Evaluation of weight-based prescription of antiretroviral therapy in children

S Dakshina,1,* ID Olaru,1,2,* P Khan,3,4 L Raman,1 G McHugh,1 M Bwakura–Dangarembizi,5 K Nathoo,5 S Munyati,1 H Mujuru5 and RA Ferrand1,2

1Biomedical Research and Training Institute, Harare, Zimbabwe, 2Clinical Research Department, London School of Hygiene and Tropical Medicine, London, UK, 3Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK, 4Interactive Research and Development, Karachi, Pakistan and 5Department of Paediatrics and Child Health College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe

Objectives
The aim of the study was to investigate the extent of and factors associated with incorrect dosing of antiretroviral therapy (ART) in HIV-infected children in Harare, Zimbabwe.

Methods
All children aged 0–10 years and children aged 11–17 years who weighed <35 kg and taking ART were recruited from the paediatric HIV clinic at Harare Hospital. Their current doses of ART drugs were compared against doses recommended by the national guidelines.

Results
Among 309 children recruited [55% male; median age 7 years (interquartile range (IQR) 5–10 years)], the median CD4 count was 899 cells/μL and the median duration of their current ART regimen was 11.2 months (IQR 4.9–17.1 months). Overall, 110 (35.6%) children were prescribed incorrect doses of at least one drug component within their ART regimen; 64 (20.7%) under-dosed and 49 (15.9%) over-dosed on at least one drug. Children receiving a higher than recommended dose of at least one drug were younger compared with correctly dosed children (median 6 versus 7 years, respectively; \( P = 0.001 \)), had been on their current ART regimen for a shorter time (median 7.2 versus 13 months, respectively; \( P = 0.003 \)) and were less likely to be receiving a three-drug fixed-dose combination (FDC; 42.9 versus 63.3%, respectively; \( P = 0.009 \)). Those who were under-dosed were also less likely to be on a three-drug FDC (25 versus 63.3%, respectively; \( P < 0.001 \)).

Conclusions
Over a third of children were prescribed incorrect doses of ART. Children taking triple-drug FDCs were likely to be correctly dosed. Our study highlights the importance of weight monitoring at each clinical contact, training of health care providers on paediatric drug dosing and the need for wider availability of FDCs for children.

Keywords: Africa, antiretroviral therapy, children, dosing

Accepted 22 November 2018

Introduction
Of the estimated 1.8 million children under the age of 15 years living with HIV globally, nearly 90% are in sub-Saharan Africa [1]. The scale-up of antiretroviral therapy (ART) has dramatically improved survival, but challenges remain in achieving sustained virological suppression in children living with HIV in resource-limited countries [2]. With the paucity of pharmacodynamic (PD) and pharmacokinetic (PK) data in children, therapeutic ranges derived from adult ART data have been adapted for paediatric prescribing [3,4].
Drug PKs and PDs in children are affected by several factors, including organ maturation and differences in drug metabolism and clearance, and changes in weight during growth [3–5]. Body surface area-based dosing has been used in the past to define dosing ranges for children, but this method was often challenging to use in resource-limited settings and, therefore, weight-based dosing was introduced [6]. Current international guidelines for paediatric ART recommend weight-based dosing with regular monitoring of a child’s weight and appropriate ART dose adjustment to avoid over- or under-dosing of ART drugs [7].

We assessed paediatric ART prescribing in a large public-sector HIV clinic in Harare, Zimbabwe, to elucidate whether children are correctly dosed with ART and factors associated with incorrect dosing.

Methods
Study site
A cross-sectional study of children attending the paediatric HIV out-patient clinic at Harare Central Hospital, Zimbabwe, the largest public-sector hospital in Harare, was carried out. An average of 100 children (defined as individuals aged 0–17 years old) attend per day. ART is initiated by the clinic doctor and children are reviewed by a doctor every 3 months (or more frequently if clinically indicated). At the doctor’s review, the child’s height and weight are recorded and ART is prescribed for 3 months. If ART stocks do not allow for 3-monthly dispensation, then children can be requested to return for a drug dispensing visit at either 1- or 2-monthly intervals. On such a visit, children are reviewed by the clinic counsellor and/or nurse to assess ART adherence and ART is then dispensed (the child’s height and weight are not monitored at these dispensing visits).

Study period and enrolment of participants
All children aged 0–10 years and children aged 11–17 years who weighed < 35 kg, should receive weight-based dosing for ART according to Zimbabwean national guidelines [8]. All children taking ART, who attended the clinic from 1 May to 31 July 2015, who were eligible for weight-based dosing and who were accompanied by a guardian were recruited. Only the first visit was included for children who attended on multiple occasions during the study period. The participant and guardian were interviewed, and clinical records were reviewed to collect data on demographics, CD4 cell count within the past 6 months, the current ART regimen, the date of initiation of the current ART regimen and the most recent record of height, weight and ART dose (from the last doctor’s review). Verbal consent for a child to participate was obtained from the accompanying guardian, and assent was obtained from the child. The study was approved by the Harare Central Hospital Ethics Committee.

Antiretroviral therapy regimens
ART prescribing followed national guidelines which included recommendations for paediatric triple-drug fixed dose combinations (FDCs), such as zidovudine/lamivudine/nevirapine (ZDV/3TC/NVP). Tenofovir disoproxil fumarate (TDF)-containing combinations were only recommended in children > 10 years old and > 35 kg and as an alternative second-line regimen. Other combinations were prescribed as a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone (as an FDC) with a nonnucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI).

Definitions of over-dosing and under-dosing of drugs
Zimbabwean paediatric ART guidelines recommend weight-adjusted dose bands for individual ART drugs and FDCs. In this study, over-dosing was defined as drugs prescribed at a dose higher than recommended for the participant’s weight-band. A drug/FDC dosed below the weight-adjusted band was considered under-dosed. We considered children to be incorrectly dosed if they were either under- or over-dosed on at least one drug. Children could simultaneously be under-dosed for one drug component and over-dosed for another.

Statistical analysis
Data were entered in an electronic form on to Nexus 7 tablets (Asus Google Nexus 7 Tablet (2013), Asus Computer International, Fremont, USA). Statistical analysis was performed using Stata version 14 (Stata-Corp, Stata version 14, TX, USA). The Mann–Whitney U-test was used to evaluate the significance of differences between groups for continuous variables. For categorical variables, the \( \chi^2 \) test was used. The level of significance was set at \( \alpha = 0.05 \).

Results
Study population
During the study period, 2199 (71%) of 3111 children aged 0–17 years registered at the clinic were on ART. We enrolled 458 consecutive attendees over the study period; 309 were eligible for weight-based dosing (age < 10 years or weight < 35 kg). The median age was 7 years [interquartile range (IQR) 5–10 years]; 55% (170) were male; 22 (7.1%) were aged 0–2 years, 187 (60.5%) were aged
3–10 years, and 100 (32.4%) were aged 11–17 years and weighed < 35 kg. The median CD4 cell count was 899 cells/µL (IQR 519–1287 cells/µL), and the median time on the current ART regimen was 11.2 months (IQR 4.9–17.1 months). Patient characteristics stratified by drug-dosage status are shown in Table 1.

Antiretroviral therapy dosing

The majority (98%; 304 of 309) of participants were prescribed ART that included an FDC: 163 (52.8%) were on a triple-drug FDC, and 141 (45.6%) were on a dual-drug FDC plus a third agent. Triple-drug FDCs [152 on ZDV/3TC/NVP and 11 on TDF/3TC/efavirenz (EFV)] were prescribed in one (4.6%) child aged 0–2 years, 123 (65.8%) children aged 3–10 years and 39 (39.0%) children aged 11–17 years. A dual-drug FDC (backbone) plus a third agent [87 on ZDV/3TC, 40 on TDF/3TC and 14 on abacavir (ABC)/3TC] was prescribed in 21 (95.5%) children aged 0–2 years, 62 (33.2%) children aged 3–10 years and 58 (58%) children aged 11–17 years. Overall, 110 (35.6%) children were prescribed incorrect doses of at least one drug within their ART regimen; 49 (15.9%) children received higher doses of at least one drug and 64 (20.7%) were under-dosed on at least one drug.

Drugs that were the most commonly over-dosed were 3TC in 49 children (16%), ZDV in 41 children (17%) and NVP in 24 children (13.8%) receiving the respective drug. 3TC was under-dosed in 62 children (20.3%), ZDV in 50 children (20.8%) and EFV in 28 children (50.9%) (Fig. 1). In children receiving a three-drug FDC, 21 (12.9%) were over-dosed for the NRTI and NNRTI components, while 27 (19.1%) children on dual-drug FDC were over-dosed for the NRTIs and the third drug component, which was in 16 of 71 children a PI and in 11 of 71 an NNRTI.

Factors associated with incorrect dosing

The proportion of children incorrectly dosed on at least one drug varied by age; seven (31.8%), 35 (18.7%) and seven (7.0%) 0–2-, 3–10- and 11–17-year-olds, respectively, were over-dosed (P = 0.004). Those on a triple-drug FDC were more likely to have all three drugs correctly dosed compared with those on a dual-drug FDC (plus a third agent; 77.3 versus 51.1%, respectively; P < 0.001).

The proportion under-dosed was higher in younger compared with older children, with eight (36.4%) 0–2-year-olds, 34 (18.2%) 3–10-year-olds and 22 (22.0%) 11–17-year-olds being under-dosed. Children who were under-dosed were less likely to be on a three-drug FDC compared with children receiving correct ART dosages (25% versus 63.3%, respectively; P < 0.001).

Children over-dosed on at least one drug component were younger than children who were correctly dosed (median 6 versus 10 years, respectively; P = 0.001), had been on their current ART regimen for a shorter time (median 7.2 versus 13 months, respectively; P = 0.003), and were also less likely to be receiving a three-drug FDC (42.9% versus 63.3%, respectively; P = 0.009).

Discussion

This study demonstrates that over a third of children were incorrectly dosed on at least one of their ART drugs. Weight-based dosing is the mainstay of the Zimbabwean as well as other international paediatric ART guidelines [7,8]. Weight-based ART dosing can be challenging as a...
child’s weight changes with growth and may drop during periods of acute illness, and doses may not be adjusted appropriately during these intervals. This was seen in the UK and Irish Collaborative HIV Paediatric Study, which demonstrated that the proportion of children aged 2–12 years prescribed < 90% of the recommended dose varied between 6 and 62% [9].

Both over- and under-dosing of drugs were observed in our study. Over-dosing may increase the risk of drug-related adverse events; for example, EFV can be associated with significant neuropsychiatric adverse effects [10,11]. Recent guidelines have recommended a decrease in the EFV dose from 600 to 400 mg [7] based on findings showing that the lower dose led to fewer adverse events in adults [12]. Under-dosing may increase risk of virological failure and promote development of drug resistance, both of which could impact on long-term treatment outcomes. This was seen in a cohort of HIV-infected children in Spain, where treatment failure was significantly more frequent in children who were under-dosed than over-dosed [13]. Routine viral load monitoring is often not accessible in resource-limited countries, which increases the difficulties in identifying treatment failure early enough to prevent drug resistance. Precise ART dosing is therefore especially important in such settings.

The majority of children were receiving FDC tablets, with those on triple FDC being more likely to be correctly dosed than children receiving dual-drug FDCs. Several studies have demonstrated that FDCs can be successfully used in children with sustained clinical and virological responses [14,15].

We observed that the frequency of weight monitoring was variable, and dosing was not reviewed at every ART dispensation. A child’s weight was only recorded at 3-monthly doctor visits, when ART is prescribed; at subsequent nonclinician visits (for ART collection), the
children are not weighed and ART is not re-prescribed. The study was conducted in a secondary care facility-based HIV clinic, served by doctors. As HIV care is increasingly decentralized to lower level facilities, where there may be fewer and less well-trained staff, and a lack of functioning equipment to monitor weight, incorrect paediatric ART dosing may be an even bigger issue.

The study had several limitations: the study was cross-sectional, and the type of visit (nurse/counsellor versus doctor visit) was not stipulated. However, it does highlight the importance of checking weight and reviewing drug doses at every visit. A review of the clinic’s policy on the frequency of a child’s visits and antiretroviral (ARV) prescribing is needed. Documentation of a child’s weight and review of ARV doses should be mandatory for every clinician review and ARV collection visit. Health care professionals who prescribe and dispense ARVs need to be adequately trained in monitoring a child’s weight and in recognizing when the ARV dose needs to be adjusted. Inadequate ARV supplies, heterogeneity of formulations and lack of paediatric formulations were concerns reported by the clinic staff. These factors may have contributed to the incorrect dosing. Further work is needed in reviewing ARV prescribing practice against national recommendations and determining the impact this has on ARV dosing and overall clinical outcome. A broader range of paediatric FDC formulations with a wider range of weight-band dosing is needed, which may alleviate suboptimal ARV dosing.

As a consequence of the lack of viral load monitoring and the cross-sectional design, we could not evaluate the relationship between incorrect drug dosing and virological outcomes, whether there were any discontinuations associated with over-dosing, whether the incorrect dosing had occurred ever since ART initiation, or the duration of the incorrect dosing. The sample size was relatively small, and the sampling was consecutive with no age-stratified sampling. The study was conducted in a hospital-based HIV clinic, where HIV care is primarily delivered by doctors. With decentralization of paediatric HIV care and treatment, nurse-led care is now standard of care and a similar study to investigate dosing in such settings is warranted.

In summary, this study has demonstrated that a large proportion of children from a central urban clinic in Zimbabwe were prescribed suboptimal ART dosage, and further research is required to investigate the extent of this problem and its impacts. Consistent availability of drugs, more user-friendly ART guidelines and adequate training and treatment monitoring facilities are essential to ensure that children are prescribed correct ART doses.

Acknowledgements

Conflicts of interest: The authors have no conflicts of interest to declare.

References

1 Global HIV & AIDS statistics — 2018 fact sheet. UNAIDS. Available at http://www.unaids.org/en/resources/fact-sheet (accessed 29 October 2018).

2 Bobat R, Archary M, Lawler M. An update on the HIV treatment cascade in children and adolescents. Curr Opin HIV AIDS 2015; 10: 411–419.

3 King JR, Kimberlin DW, Aldrovandi GM, Acosta EP. Antiretroviral pharmacokinetics in the paediatric population: a review. Clin Pharmacokinet 2002; 41: 1115–1133.

4 Neely MN, Rakhamanina NY. Pharmacokinetic targets of antiretroviral therapy in children and adolescents. J Pediatr Neonat Individual Med 2013; 2: 1–13.

5 Rakhamanina NY, van den Anker JN, Soldin SJ, van Schaik RH, Mordwinkin N, Neely MN. Can therapeutic drug monitoring improve pharmacotherapy of HIV infection in adolescents? Ther Drug Monit 2010; 32: 273–281.

6 Weidle PJ, Abrams EJ, Gvetadze R, Rivadeneira E, Kline MW. A simplified weight-based method for pediatric drug dosing for zidovudine and didanosine in resource-limited settings. Pediatr Infect Dis J 2006; 25: 59–64.

7 World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach, 2nd ed. Geneva, Switzerland, 2016. Available at http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf (accessed 30 November 2017).

8 The National Medicine and Therapeutics Policy Advisory Committee and The AIDS and TB Directorate, Ministry of Health and Child Care, Harare. Guidelines for Antiretroviral Therapy for the Prevention and Treatment of HIV in Zimbabwe, 2013. Harare, Zimbabwe, Ministry of Health and Child Care. Available at http://www.nac.org.zw/sites/default/files/2013%20Zimbabwe%20ARV%20Guidelines%20%20Main%20Document%20(1).pdf (accessed 01 October 2017).

9 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: 1183–1187.

10 Gutierrez F, Navarro A, Padilla S et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. Clin Infect Dis 2005; 41: 1648–1653.
11 Shubber Z, Calmy A, Andrieux-Meyer I et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. *AIDS* 2013; 27: 1403–1412.
12 Group ES. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. *Lancet* 2014; 383: 1474–1482.
13 Fernandez-Cooke E, Rojas P, Holguin A et al. Description and consequences of prescribing off-label antiretrovirals in the Madrid Cohort of HIV-infected children over a quarter of a century (1988–2012). *Antivir Ther* 2016; 21: 65–70.
14 Barlow-Mosha LN, Bagenda DS, Mudiope PK et al. The long-term effectiveness of generic adult fixed-dose combination antiretroviral therapy for HIV-infected Ugandan children. *Afr Health Sci* 2012; 12: 249–258.
15 O’Brien DP, Sauvageot D, Zachariah R, Humblet P, Medecins Sans F. In resource-limited settings good early outcomes can be achieved in children using adult fixed-dose combination antiretroviral therapy. *AIDS* 2006; 20: 1955–1960.