High Prevalence of Clinical Jaundice Associated with Poor Adherence Among Adults on Boosted Atazanavir Antiretroviral Therapy Regimen at the Infectious Disease Institute HIV/AIDS Clinic in Kampala, Uganda

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Abstract

Background

Boosted atazanavir (ATV/r)-based Antiretroviral Therapy (ART) regimen is recommended by the World Health Organization (WHO) as second line treatment for HIV/AIDS. ATV/r is known to cause clinical jaundice, which may lead to non-adherence to treatment and the attendant treatment failure and drug resistance. We sought to determine the prevalence of clinical jaundice and explore its effect on adherence to the ART regimen.

Methods

We conducted a cross-sectional study among 236 adult patients taking ATV/r-based ART regimens attending the Infectious Disease Institute (IDI) HIV/AIDS clinic in Kampala, Uganda from April to May 2019. We assessed the study participants by self-report for existing or previous experience of clinical jaundice after their start on ATV/r-based ART regimen. Adherence to the ATV/r-based ART was determined using the 8-item Morisky scale; score <3 and ≥3 was interpreted as good and poor adherence to ART, respectively. Logistic regression was used to explore the effect of clinical jaundice and other sociodemographic factors on adherence to ART regimen.

Results

Of the 236 participants, majority were female (66.5%) with a mean age of 39.9 (SD 10.8) years and had been on ART for 10 to 13 years (42.8%). Most (69%) were on TDF/3TC backbone and 24% on AZT/3TC backbone. The period and point prevalence of clinical jaundice was 31.8% (95% confidence interval [CI]: 26.1% – 38.1%) and 21.1% (95% CI: 14.9% – 37.5%) respectively. Up to 8.5% (95% CI: 5.5 – 12.8) had poor adherence (≥ 3). At multivariable analysis, clinical jaundice was the only predictor of poor adherence (adjusted odds ratio= 2.9, 95% CI: 1.15 – 7.34, p=0.024). Sex, alcohol use, and stigma and discrimination did not achieve statistical significance.

Conclusion

Our study indicates a high prevalence of clinical jaundice among patients on ATV/r ART regimen and there is association between experiencing clinical jaundice and poor adherence. For patients whose ART adherence is affected by the presence of clinical jaundice; they should be switched to another second-line ART alternative.

Introduction

An estimated 38.0 million people live with HIV (PLHIV) globally; with majority (68%; 25.7 million) residing in Africa [1]. Of these, 27.5 million are currently receiving antiretroviral therapy (ART) [1]. The total population of PLHIV in Uganda is 1.4 million and about 1.3 million (~ 90%) are on ART, with 82% virally suppressed [2]. ART is key to reduced morbidity and mortality among PLHIV, however, its success is highly dependent on adherence [3]. Adherence varies between individuals because of innumerable reasons including side effects of the medicines [3–6]. Poor adherence has been reported as a single predictor of mortality in PLWHIV [7].

About 5% of PLHIV are on second-line ART [8]. Conferring to consolidated guidelines for the prevention and treatment of HIV and AIDS in Uganda, the recommended second line ART regimen is two nucleos(t)ide reverse

transcriptase inhibitors (NRTIs) and Dolutegravir (DTG) or a boosted Atazanavir (ATV/r)[9]. ATV/r is preferred over boosted lopinavir because its: better tolerated in the gastrointestinal tract, higher genetic barrier, once daily dosing with lower pill burden, virologic potency, less associated with dyslipidemias, and more affordable [9–11]. However, ATV/r is associated with indirect hyperbilirubinemia which can progress to jaundice[11, 12].

Jaundice occurs when blood bilirubin levels raise above 3mg/dl [13]. Jaundice can be subclinical without signs and symptoms or clinical with yellowing of eyes, yellowing of mucous membranes, yellowing of skin, dark urine, pale stools, nausea, among others [14]. Jaundice caused by protease inhibitors including ATV/r is non pathological but rather, due to inhibition of Uridine 5'-Diphospho-Glucuronosyl Transferase 1A1 (UGT1A1); which is responsible for conjugation of bilirubin [15]. Clinical jaundice is of main concern because it can lead to non-adherence or discontinuation of medication among PLWHIV [15].

Many studies have assessed adherence to ART[3],[16],[17],

Several studies have reported hyperbilirubinemia associated with ATV/r based ART regimen [12, 18, 19]. Bissio and colleagues reported a prevalence of jaundice of up to 59% among HIV patients receiving ATV/r based regimen [12]. McDonald et al., reported that while hyperbilirubinemia was common among patients on ATV/r regimen, there was no negative impact of ATV/r associated hyperbilirubinemia on clinical outcomes of PLHIV [18]. However, limited studies have addressed the prevalence of clinical jaundice and its clinical significance or how it affects ART adherence among patients taking ATV/r. Nevertheless, none of these studies have been carried out in Uganda. Therefore, this study aimed to determine the prevalence of clinical jaundice in adults on ATV/r and its association with adherence among people on ATV/r attending an HIV clinic in Kampala, Uganda.

Methods

Study design and setting

A cross-sectional study was carried out at the HIV clinic of Infectious Disease Institute (IDI),Makerere University, Kampala, Uganda among adult PLHIV on atazanavir containing ART regimen from 8th April to 5th May 2019. IDI is a Ugandan not-for-profit organization established under Makerere University in 2002 located in Kampala. The HIV clinic is located within Mulago National Referral Hospital. As of 2021, the adult infectious disease clinic at IDI provides ART services to over 7000 PLWHIV among whom about 900 have ATV based ART regimen.

Sample size,

A sample size of 270 participants was calculated using Cochran's formula [20]. Using an estimated population of 871 PLWHIV on ATV/r regimen at IDI, 50% estimated prevalence of clinical jaundice since no study has been conducted in a similar setting, 5% acceptable margin of error at 95% confidence interval, a sample size of 270 was calculated.

Selection criteria and sampling

The following criteria was used to enroll eligible participants: (1) Laboratory confirmed HIV positive patients, (2) aged 18 years and above, (3) on ATV/r based regimen for at least 3 months. Patients too ill to participate in

the study, were to be excluded. Consecutive sampling was used enroll the participants until the targeted sample size was reached.

Data collection and data variables

We collected data using a pre-tested interviewer-based questionnaire with semi-structured questions. The study's dependent variable was adherence to ART; assessed using the 8-item Morisky Medication Adherence Scale (8-MMAS)[21]. The 8-MMAS has 8 questions; numbers were assigned to each response and then summed up for everyone. Results were dichotomized; <3 and ≥3 were interpreted as good adherence to ART and, poor adherence to ART respectively. Furthermore, to ascertain ART adherence, pill count was done for those who came with their pill containers.

The independent variables were clinical jaundice (both prior or current while on ATV/r based regimen), duration on ART, comorbidities (hypertension, diabetes and tuberculosis), social support, pill burden, disclosure, stigma score and discrimination and, socio-demographic characteristics: age, tribe, gender, religion, education level, employment, economic status, marital status. Clinical jaundice was based on the participants' self-report and the interviewers' observance of the clinical signs: yellow mucous membranes and yellow tinge to the skin on the day of the interview. Social support was assessed using the Oslo support scale where numbers were assigned to each response. Total scores were obtained for each individual and results were categorized into 3; 3-8, 9-11 and 12-14: representing poor, moderate, and strong social support respectively. Stigma score and discrimination was assessed using the 8-item stigma score for chronic illnesses (8-SSCI) [22]. Scores were assigned to each response: > 5 and <5 indicated that the patient was stigmatized and not stigmatized respectively.

Data analysis

Data was entered and coded in EpiData software, it was then exported and analyzed in the Statistical Package for the Social Sciences (SPSS) database version 25. Continuous data was summarized into means and standard deviation for the general descriptions. Categorical data was summarized into frequency distribution tables, proportions, and percentages. The prevalence of clinical jaundice was calculated as a percentage with 95% confidence interval. It was categorized into point or period prevalence denotating; a patient had clinical jaundice at the time of the study or has ever had clinical Jaundice due to ATV/r respectively. We carried out bivariate analysis for each independent variable and adherence. After this level of analysis, statistically significant ($p<0.2$) variables were clinical jaundice, sex, alcohol use, patient's ability to speak to the doctor about jaundice, and stigma and discrimination. Thereafter, these variables were considered for multivariable analysis using multiple logistic regression [23]. The extraneous variables were then eliminated ($p >0.05$) using stepwise elimination methods. A $p<0.05$ was considered statistically significant at all levels of hypothesis testing.

Ethics statement

Ethics review and approval was sought from the Makerere University School of Health Sciences Research and Ethics Committee (MakSHS-REC), reference number 2018-086. Administrative permission was obtained from

the IDI Scientific Review Committee (SRC). Written informed was obtained from every study participant before the interview.

Results

Study participants

Overall, 242 study participants were enrolled (response rate=90%) and complete data of 236 respondents were analyzed. **Table 1** shows the participants' sociodemographic characteristics. The mean age for the study participants was 39.9 years (SD=10.8), with majority being females (66.5%). The popular tribe and religion among the study participants were the Baganda (56.1%) and Roman Catholics (33.2%), respectively. About one-third had completed primary level of education (36.4%) and were married (33.9%). Alcohol consumption among the study participants was 16.1% with a low proportion of smokers (1.3%) and other drug abusers (2.1%).

Table 1. Socio-demographic characteristics of 236 study participants

Characteristics	Frequency (n)	Percentage (%)
Age: mean (standard deviation) years	39.9	10.8
Sex		
Female	157	66.5
Male	79	33.5
Tribe		
Baganda	133	56.4
Ankole	24	10.2
Others	79	33.4
Religion		
Anglican	67	28.5
Catholic	78	33.2
Muslim	39	16.6
Pentecostal	47	20
Seventh day Adventist	4	1.7
Education level		
None	23	9.8
Primary	86	36.4
Secondary	83	35.2
Tertiary	44	18.6
Marital status		
Married	80	33.9
Cohabiting	45	19.1
Separated	39	16.5
Widowed	29	12.3
Single	43	18.2
Alcohol consumption		
Yes	38	16.1
No	198	83.9
Cigarette smoking		
Yes	3	1.3

No	233	98.7
Abuse other drugs		
Yes	5	2.1
No	231	97.9

Prevalence of clinical jaundice and ART adherence

The point and period prevalence of clinical jaundice were 21.1% and 31.8% respectively (Table 2). Majority of the patients had good adherence (Table 2; MMAS-8: good adherence <3 = 91.5%) and a visual analog score of 0 – 3 (Table 2: 84.7%)

Table 2. Prevalence of clinical jaundice and adherence among study participants.

Characteristic	Response	Frequency (n)	Percentage (%)	95% CI
Clinical Jaundice (point prevalence)	Yes	50	21.1	14.9 – 37.5
	No	186	79.9	62.5 – 85.0
Clinical Jaundice (Period prevalence)	Yes	75	31.8	26.1 – 38.1
	No	161	68.2	61.9 – 73.9
Visual analog score	0 – 3	47	84.7	
	4 – 7	16	8.9	
	8 – 10	7	6.4	
Adherence (MMAS–8)	Poor ≥ 3	20	8.5	5.5 – 12.8
	Good <3	216	91.5	87.2 – 94.5

Determinants of ART adherence.

Bivariate analysis

At bivariate analysis, clinical jaundice, sex, alcohol use, patient's ability to speak to the doctor about jaundice, and stigma and discrimination, were statistically significant (**Table** 3;

Table 3. Unadjusted association between ART adherence and the independent variables: sociodemographic characteristics, clinical characteristics, and perception.

Variables	Response	Odds ratio (95% CI)	P value
Sociodemographic characteristics			
Age	Years	0.99 (0.99 – 1.03)	0.699
Sex	Female	1.00	
	Male	2.13 (0.69 – 6.59)	0.191
Tribe	Muganda	1.00	
	Ankole	1.25 (0.25 – 6.19)	0.782
	Others	1.77 (0.67 – 4.67)	0.248
Religion	Anglican	1.00	
	Catholic	1.33 (0.44-3.93)	0.611
	Muslim	0.55 (0.10-2.87)	0.477
	Pentecostal	0.45 (0.09-2.3)	0.344
	SDA	1.00	
Education level	None	1.00	
	Primary	2.57 (0.31-21.4)	0.382
	Secondary	1.75 (0.20-14.9)	0.609
	Tertiary	2.28 (0.22-23.4)	0.449
Marital status	Married	1.00	
	Cohabiting	0.65 (0.19-2.25)	0.496
	Separated	0.43 (0.08-2.37)	0.334
	Widowed	0.82 (0.21-3.29)	0.78
	Single	0.92 (0.20-4.20)	0.917
Alcohol	Yes	2.5 (0.88 – 6.88)	0.085
	No		
Clinical characteristics			
ATV/r induced Clinical Jaundice	Yes	2.9 (1.15 – 7.34)	0.024
	No	1.00	
Medical condition (co-morbidities)	None	1.00	NA
	Hypertension		
	Diabetes		
	Hypertension & Diabetes		

	Hepatitis B		
	Others		
Visual analog score (0-10)	0-3	1.00	
	4 - 7	0.54 (0.07-4.26)	0.557
	8 - 10	1.66 (0.34-7.96)	0.529
Talked to the doctor about Jaundice	Yes	2.33 (0.90-6.03)	0.081
	No	1.00	
Perception			
Disclosure of HIV status	Yes	0.58 (0.12 – 2.75)	0.49
	No	1.00	
Stigma and discrimination (8 item score > 5)	Yes	3.32 (0.64 – 17.16)	0.153
	No	1.00	
Pill burden (they take a lot of pills)	Yes	0.76 (0.08 – 7.01)	0.811
	No	1.00	

Multivariable analysis

In this study, clinical jaundice was significantly associated with adherence while controlling for other extraneous variables. (Table 3: OR= 2.9, 95% CI 1.15 – 7.34). The odds for non-adherence were 2.9 times higher among patients with clinical jaundice and this was statistically significant while controlling for other variables.

Table 4. Association between clinical jaundice and adherence

Variable		Frequency (n)	Odds Ratio (OR)	95 % CI	P value
ATV/r Induced Clinical Jaundice	Yes	75	2.90	1.15 – 7.34	0.024
	No	161	1.00		

Discussion

Side effects of ART can facilitate poor adherence among PLWHIV hence leading to poor viral suppression, high incidence of opportunistic infections and increased mortality [24, 25]. The findings in this study suggest a high prevalence of clinical jaundice among patients taking boosted atazanavir (ATV/r) and an association between ATV/r induced Jaundice and adherence.

The point prevalence of clinical jaundice (21.1%) in this study is higher that findings from a randomized controlled, 2-arm study [26] and the CASTLE study carried out in which patients were followed for 96 weeks [18]. In the CASTLE study, 5% of the patients had scleral icterus at any one point during the study[18]. Since our study was carried out in blacks and the above mentioned studies in whites, the difference in results may be due to the variance in expression of UGT1A1, the enzyme required for bilirubin conjugation, between the black and white populations [27]. Decreased UGT1A1 leads to hyperbilirubinemia, this is due to UGT1A1*28 allele expression[28, 29] which was found to be higher in Africans (40%) than in whites (31%) [27].

The period prevalence of clinical jaundice (31.8%) in our study was also higher than that in a cohort study carried out among Hispanics where 21% of the study participants experienced clinical jaundice; with > 80% experiencing scleral icterus [12]. This still could be explained by variation in the UGT1A1 enzyme, caused by the presence of UGT1A1*28 allele; which is higher in Africans (40%) than in Hispanics (38%) [27].

Majority of the participants in our reported good adherence (91.5%). This is similar to a multicenter study carried out in Uganda; out of 1824 adolescents who were active on ART, 90.4% had good adherence[17]. The good adherence is attributed to the good counselling skills, motivation schemes and reminders to the patients about their refill dates by the IDI staff. However, adherence was likely to be impeded by presence of clinical jaundice; with the odds of non-adherence among patients with clinical jaundice being 3 times higher than those without clinical jaundice. Furthermore, less than 1% (2 out of 236) discontinued treatment because of the yellowing of the scleral icterus. This finding is similar to other studies [26, 30] and the castle study; where less than 1% discontinued ART because of scleral icterus or Jaundice [18].

Still worthy to note, from the research findings of the current study, the appearance and disappearance of clinical jaundice varies from one week onwards and within two weeks onwards respectively and it can be recurrent.

Majority of the patients were unbothered by the clinical jaundice as shown by 84.7% with the visual analog score of 0–3. This is because most of them had been talked to by their doctors and counselors about the symptoms of jaundice on initiation of an ATV/r containing regimen. Our study suggests the importance of pre-ART counselling for all patients who are starting ART/r-based regimen to improve adherence. Recent studies have reported lower incidences of hyperbilirubinemia and jaundice when unboosted ATV is given instead of ATV/r with comparable efficacy.

While other studies are looking at ATV/r induced hyperbilirubinemia, this study focuses on clinical jaundice which is a major concern regarding ART adherence especially in people taking ATV/r. However, the results in our study have some important limitations that may affect its generalizability. Period prevalence of clinical jaundice based on self-report may be subject to recall and report bias leading to an over or under estimation.

Conclusion

A significant proportion of PLWHIV on ATV/r-based regimen in Uganda experience clinical jaundice and this is significantly associated with poor adherence. Intensive pre-ART counselling aimed at increasing the patients' awareness on the likely side effects of the medications and re-assuring them is important to curb down poor ART adherence, ART-failure and associated morbidity and mortality.

Abbreviations

EA Enumeration area

AOR Adjusted Odds Ratio

CI Confidence Interval

COR Crude Odds Ratio

DHS Demographic Health Survey

UDHS Uganda Demographic Health Survey

OR Odds Ratio

SD Standard Deviation

WHO World Health Organization

SPSS Statistical Package for Social Science

USAID United States Agency for International Development.

Declarations

Ethics approval and consent to participate

The research and ethics committees at Makerere University School of Health Sciences, Uganda National Council of Science and Technology reviewed and approved the study. Informed consent was obtained from all the research participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no competing interests. AKN, SKN, EL, EK, NO, IL, BC, ML and FEK

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Authors' contributions

AKN, SKN, EL and FEK conceived the idea and conducted the study. AKN developed the first draft of the manuscript. AKN, SKN, EK and FEK performed analysis and interpreted the results. AKN, SKN, EL, EK, NO, IL, BC, ML and FEK contributed to results interpretation, reviewed the first draft and drafted the subsequent versions of the manuscript. All authors read and approved the final manuscript.

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