0000000000000929
 16. Rodríguez de Schiavi MS, Scrigni A, García Arrigoni P, et al. [Highly active antiretroviral therapy in HIV sero-positive children. Disease progression by baseline clinical, immunological and virological status]. *Arch Argent Pediatr*. 2009;107(3):212-220. doi:10.1590/S0325-00752009000300008
 17. Zanoni BC, Phungula T, Zanoni HM, France H, Cook EF, Feeney ME. Predictors of poor CD4 and weight recovery in HIV-infected children initiating ART in South Africa. *PloS One*. 2012;7(3):e33611. doi:10.1371/journal.pone.0033611
 18. Yokoi T. Essentials for starting a pediatric clinical study (1): Pharmacokinetics in children. *J Toxicol Sci*. 2009;34 Suppl 2:SP307-312.
 19. Bartelink IH, Rademaker CMA, Schobben AFAM, van den Anker JN. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin Pharmacokinet*. 2006;45(11):1077-1097. doi:10.2165/00003088-200645110-00003
 20. L'homme R, Warris A, Gibb D, Burger D. Children with HIV are not small adults: what is different in pharmacology? *Curr Opin HIV AIDS*. 2007;2(5):405-409. doi:10.1097/COH.0b013e3282ced13f
 21. Mahmood I. Dosing in children: a critical review of the pharmacokinetic allometric scaling and modelling approaches in paediatric drug development and clinical settings. *Clin Pharmacokinet*. 2014;53(4):327-346. doi:10.1007/s40262-014-0134-5

22. Turkova A, Webb RH, Lyall H. When to start, what to start and other treatment controversies in pediatric HIV infection. *Paediatr Drugs*. 2012;14(6):361-376. doi:10.2165/11599640-000000000-00000
23. WHO | Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. WHO. <http://www.who.int/hiv/pub/arv/arv-2016/en/>. Accessed January 14, 2018.
24. WHO | IATT paediatric ARV formulary and limited-use list: 2016 update. WHO. <http://www.who.int/hiv/pub/paediatric/iatt-paediatric-hiv-2016/en/>. Accessed January 14, 2018.
25. de Vries-Sluijs TEMS, Dieleman JP, Arts D, et al. Low nevirapine plasma concentrations predict virological failure in an unselected HIV-1-infected population. *Clin Pharmacokinet*. 2003;42(6):599-605. doi:10.2165/00003088-200342060-00009
26. Durant J, Clevenbergh P, Garraffo R, et al. Importance of protease inhibitor plasma levels in HIV-infected patients treated with genotypic-guided therapy: pharmacological data from the Viradapt Study. *AIDS Lond Engl*. 2000;14(10):1333-1339.
27. Al-Ramahi R, Hmedat B, Alnjajrah E, Manasrah I, Radwan I, Alkhatib M. Medication dosing errors and associated factors in hospitalized pediatric patients from the South Area of the West Bank - Palestine. *Saudi Pharm J SPJ*. 2017;25(6):857-860. doi:10.1016/j.jsps.2017.01.001
28. Wong ICK, Ghaleb MA, Franklin BD, Barber N. Incidence and nature of dosing errors in paediatric medications: a systematic review. *Drug Saf*. 2004;27(9):661-670.
29. Menson EN, Walker AS, Sharland M, et al. Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study. *BMJ*. 2006;332(7551):1183-1187. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1463938/>. Accessed January 3, 2018.
30. Hoyle JD, Davis AT, Putman KK, Trytko JA, Fales WD. Medication dosing errors in pediatric patients treated by emergency medical services. *Prehospital Emerg Care Off J Natl Assoc EMS Physicians Natl Assoc State EMS Dir*. 2012;16(1):59-66. doi:10.3109/10903127.2011.614043
31. Koumpagiotti D, Varounis C, Kletsiou E, Nteli C, Matziou V. Evaluation of the medication process in pediatric patients: a meta-analysis. *J Pediatr (Rio J)*. 2014;90(4):344-355. doi:10.1016/j.jpmed.2014.01.008
32. Aronson JK. Medication errors: what they are, how they happen, and how to avoid them. *QJM Int J Med*. 2009;102(8):513-521. doi:10.1093/qjmed/hcp052

33. King JR, Kimberlin DW, Aldrovandi GM, Acosta EP. Antiretroviral pharmacokinetics in the paediatric population: a review. *Clin Pharmacokinet*. 2002;41(14):1115-1133. doi:10.2165/00003088-200241140-00001
34. Ghaleb M, Barber N, Franklin B, W S Yeung V, F Khaki Z, C K Wong I. *Systematic Review of Medication Errors in Pediatric Patients*. Vol 40.; 2006. doi:10.1345/aph.1G717
35. Naik NM, Mbwaji RN, Mgawe M, et al. Pharmaceutical Dosing Errors at a Pediatric HIV Clinic in Mwanza, Tanzania. *Pediatr Infect Dis J*. 2017;36(10):973-975. doi:10.1097/INF.0000000000001639
36. Prevalence, Risk Factors and Root Cause Analysis of Medication Errors among Paediatric In-Patients at Kisii Level 5 Hospital | Department of Pharmacology And Pharmacognosy. <http://pharmacology.uonbi.ac.ke/node/1156>. Accessed January 8, 2018.
37. Kaushal R, Bates DW, Landrigan C, et al. Medication Errors and Adverse Drug Events in Pediatric Inpatients. *JAMA*. 2001;285(16):2114-2120. doi:10.1001/jama.285.16.2114
38. Mikhael EM. Evaluating the Accuracy of Drug Dosing in the Prescriptions for Children under 5 Years Old from Non Pediatric Physicians in Outpatient Clinics. *Am J Pharmacol Sci*. 2014;2(4):61-64. doi:10.12691/ajps-2-4-1
39. Mekonnen AB, Alhawassi TM, McLachlan AJ, Brien JE. Adverse Drug Events and Medication Errors in African Hospitals: A Systematic Review. *Drugs - Real World Outcomes*. November 2017:1-24. doi:10.1007/s40801-017-0125-6
40. Alsulami Z, Conroy S, Choonara I. Medication errors in the Middle East countries: A systematic review of the literature. *Eur J Clin Pharmacol*. 2013;69(4):995-1008. doi:10.1007/s00228-012-1435-y
41. Katende-Kyenda NL, Lubbe M, Serfontein JHP, Truter I. Are antiretrovirals prescribed according to the recommended prescribed daily doses in the private healthcare sector in South Africa. *Health SA Gesondheid*. 2011;16(1):9. <https://hsag.co.za/index.php/hsag/article/view/604>. Accessed January 8, 2018.
42. Agu KA, Oqua D, Adeyanju Z, et al. The Incidence and Types of Medication Errors in Patients Receiving Antiretroviral Therapy in Resource-Constrained Settings. *PLOS ONE*. 2014;9(1):e87338. doi:10.1371/journal.pone.0087338
43. Guidelines-on-Use-of-Antiretroviral-Drugs-for-Treating-and-Preventing-HI....pdf. <https://www.faces-kenya.org/wp-content/uploads/2016/07/Guidelines-on-Use-of-Antiretroviral-Drugs-for-Treating-and-Preventing-HI....pdf>. Accessed January 10, 2018.
44. Information NC for B, Pike USNL of M 8600 R, MD B, Usa 20894. *PRESCRIBING INFORMATION AND WEIGHT-BASED DOSING OF AVAILABLE ARV FORMULATIONS FOR*

INFANTS AND CHILDREN. World Health Organization; 2010.

<https://www.ncbi.nlm.nih.gov/books/NBK138586/>. Accessed January 10, 2018.

45. McPhillips HA, Stille CJ, Smith D, et al. Potential medication dosing errors in outpatient pediatrics. *J Pediatr*. 2005;147(6):761-767. doi:10.1016/j.jpeds.2005.07.043
46. Miller MR, Robinson KA, Lubomski LH, Rinke ML, Pronovost PJ. Medication errors in paediatric care: a systematic review of epidemiology and an evaluation of evidence supporting reduction strategy recommendations. *Qual Saf Health Care*. 2007;16(2):116-126. doi:10.1136/qshc.2006.019950
47. Kenya-AIDS-Progress-Report_web.pdf. http://nacc.or.ke/wp-content/uploads/2016/11/Kenya-AIDS-Progress-Report_web.pdf. Accessed November 18, 2017.

Annex.

Annex 1: Kenya Pediatric ARV dosing Chart

Drug	Strength of tablets	Number of tablets by weight band morning and evening										Strength of adult tablet	Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
AZT/3TC	Tablet (dispersible) 60/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 /150 mg	1	1
AZT/3TC/NVP 2	Tablet (dispersible) 60/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 /150 /200 mg	1	1
ABC/3TC	Tablet (dispersible) 60/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600 /300	0.5	0.5
ABC/3TC	Tablet (dispersible) 120/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600 /300 mg	0.5	0.5
SOLID SINGLE FORMULATIONS														
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
NVP2	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200 mg	1	1
	Tablet 200 mg	–	–	–	–	0.5	0.5	1	0.5	1	0.5	200 mg	1	1
	Tablet 100/25 mg	–	–	–	–	2	1	2	2	2	2	100/25 mg	3	3
	Tablet 200/50 mg	–	–	–	–	–	–	1	1	1	1	200/50 mg	2	1

LPV/r	Pellets/Capsules 40/10 mg	2	2	3	3	4	4	5	5	6	6			
DRV	Tablet 75 mg	-	-	-	-	3	3	5	5	5	5			
RAL	Chewable tablets 25 mg	-	-	-	-	3	3	4	4	6	6	400 mg	1	1
	Chewable tablets 100 mg	-	-	-	-	-	-	1	1	1.5	1.5	400 mg	1	1
	Granules (100 mg/sachet)	0.25	0.25	0.5	0.5	-	-	-	-	-	-		-	-
LIQUID SINGLE FORMULATIONS														
AZT	10 mg/ml	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	-	-	-	-	-	-	-
ABC	20 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	-	-	-	-	-	-	-
3TC	10 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	-	-	-	-	-	-	-
NVP	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	-	-	-	-	-	-	-
LPV/r	80/20 mg/ml	1 ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml	-	-	-
DRV	100 mg/ml	-	-	-	-	2.5 ml	2.5 ml	3.5 ml	3.5 ml	-	-			
EFV	200 mg					-	1	-	1.5	-	1.5		-	2