Evaluation of weight-based prescription of antiretroviral therapy in children

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ABSTRACT

Objective

To investigate the extent of and factors associated with incorrect dosing of antiretroviral therapy (ART) in HIV-infected children in Harare, Zimbabwe.

Methods

Children aged 0-17 years or under 35kgs (if aged >10 years), 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 (IQR 5-10)), the median CD4 count was 899 cells/mm3 and the median duration of their current ART regimen was 11.2 months (IQR 4.9-17.1). 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 ≥1 drug were younger (median 6 vs. 7 years, p=0.001), had a shorter time on their current ART regimen (median 7.2 vs. 13 months, p=0.003 and were less likely to be receiving a three-drug fixed-dose combination (FDC) (42.9% vs. 63.3%, p =0.009) compared to correctly-dosed children. Those who were under-dosed were also less likely to be on a three-drug FDC (25% vs. 63.3%, 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 healthcare providers on paediatric drug dosing and the need for wider availability of FDCs for children.

Background

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 (3). 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 (4, 5).

Drug PK and PD in children is affected by several factors including organ maturation and difference in drug metabolism and clearance, and changes in weight during growth (4-6). 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 (7). 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 (12).

We assessed paediatric ART prescribing in a large public-sector HIV clinic in Harare, Zimbabwe to understand if 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 outpatient clinic at Harare Central Hospital, Zimbabwe, the largest public-sector hospital in Harare. An average of 100 children (defined as individuals aged 0-17 year-olds) attend per day. ART is initiated by the

clinic doctor and children are reviewed by a doctor every three months (or more frequently if clinically indicated). At the doctor's review the child's height and weight is recorded and ART is prescribed for three months. If ART stocks do not allow for three 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/or weight is not monitored at these dispensing visits).

Study period and enrolment of participants

Children aged 0-17 years, and those aged above 10 years but weighing less than 35 kilogrammes (kgs) should receive weight-based dosing for ART according to Zimbabwe national guidelines (8). All children taking ART, who attended the clinic from the 1st May to 31st July 2015, eligible for weight-based dosing and 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 six months, the current ART regimen, the date of initiation of 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 recommended possible paediatric triple drug fixed dose combinations (FDCs), zidovudine/lamivudine/nevirapine (AZT/3TC/NVP). TDF containing combinations were only recommended in children over 10 years and >35kgs

and as an alternative second-line regimen. Other combinations were prescribed as a dual NRTI backbone (as an FDC) with a non-nucleotide 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 was entered in an electronic form on to Nexus 7 tablets. Statistical analysis was performed using Stata version 14 (Stata-Corp, TX, USA). The Mann-Whitney U-test was used to evaluate for 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 under 10 years or weight under 35kgs). The median age was 7 years (IQR 5-10); 55% (170) were male; 22 (7.1%) aged 0-2 years, 187 (60.5%) aged 3-10 years and 100 (32.4%) aged 11-17 years and weighed <35kgs. The median CD4 cell count was 899 cells/mm^3 (IQR 519-1287) and the median time on the current ART regimen was 11.2 months (IQR 4.9-17.1) Patient characteristics stratified by drug-dosage status are shown in Table 1.

Antiretroviral therapy (ART) dosing

The majority (98%, 304/309) 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 AZT/3TC/NVP and 11 on TDF/3TC/EFV) were prescribed in 1 (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 AZT/3TC, 40 on TDF/3TC and 14 on ABC/3TC) were prescribed in 21 (95.5%) children aged 0-2 years, 62 (33.2%) children aged 3-10 years and 58 (58%) children aged over 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 (16%), AZT in 41 (17%) and NVP in 24 (13.8%) children receiving the respective drug. 3TC was under-dosed in 62 (20.3%), AZT in 50 (20.8%) and EFV in 28 (50.9%) children (Figure 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 16/71 children a PI and in 11/71 an NNRTI.

Factors associated with incorrect dosing

The proportion of children incorrectly dosed on at least one drug varied by age; 7 (31.8%), 35 (18.7%) and 7 (7.0%) of 0-2, 3-10 and 11-17-year olds respectively were over-dosed, p=0.004. Those on triple drug FDC, were more likely to have all three drugs correctly dosed compared to those on a dual drug FDC (plus a third agent) (77.3% vs, 51.1%, p<0.001).

The proportion under-dosed was higher in younger compared to older children, with 8 (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 (25% vs. 63.3%, p<0.001) compared to children receiving correct ART dosages. Children over-dosed on at least one drug component were younger (median 6 vs. 7 years, p=0.001, had a shorter time on their current ART regimen (median 7.2 vs. 13 months, p=0.003), and were also less likely to be receiving a three-drug FDC (42.9% vs. 63.3%, p =0.009) compared to children who were correctly dosed.

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 with the use of FDCs simplifying ART regimens (8,12). 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 the proportion of children aged 2-12 years prescribed less than 90% of the recommended dose varied between 6% and 62% (9).

Both over and under-dosing of drugs was observed in our study. Over-dosing may increase the risk of drug-related adverse events, e.g. EFV can be associated with significant neuropsychiatric adverse effects (10, 11). Recent guidelines have recommended a decrease in the EFV dose from 600mg to 400mg (12) based on findings showing that the lower dose led to fewer adverse events in adults (13). 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 from Spain where treatment failure was significantly more frequent in children who were under-dosed than over-dosed (14). 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 response (15, 16).

We observed that frequency of weight monitoring was variable, and dosing was not reviewed at every ART dispensation. A child's weight was only recorded at three-monthly doctor visits when ART is prescribed and at subsequent non-clinician 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 decentralised 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 vs 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 visit and 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 visits. Healthcare professionals who prescribe and dispense ARVs need to be adequately trained in monitoring a child's weight and in recognising when 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 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.

Due to the lack of viral load monitoring and the cross-sectional design, we could not evaluate the relationship between incorrect drug dosing and virological outcomes, if there were any discontinuation associated with over-dosing, if the incorrect dosing had occurred since ART initiation or the duration in which the incorrect dosing had persisted. 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 decentralisation 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 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 children are prescribed correct ART doses.

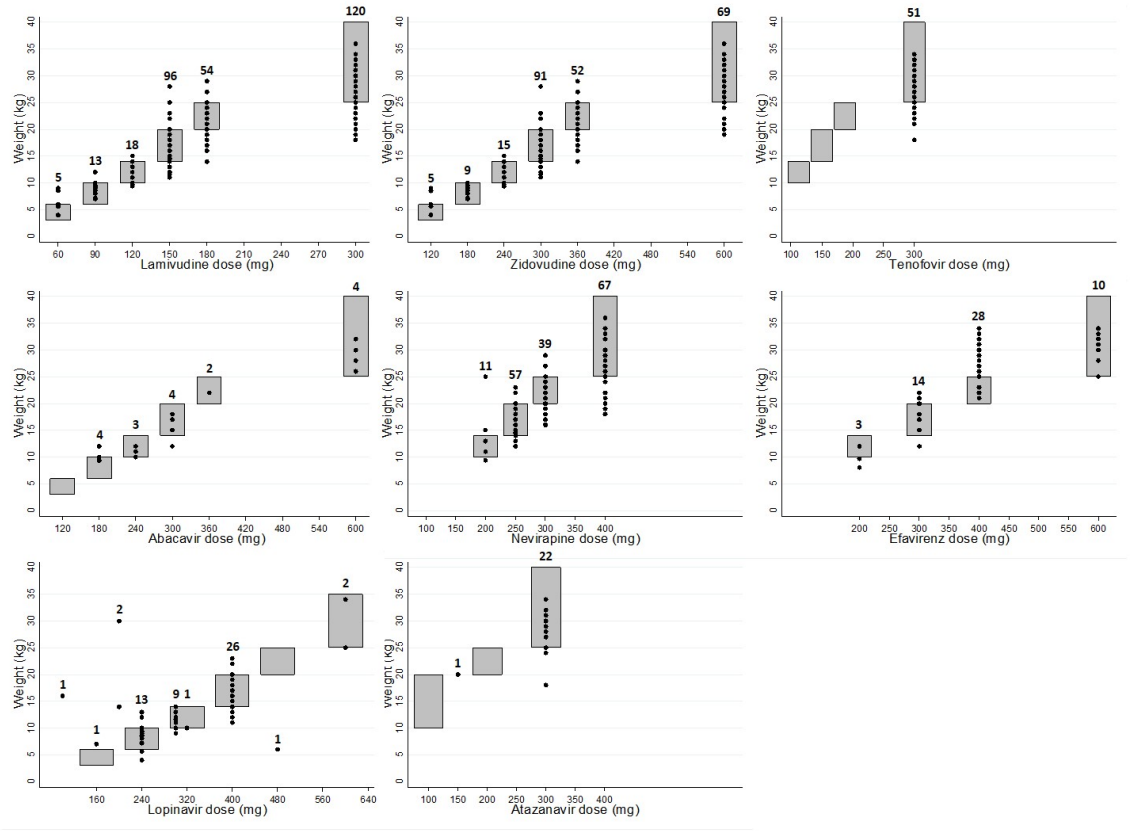
Table 1. Characteristics of patients by drug-dosage status

	Total n=309	Correct dosage for all ART drugs n=199	Over-dosed on ≥1 drug n=49	p-value correct vs. over-dosed	Under-dosed on ≥1 drug n=64	p-value correct vs. under-dosed
Male, n (%)	170 (55.0)	113 (56.8)	27 (55.1)	0.832	30 (46.9)	0.166
Age at study visit (years), median (IQR)	7 (5-10)	7 (5-11)	6 (3-8)	0.001	8 (5-10)	0.776
Age at initiation of current regimen (years), median (IQR)	6.5 (4-9.8)	6.8 (4.2-10.0)	5.2 (3.2-7.8)	0.003	7.4 (3.6-10.0)	0.672
Time on current ART regimen (months), median (IQR)	11.2 (4.9-17.1)	13 (5.3-17.6)	7.2 (3.5-12.1)	0.003	10.1 (5.4-19.3)	0.810
Current weight (kg), median (IQR)	21 (16-28)	22 (17-30)	17 (12-21)	<0.001	23 (20-29)	0.959
Current CD4 cell count (cells/µl), median (IQR)*	899 (519-1287)	894 (556-1260)	959 (473-1300)	0.933	912 (513-1445)	0.848
Dual drug FDC, n (%)	141 (45.6)	72 (36.2)	27 (55.1)	0.015	45 (70.3)	<0.001
Any three-drug FDC, n (%)	163 (52.8)	126 (63.3)	21 (42.9)	0.009	16 (25)	<0.001

3TC lamivudine, ART antiretroviral therapy, AZT zidovudine, EFV efavirenz, FDC fixed-dose combination, NVP nevirapine, TDF tenofovir.

*CD4 was considered current if measured within 6 months of the study visit. p-values are shown for the comparisons between correct dosing vs. over-dosing and correct dosing vs. under-dosing. One patient was missing the dose for the third drug component.

Figure 1: Daily drug doses according to weight for lamivudine, zidovudine, tenofovir, abacavir, nevirapine, efavirenz, lopinavir and atazanavir.



The shaded rectangle represents the correct dosing for the respective weight band. The dots represent the actual weights of the children given the drug. The numbers above the dots represent the total number of children in the respective dosage category. The number of dots does not represent the number of children since dots corresponding to children with the same weight and drug dose would overlap.

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