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Irrational Anti-Retroviral Therapy Prescription among Children Under 15 Years in Eastern Uganda

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Abstract

Background: Highly Active Anti-Retroviral Therapy (HAART) has transformed HIV/AIDS into a manageable chronic illness with HIV-infected children having near-normal growth milestones as a result of virologic control and immunologic reconstitution. However, for HAART to be beneficial, it needs to adhere to standard guidelines. Prescribing HAART for children is complex and there is little information available on prescription patterns for children in Africa. This study aimed to determine the prevalence of irrational prescriptions, describe the types of errors and identify the factors associated with these errors.

Methods: We conducted a retrospective chart review of children receiving HAART from April 2013 to September 2013 at two hospitals in East Central Uganda. Prescriptions for children aged 0 to 15 years, health facility inventory and stock documents were reviewed.

Results: We assessed 166 children. Of these, 58% had at least one irrational prescription. Errors of commission, majority of which (57%) related to prescription of adult formulations, were the most predominant comprising 83% of all errors. Errors of omission, all of which concerned missing weight, constituted 11%. Integration errors (6%) included regimens that were not HAART (3%). Laboratory investigations such as CD4 and hemoglobin counts were not done at the frequency recommended by treatment guidelines. Being on treatment for less than a year; OR=14.07 (95% CI: 2.746-72.085), P-value=0.002 and receiving care from a private facility; OR=2.68 (95% CI: 1.282-5.599), P-value=0.009 were associated with receiving at least one irrational prescription.

Conclusion: The prevalence of irrational prescriptions is high among children in Uganda. Children receiving care in private health facilities and those newly initiated on treatment are at particularly high risk of receiving these prescriptions. Quality improvement strategies such as clinical audits, mentorship and automated prescribing systems should be implemented to mitigate their occurrence.

Keywords: Prescription errors; Children; Anti-Retroviral Agents; Cross- sectional studies; Retrospective studies

List of Abbreviations: AIDS: Acquired Immune Deficiency Syndrome; ARV: Anti-retroviral; FDC: Fixed Dose Combination; HAART: Highly Active Anti-retroviral Therapy; HIV: Human Immunodeficiency Virus; PMTCT: Prevention of Mother to Child Transmission; TB: Tuberculosis

Introduction

HIV/AIDS has had a significant impact on mortality worldwide since the epidemic began [1]. In 2014 alone, 1.2 million people died due to AIDS-related causes worldwide. Sub-Saharan Africa has been disproportionately affected with 66% of new infections and deaths occurring in the region [1]. Uganda has approximately 6% of the total number of children living with HIV worldwide and contributed almost 3% to new pediatric infections in Sub-Saharan Africa in 2014 [2-4].

Dramatic gains in survival have, however, been attained using Highly Active Anti-retroviral Therapy (HAART), a combination of medicines that reduces the rate of replication of HIV and halts its progression into AIDS. When used optimally, HAART has been shown to improve growth virologic and immune responses in children [5-8] thereby reducing morbidity and mortality [9]. Between 2004 and 2011, the estimated number of children who died from AIDS-related causes decreased by almost 30% worldwide largely as a result of HAART [10,11].

For HAART to remain clinically effective throughout the lifetime of the patient, prescribers need to adhere to standard treatment guidelines. The World Health Organization (WHO) states that failure to prescribe according to guidelines is regarded as irrational use of medicines, and recommends their appropriate use as a strategy to improve patient outcomes, reduce the incidence of adverse drug reactions and decrease health care costs [12,13]. Rational drug use is defined as 'Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community' [14]. In order to ascertain the existence of irrational prescribing, a standard is required to outline the most optimal algorithms for medicines use [15]. At the time this study was conducted, Uganda was implementing HAART under 2012 national guidelines [16].

Prescribing HAART for children is complex. Attention must be paid to age, weight bands, CD4 counts and history of Prevention to Mother to Child Transmission (PMTCT) uptake, WHO staging as well as co-infections like Tuberculosis (TB). With all these factors to consider, there is considerable room for error [16-18].

Irrational use of HAART is associated with a number of negative effects including adverse drug reactions, drug resistance, treatment failure and higher chances of mortality [19-21]. Children are more prone to harm from irrational medicines use stemming from their under-developed renal and hepatic drug clearance systems [22]. Furthermore, 25% higher costs are experienced by patients with an irrational prescription for HAART as compared to those with rational prescriptions [23].

There is currently little information available on prescription patterns of HAART in Sub-Saharan Africa where over 85% of new infections in children occur [1,3]. This study sought to determine the extent of irrational prescribing of HAART in children under 15 years in East Central Uganda, describe the types of irrational prescriptions and assess the factors associated with these practices.

Methods

Study Design

This retrospective cross-sectional study was conducted at TASO Jinja, a private not-for-profit facility and Iganga hospital, a public hospital in East Central Uganda. The clinic charts of children aged less than 15 years who received at least four prescriptions for HAART between April 2013 and September 2013 were reviewed. This ensured that all patients received an average to maximum number of prescriptions and hence relatively equal risk of exposure to existing prescribing practices. Exclusion criteria included children who received less than four prescriptions, those who turned 15 before they received the four prescriptions and those without a prescriber signature for any prescription in the timeframe. Facility inventory lists and stock cards were reviewed to assess the availability of equipment, reagents and medicines.

Ethical approval was obtained from TASO and London School of Hygiene and Tropical Medicine Institutional Review Committees, and Uganda National Council of Science and Technology.

Sampling

The active number of children on HAART as of December 2013 for each of the two facilities was obtained; 259 at TASO Jinja and 150 at Iganga hospital. The sample size was determined using the Leslie- Kish formula and the sampling unit was a patient. The total sample size generated was 246 children using a population prevalence of 20%. Studies in resource-rich countries had shown this to range from 4%-10% [24,25]. It was anticipated that this prevalence would be higher in resource-limited settings. A finite population correction factor was incorporated due to the small number of already existing pediatric patients from which the sample was drawn. This yielded 154 patients. An additional 10% patient was included to cater for any patient charts that had missing information and were subsequently excluded. A total of 169 children were therefore evaluated in the study. Using proportionate sampling based on the original patient numbers as of December 2013, a representative sample of active children per facility was determined from the total sample. TASO Jinja had 107 children while Iganga hospital had 62 children. Systematic sampling using the K^{th} factor was then used to select the patient files whose prescriptions were reviewed. All prescriptions received by each child in the study period were assessed.

Data collection

Exposure variables were in two categories: Patient-related factors included age, gender, weight, PMTCT history, TB status and were derived from patient files while facility-related factors included the ownership, patient load, availability of medicines and equipment. These were extracted from stock cards, facility equipment inventory and the HAART register.

Analytical approach

Error definition: Khalid et al postulated three major types of medication errors derived from Ferner and Aronson's psychological approach [26,27]. The types of irrational prescriptions were extrapolated from this study. Errors of commission were defined as errors related to indication of wrong information about a drug such as wrong strength, frequency and duration. Errors of

integration were 'knowledge-based errors' due to a prescriber's inability to incorporate complementary information about the patient and/or the drug to formulate an appropriate prescription. Errors of omission were categorized as 'absent, vagueness, incompleteness or illegibility of any component of the body of a prescription' [26]. Prescriptions were coded into rational and irrational prescriptions according to the treatment guidelines.

Statistical analysis was done using STATA version 12 (StataCorp. College Station, Texas. 1985). The association between irrational prescription and the exposure variables was examined using crude Odds Ratios (ORs) and their 95% Confidence Intervals (95% CI). These associations were tested for statistical significance using the Pearson Chi-square test with a 5% level of significance denoting a statistically significant association. Logistic regression was used to assess the association between prescribing practice and independent risk factors.

Results

Patient characteristics

Data was collected from 62 children in Iganga hospital and 104 in TASO Jinja. A total of 890 prescriptions were obtained from the 166 children over the 6 months making an average of five prescriptions per child. Table 1 shows the characteristics of these children. The median age was 5 years with an interquartile range of 2 to 7 years. Only 12 (7%) of these patients had newly initiated HAART within the study period. A total of 96 (58%) children did not have a CD4 test done in the review period and these made up the majority in each age category. 2% (n=4) of children were co-infected with TB while 4% (n= 7) had previously been exposed to PMTCT.

Variable	Frequency	Percentage (%)
Sex		
Male	70	42
Female	96	58
Age (years)		
<2	34	21
2 to <5	40	24
5 to <15	92	55
Type of patient		
New	12	7
Existing	154	93
CD4 (most current CD4 within the review period)		
<2 years		
<750	3	9
>=750	6	18
Missing CD4	25	74
2 to <5 years		
<750	8	20
>=750	9	23
Missing CD4	23	58
5 to <15 years		
<350	12	13
>350	32	35
Missing CD4	48	52
TB co-infection		
Yes	4	2
No	162	98
Previous PMTCT exposure		
Yes	7	4
No	159	96

Table 1: Baseline characteristics of children under 15 years on HAART at TASO Jinja and Iganga hospital in East Central Uganda between April and September 2013

Facility characteristics

TASO had a total of 6,035 patients while Iganga had 1,844. There were 38 prescribers (27 in TASO and 11 in Iganga) for all 890 prescriptions. Current HAART guidelines were available and accessible in both health centers and they each had a pediatric weighing scale and a hemoglobinometer. While Iganga hospital had an in-house CD4 machine, TASO relied on the national sample transportation system to the nearest laboratory hub to access CD4 testing. This hub is located about half a kilometer from TASO within the same hospital complex and therefore was not significantly far from the point of care to impede service delivery.

With regard to medicines, both Iganga and TASO reported a stock out of only one formulation each; (Abacavir/Lamivudine 60/30mg and Efavirenz 200mg respectively) during the study period. Notably, a number of recommended pediatric formulations had never been carried as products by TASO including Nevirapine 50mg, Lopinavir/ritonavir 80/20mg/ml and Abacavir 60mg.

Prevalence of irrational prescriptions

Of all children in the study, 58% (n=97) had at least one irrational prescription; 71% (n=69) from TASO and 29% (n=28) from Iganga. The biggest proportion of children in Iganga hospital had only one irrational prescription (61%) while the greater proportion of children in TASO (46%) had two to four irrational prescriptions. A substantial proportion in TASO (39%) also had more than four irrational prescriptions as shown in Table 2.

Variable	Rational prescription (%)	Irrational prescription (%)
Patient characteristics		
Sex		
Male	30 (43)	40 (57)
Female	39 (41)	57 (59)
Age		
< 2 years	13 (38)	21 (62)
2-<5 years	14 (35)	26 (65)
5-<15 years	42 (46)	50 (54)
Type of patient		
New	0 (0)	12 (100)
Existing	69 (42)	85 (58)
TB co-infection		
Yes	1 (25)	3 (75)
No	68 (42)	94 (58)
PMTCT exposure		
Yes	5 (71)	2 (29)
No	64 (40)	95 (60)

Table 2: Prevalence of at least one irrational prescription for children under 15 years on HAART by patient characteristics in TASO Jinja and Iganga hospital in East Central Uganda

There was almost no difference in the proportion of children with at least one irrational prescription among the male (57%) and female (59%) gender. Children aged two to less than five years had the most irrational prescriptions (65%) followed by children aged less than two years (62%). All newly enrolled children (n=12) during the review period had at least one irrational prescription.

Of the 96 children who did not have a CD4 result, 85 (89%) were from TASO. There were four TB co-infected patients (2%); one in Iganga and three in TASO. All the three in TASO had at least one irrational prescription whereas the one in Iganga did not have any irrational prescription. Seven (4%) children had been exposed to PMTCT; four of these were in Iganga. None of these children had an irrational prescription while 67% of those in TASO had at least one irrational prescription.

Types of irrational prescribing: As shown in Table 3, errors of commission were the most common type of error comprising 83% (n=260). In over half of these errors (57%), prescriptions were for an adult formulation that would necessitate breaking the tablet to cater for the weight of the child. This was followed by under- or over-dosing in relation to the child's weight at 20% (n=62).

	TASO Jinja	Iganga Hospital	Overall
Type of error and reason	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**
Error of omission	**31 (86)**	**5 (14)**	**36 (11)**
No weight indicated	31 (86)	5 (14)	36 (11)
Error of commission	**221 (85)**	**39 (15)**	**260 (83)**

	TASO Jinja	Iganga Hospital	Overall
Type of error and reason	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**
Adult formulations were prescribed and tablets were broken	178 (99)	1 (1)	179 (57)
Dosing	41 (66)	21 (34)	62 (20)
Use of a brand name	0 (0)	16 (100)	16 (5)
Scheduling	1 (50)	1 (50)	2 (1)
Adult formulations were prescribed but tablets were not broken	1 (100)	0 (0)	1 (0)
Error of integration	**11 (58)**	**8 (42)**	**19 (6)**
Regimen not HAART	7 (88)	1 (12)	8 (3)
No 'lead in' for new patients on Nevirapine-based regimens	4 (57)	3 (43)	7 (2)
Switching from second line to first line	0 (0)	4 (100)	4 (1)

Description of irrational prescriptions

Table 3: Types of irrational prescriptions of HAART and their description for children under 15 years at TASO Jinja and Iganga hospital in East Central Uganda between April and September 2013

Errors of omission were the second most common comprising 11% (n=36) of the total prescription errors. All were related to missing weight of the child.

Errors of integration were the least common making up 6% (n=19) of all prescriptions. Of these, majority were related to prescriptions that were not considered to be HAART. Seven initial prescriptions out of the twelve for new patients did not have appropriate 'lead in' dosing to reduce the likelihood of an adverse drug reaction due to Nevirapine. Only one child out of the ten initiated on Zidovudine-based regimens was given a hemoglobin test. Most notably, however, one child was prescribed a first line regimen on four occasions after having initially received a second line regimen.

Factors associated with irrational prescribing: In the multivariate analysis, prescriptions for 161 patients were assessed as five children did not have weight indicated at any of their visits. After adjusting for various factors, the odds of having an irrational prescription and having been on HAART for less than one year increased from eleven to fourteen times that of those who were on HAART for more than a year (P-value = 0.002) as shown in Table 4 Children in TASO were 2.7 times more likely to have an error in at least one of their prescriptions as compared to Iganga hospital (P-value = 0.009).

Variable	Number of children with irrational prescriptions (%)	Unadjusted Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
Type of patient					
On treatment for > 1 year	**73(75)**				
On treatment for <= 1 year	24(25)	11.00(2.506-48.386)	0.001*	14.07 (2.746-72.085)	0.002*
Weight					
≥35kg	6(6)				
3-34.9kg	88(94)	2.90(1.008-8.229)	0.05*	2.62 (0.842-8.126)	0.1
Sex					
Male	40(41)				
Female	57(59)	1.09 (0.587-2.046)	0.8		
Age					
<5	47(49)				
5-<15	50(52)	0.68(0.365-1.279)	0.2		
CD4					
Low (<750 and <350)	15(35)				
High (>750 and >350)	28(65)	0.78(0.278-2.217)	0.6		
TB Co-infection					
Yes	3(3)				
No	94(97)	0.46(0.046-4.525)	0.5		
PMTCT exposure					
Yes	2(2)				

Variable	Number of children with irrational prescriptions (%)	Unadjusted Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
No	95(98)	3.71(0.698-19.716)	0.1	8.433 (0.903-78.750)	0.1
Health facility-related factors					
TASO Jinja (private sector)	28(29)				
Iganga Hospital (Public sector)	69(71)	2.39(1.256-4.561)	0.008*	2.68 (1.282-5.599)	0.009*

***P-value significant at P=0.05**

Factors associated with irrational prescriptions

Table 4: Association of patient-related and health facility-related characteristics with number of children under 15 years on HAART who received at least one irrational prescription at TASO Jinja and Iganga hospital in East Central Uganda between April and September 2013

Discussion

This study was aimed at determining the prevalence of irrational HAART prescriptions among children aged less than 15 years, characterizing the types of irrational prescriptions as well as identifying any factors that could be associated with these errors.

Slightly over half of the children (58.4%) had received at least one irrational prescription. Of these, 71.1% were from the private facility - TASO. All new patients within the study period had at least one irrational prescription. Errors of commission were the most common type of error accounting for 83% of all irrational prescriptions. These were predominantly about formulations that were not appropriate for the age of the child. Errors of omission were all related to missing weight and were the next most common in occurrence constituting 11%. Errors of integration, largely regarding regimens that were not considered to be HAART, made up only 6% of the total burden of errors. Being on treatment for less than a year; OR=14.07 (95% CI: 2.746-72.085), P-value=0.002 and receiving care from a private facility; OR=2.68 (95% CI: 1.282-5.599), P-value=0.009 were associated with receiving at least one irrational prescription.

There has been very little investigation of HAART prescribing patterns and virtually none in Sub-Saharan Africa. Review of literature highlighted twenty four papers that were directly related to prescribing HAART according to guidelines. Of these, only one study was conducted specifically among children in the United Kingdom [28]. To our knowledge, this has been the first attempt to document HAART prescription patterns for children in Africa.

Prevalence of Irrational Prescriptions

The proportion of children with irrational prescriptions was six to thirteen times higher than that encountered in three other studies [24,25,29]. However, two of these studies addressed essential medicines and were conducted in developed countries. It is expected that the prevalence rates would be lower in higher income countries given the level of resources available to implement quality care programs. However, these results also suggest that prescribing essential medicines is easier than ARVs. No study made this comparison in our literature review.

Two of the above studies had prolonged follow up times of two and four years and went further on to intervene when there were errors noted in the prescription making it possible that prescribers became more careful at prescribing over time and hence the lower error rates observed [24,29]. The timeframe covered in the cross-sectional study was also short at one week as compared to the 6 months that were investigated in this study potentially yielding fewer irrational prescriptions [25].

Types of Irrational Prescriptions

Errors of commission have been documented in this study as the most common type of error. Previous studies have indicated that errors of omission are higher [26,30,31]. It would be expected that this study would have similar results as Khalid et al as both were observational studies conducted in primary care settings without any intervention by pharmacists. However, this was not the case probably because standardized templates from the Ministry of Health in Uganda are available to guide prescribers on information that must be written on the prescription. Van Rosse *et al.* showed that tools that required minimal cognitive processing by prescribers such as 'Computerized Physician Order Entry' (CPOE) systems reduced errors [32].

This study documented that children were still being prescribed adult formulations despite the fact that pediatric Fixed Dose Combination (FDC) formulations were introduced in Uganda in 2008 [33]. A probable cause for this was gaps in the support supervision and mentorship processes for prescribers.

While scheduling was a challenge in other studies with error rates ranging between 16.6% and 28.3% [26,29,34], this type of error only constituted 1% of the total number of irrational prescriptions. This is as a result of the standardized dosage plan of most pediatric HAART prescriptions with many patients getting one to three months' supply, each patient receiving a pack per month and all formulations being dosed once or twice a day [16]. This contrasts with essential medicines majority which may be dosed in the range of once to four times daily.

Errors of integration were higher than those found in studies that were conducted on essential medicines [25,26] and yet were

substantially lower than in research done for HAART [29,35-37]. It should be noted that the studies that were done for HAART comprised both adult and child participants. Incomplete regimens were fairly common in prescriptions in other studies compared to the 3% in this study. Several studies have attributed prescription of incomplete regimens to patients not providing adequate information about their medicines on presenting to clinics attesting to the need for continuity in documentation [31,38,39]. This is provided for by the nature of ART records ('HIV care/ART continuation card') in the Ugandan HIV care and treatment program. In addition, provision of FDC formulations is also vital in reducing the risk of receiving incomplete regimens. Pastakia et al found that patients on non-FDCs were almost twice as likely to receive incomplete regimens as those on FDCs [40].

It is also of note that 57.8% of the children did not have a CD4 test done during the study period within range of the 55.9% and 64.8% found in other studies [41,42]. This contravened the treatment guidelines which recommended a minimum of one CD4 test in six months to monitor treatment response [16]. Each child who did not receive a test in the review period could potentially have been receiving an irrational prescription making the proportion of these prescriptions even higher.

Factors Associated with Irrational Prescriptions

Being on treatment for less than a year was associated with having at least one irrational prescription. Of particular concern is that the median age of these new patients at initiation was six years. These children do not have well-developed excretory systems making any irrational prescriptions harmful. Furthermore, any adverse events that are experienced by new patients are likely to deter them from continuing with treatment leading to treatment interruption and potentially drug resistance. To the best of our knowledge, this is the first study that has demonstrated that treatment-naïve patients are more likely to have an irrational prescription than their experienced counterparts.

There were more patients with irrational prescriptions in the private than the public sector. This is consistent with findings in several systematic reviews and medicines policy evaluations that have highlighted that the private sector faces particular challenges in adhering to guidelines [33,43,44]. Majority of these findings were focused on essential medicines and therefore it is plausible that private facilities were targeting higher profit margins. However, ARVs are provided free of charge in most clinics in Uganda. As profit is not a motive, other factors were probably responsible for the high prevalence of patients with irrational prescriptions in TASO.

One of these factors could be the size of the clinic. This facility had almost three times the number of patients compared to Iganga hospital. The average number of health workers assigned to a clinic in TASO was nine contrasted with seven in Iganga. A systematic review that projected the number of health care workers needed to run a HAART clinic in a resource-limited setting suggested between 8.5 and 10 personnel for every 1,000 patients [45]. TASO consequently required at least six times the number of health workers it had based on its patient population. It should also be noted that these estimates refer to HAART only. Prescribers in health centers will typically attend to both pre-ART and ART patients and as such, the need for additional staff becomes greater. This corroborates with findings in Uganda where prescribers admitted to being too busy to reference treatment guidelines [46].

Secondly, lack of access to key medicines and equipment have played a role in irrational prescribing. 89% of the children who did not have a CD4 test within the study period were from TASO and this could have been because they did not have a CD4 machine on site. Much as the CD4 machine was not far from the health facility, Point of Care testing platforms should be provided to high volume health centers to reduce the number of patients who might miss a test. Nevertheless, health workers need to be encouraged to use these monitoring tests. Only 10% of children who were started on a Zidovudine-based regimen received a hemoglobin test and 5 children did not have weight taken at all their visits despite hemoglobinometers and weighing scales being available at both facilities.

Limitations of the study

This study was conducted in two purposively selected urban health facilities and may not be representative of other facilities nationwide. Furthermore, the study assessed a period of 6 months. It would be difficult to identify treatment failure or any related adherence problems and therefore the need to switch a regimen in such a short period of time. Other drugs prescribed that might have been contraindicated with the children's HAART regimen were not assessed.

Conclusion

The prevalence of irrational prescriptions in Uganda is high. Children receiving care in private health facilities and those newly initiated on treatment are at particularly high risk of receiving these prescriptions. Knowledge gaps amongst prescribers must be addressed through quality improvement strategies including mentorship, clinic audits, pharmacy reviews and automated prescribing systems where possible. Future research should identify whether children receive these irrational prescriptions at the dispensing point and the impact of such prescriptions on virologic control and the cost of care.

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