Incidence and Predictors of Severe Adverse Drug Reaction Among Patients on Antiretroviral Therapy in Tigray, Ethiopia: A Retrospective Cohort Study

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Background: The aim of the present study was to assess the incidence and predictors of severe adverse drug reactions among patients on antiretroviral therapy (ART) in Tigray, North Ethiopia.

Methods: We employed four years retrospective cohort study using a structured data extraction sheet. The study populations were HIV patients on ART follow-up from January 2017 to February 2020 in the study area. Severe adverse drug reaction (ADR) was an outcome variable and defined as having any one of the complaints related to ARV drug reaction due to regimen change, discontinuation, and/or in-patient care. Data were collected using a structured data extraction sheet. A Cox proportional hazard regression model was used to determine the relationship between the predictors and the outcome variable. The mean survival time of the cohort was estimated using the Kaplan–Meier method.

Results: The incidence rate of ADRs was 3.6 (95%CI: 2.9–4.35) per 100-person years. HIV patients with no formal education (adjusted hazard ratio=1.58, 95%CI: 1.03–2.41), with experience of regimen change (adjusted hazard ratio=1.59, 95%CI: 1.12–2.91), who ever took other medication (adjusted hazard ratio=1.49, 95%CI: 1.05–2.15) and with lower body mass index (adjusted hazard ratio=3.24, 95%CI: 1.18–4.91) were more likely to develop severe adverse drug reaction.

Conclusion: ADRs were diagnosed an inconsiderable number of HIV patients on ART and factors were patient and drug-related. To minimize it, special attention is sought for patients with no formal education, previous regime change, whoever took other medication, and who have lower body mass index levels.

Keywords: human immunodeficiency virus, adverse drug reactions, antiretroviral therapy

Introduction

For people living with HIV and AIDS (PLWHA), the persons with HIV may continue to live well and productively for many years.¹ Worldwide, by the end of 2019, 81% of people living with HIV were aware of their HIV status and 67% of them were on ART, the same with an estimated 25.4 million of the 38.0 million people living with HIV—a number that has more than tripled since 2010.² Women and girls in sub-Saharan Africa, accounting for 59% of new HIV infections in the region by 2019.³ Widespread ART blocks approximately 12.1 million AIDS-related deaths by 2010. The estimated 690,000 lives lost due to AIDS-related illnesses

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worldwide in 2019 is a 39% reduction since 2010, but still, far too many people are dying unnecessarily.²

The Federal Democratic Republic of Ethiopia has observed remarkable progress over the past two decades in reducing the HIV prevalence rate from 3.3% in 2000 to 0.9% in 2017, and AIDS-related deaths were reduced from 83,000 people in 2000 to 15,600 in 2017. The Joint United Nations Program on HIV/AIDS (UNAIDS) unites the efforts of 11 United Nations organization works closely with global and national partners towards ending the AIDS epidemic by 2030 as part of the sustainable development goals.³ However, the gains made so far seem to be challenged by complacency regarding severe adverse drug reactions (SADRs).⁴

Adverse drug reactions (ADRs) are defined as “is a harmful and unintended reaction to the use of humans for the prevention, diagnosis, or treatment of health or physiology”.⁵ The incidence of ADRs is variably reported from 90% in India,⁶ 4.6% in Nigeria,⁷ to 9% in Ethiopia.⁸ There are several predicting variables to ADR including but not limited to higher CD4 cell count,⁹ tuberculosis/HIV (Tb/HIV) co-infection,^{10,14} alcohol intake, pregnancy, breastfeeding, and kidney problems.¹¹ There are, however, limited data on the incidence and predictors of ADR in Tigray, North Ethiopia. Therefore, this study assessed the incidence and predictors of severe adverse drug reactions among patients on ART in Tigray, North Ethiopia.

Methods and Materials

Study Design and Period

A health facility-based retrospective cohort study was conducted among people living with HIV from January 2017 to February 2020. All adults aged 15 years and older on ART follow-up having at least one repeated follow-up visit were included in the study.

Study Setting

The study was conducted in Aksum St Mary general hospital in Tigray regional state, northern Ethiopia. Aksum is the capital of the central zone of Tigray which is located 1024 km north of Addis Ababa and 247 km from Mekele, the capital city of Tigray. Axum city has one referral and teaching hospital, one general hospital, two health centers, four health posts, and 10 different level private clinics.

Aksum St Mary general hospital, the other study setting in Axum, was established in 1961 and has 368 health-care workers including 17 general practitioners (GPs) and five

specialists. The hospital provides emergency, in-patient, and outpatient services at different departments. It provides comprehensive HIV/AIDS care and support services including voluntary counseling and testing (VCT), prevention of mother-to-child transmission (PMTCT), provider-initiated HIV testing and counseling (PITC), ART, and treatment for opportunistic infections (OIs) since 2003.

Since the end of 2016, Ethiopia has started the “test and treat” strategy where every HIV-positive person who starts the treatment was eligible for ART and both hospitals in the study setting also started the program.¹²

Study Participants and Sampling

The populations included in the current study were HIV patients who are on ART follow-up for a minimum of 36 months enrolled in the study setting. The list of all eligible participants on ART follow-ups was obtained from the ART clinic in each hospital. A total of 452 HIV-positive adolescents and adults were recruited using a computer-generated simple random sampling method using unique ART numbers as a sampling frame. The data extraction sheet was prepared in English and then translated into the local language (Tigrigna) and back into English by a professional person. To establish face validity and translation quality the questionnaire was tested on 5% of the total sample size determined for this study participant outside of the study site by data collectors and supervisors during training. Data were collected from the ART registry logbook and patients charts. The data were collected by health professionals who were trained on ART.

Variables in the Study

The outcome variable in the study was severe adverse drug reaction “Yes” if any one of the following features recorded as ARV drug reaction complaints about seeking care and resulted in either regimen change, discontinuation, and/or in-patient care (including all available laboratory test results): diarrhea, hepatotoxicity, peripheral neuropathy, Severe skin rash and hypersensitivity reaction (Stevens–Johnson syndrome), anemia, pancreatitis, abdominal pain, jaundice, fat changes, anxiety, depression, vomiting, and other rare conditions; and “No” if none of the above complaints were recorded. The exposure variables included: age, gender, marital status, educational status, previous diagnosis of opportunistic infection, the experience of regimen change, history of antituberculosis prophylaxis taking, ever taking of one or more medications other than ART, and body mass index (BMI). BMI was defined as “underweight” if $<18.5 \text{ kg/m}^2$; “normal” if $18.5\text{--}24.99 \text{ kg/m}^2$; and “overweight” $\geq 25 \text{ kg/m}^2$.

Data Extraction and Analysis

Data were extracted from the ART registry logbook and electronic medical record (EMR) system in Aksum St Mary general hospital designed in 2018. Four trained ART nurses and data clerks extracted the data and were supervised by one GP. Data were initially checked manually for completeness and consistency by the supervisor and principal investigator during the fieldwork and rechecked before data entry. Data were then coded, entered, and cleaned using Epi Info version 7 to exported to Stata version 14.0 software for analysis and interpretation. The mean survival time was estimated using the Kaplan–Meier method. To model the relationship between exposure variables and the outcome variable, the Cox proportional hazard regression model was implemented.

Result

Sociodemographic Characteristics

In this study, 452 participants were included for analysis of which 233 (51.5%) were women and one out of five participants were youths. Nearly half of the participants 46% were married, one third (28.5%) of participants had no formal education, and about 59% lived within the catchment area of the study settings (Table 1).

Baseline Clinical Characteristics and Follow-up Measurements

Of the total, four in five patients (81.6%) had a CD4 count ≤ 200 ; half (49.8%) of the participants' BMI were underweight and one third (32.1%) of participants were diagnosed clinical stage III and IV. Table 2 demonstrates the

Table 1 Sociodemographic Characteristics of Patients on ART

Characteristics		Frequency (N)	Percent (%)
Age in years	15–24	85	18.8
	25–34	133	29.4
	35–44	133	29.4
	≥ 45	101	22.3
Gender	Male	219	48.5
	Female	233	51.5
Marital status	Never married	130	28.8
	Divorced	71	15.7
	Married	208	46
	Widowed	43	9.5
Residence	Within catchment area	266	58.8
	Without catchment area	186	41.2
Educational status	No formal education	129	28.5
	Primary education	139	30.8
	Secondary education	144	31.9
	Tertiary education	40	8.8
Occupation	Sex worker	25	5.5
	Driver	32	7.1
	Daily laborer	64	14.2
	Merchant	34	7.5
	Farmer	49	10.8
	Government employee	43	9.5
	Private employee	28	6.2
	Student	22	4.9
	Housewife	63	13.9
	No job	92	20.4
Religion	Orthodox	416	92
	Muslim	32	7.1
	Protestant	4	0.9

Table 2 Baseline Characteristics and Follow-up Measurements of Patients on ART

Characteristics		Frequency (N)	Percent (%)
CD4 count in cells/ μ L	≤ 200	369	81.6
	≥ 200	83	18.4
BMI	Underweight	222	49.8
	Normal	216	48.5
	Overweight obese	14	1.8
WHO clinical stage	Stage I and II	307	67.9
	Stage III and IV	145	32.1
Baseline regimen	Ie=TDF-3TC-EFV	423	93.6
	Ij=TDF-3TC-DTG	23	5.1
	Other	6	1.3
Experience of TB infection	Yes	78	17.3
	No	374	82.7
Experience of other OIs	Yes	83	18.4
	No	369	81.6
Poor ART adherence before ADR	Yes	50	11.1
	No	402	88.9
Experience of regimen change	Yes	329	71.2
	No	133	28.8
If there is regiment change	Toxicity/SE	15	3.3
	New drug available	128	28.3
	No change	309	68.4
History of CPT	Yes	340	75.2
	No	112	24.8
Poor adherence in CPT	Yes	47	10.4
	No	405	89.6
Anti-TB prophylaxis	Yes	336	74.3
	No	116	25.7
Other medication/nutritional supplement	Yes	133	31.6
	No	319	68.4

Note: Other: Ia=d4t-3TC-NVP, Ib=d4t-3TC-EFV, Ic=AZT-3TC-NVP, Id=AZT-3TC-EFV

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; ADR, adverse drug reaction; BMI, body mass index; CD4, cluster for differentiation 4; CPT, cotrimoxazol preventive therapy; DTG, dolutegravir; EFV, efavirenz; TB, tuberculosis; TDF, tenofovir; d4t, stavudine, NVP, nevirapine, EFV, efavirenz, AZT, zidovudine.

clinical characteristics of the study participants included in the study.

Incidence Rates of Adverse Drug Reactions

Out of the total 452 participants, 151 (17.8%; 95%CI: 15.2%, 20.9%) had experienced severe adverse drug reactions (ADRs). Anemia was the common complaint of ADRs. The incidence rate of ADR was 3.6 (95%CI: 2.9–4.35) per 100-person years. The incidence rates in males and females were 18.9 and 16.7 per 1000-person years of

follow-up respectively. The incidence rate in underweight, normal weight and overweight were 15.9, 18.7, and 57.5 per 1000-person years of follow-up, respectively. The patients were followed for a median time of 18 months (a minimum of one and a maximum of 43 months of the follow-up). [Figures 1](#) and [2](#), respectively demonstrate the ADR status of study participants by the experience of regimen change and diagnosis of OIs using Kaplan–Meier graphs. The hazard distribution of experience of regimen change was found to be statistically significant but not for the OIs.

Figure 1 Kaplan–Meier curves for time to the development of ADRs among HIV patients on ART by the experience of regimen change, St Mary Hospital.

Figure 2 Kaplan–Meier curves for time to the development of ADRs among HIV patients on ART by the experience of opportunistic infection, St Mary Hospital.

Survival Probability

Due to the smaller proportion of the event in the cohort, the median survival time was not estimable. So, we used the survival mean to estimate the mean survival time. In this regard, the survival mean will be estimated better

considering the maximum event time, which is reported as restricted mean survival time. The estimated mean survival time using the restricted mean was 66.5 (95%CI: 62.4–70.5) months. The overall survival history of the cohort is displayed in [Figure 3](#).

Figure 3 Cumulative survival Kaplan–Meier curve for time to the development of ADRs among HIV patients on ART St Mary Hospital.

Predictors of Severe ADRs Among Patients on ART

Age, marital status, education status, the experience of OI, the experience of regime change, ever took anti-TB prophylaxis, ever took other medication or nutrition and BMI were the candidate variables for the multivariable Cox proportional model. Finally, education status, the experience of regime change, ever took other medication, and BMI were found predictors of severe ADRs.

Those patients with no formal education were about two times (AHR=1.58, 95%CI: 1.03–2.41) at higher risk of developing ADR compared to those with tertiary education. The risk of ADRs among patients with experience of regimen change was double (AHR=1.59 95%CI: 1.12–2.91) compared to those patients with no experience of regimen change. Patients who ever took other medication were 50% (AHR=1.49 95%CI: 1.05–2.15) more likely to develop ADR than those with no such experience. Patients with BMI underweight were three times (AHR=3.24 95%CI: 1.18–4.91) at higher risk of developing ADR at any time. Table 3 shows the predictors of ADR among patients on ART (Table 3).

Discussion

The present study determined the incidence and predictors of severe adverse drug reactions among patients on ART in Central Tigray, Ethiopia.

Most patients in the present study are women and between the ages of 25 and 44, implying the concentration of HIV among women and the youth. We found that the incidence of severe adverse drug reaction was 3.6 per 100-person years of follow-up, a finding consistent with studies in Debre Markos Referral Hospital, Northwest Ethiopia (3.0/100 PY).¹³ But this finding was different from studies conducted in Nigeria reporting 4.6/100 PY and 4.05/100 PY,^{7,14} and Bahir Dar, Ethiopia reporting 4.3/100 PY.¹⁵ This may be attributed to some reasons. First, the level of adherence in these facilities may be different. Previous studies showed that poor adherence determined the incidence of ADR.^{11,16} Second, the capacity and commitment of prescribers also determine the incidence of ADR. For example, a health worker assessing careful medication history could assist in identifying the previous history of ADRs that may preclude re-exposure to the drug.¹⁷ Third, the presence of incomplete laboratory data could also underestimate the incidence of ADR.¹⁸

There are several predictive variables for the occurrence of ADRs in the present setting. Those patients with no formal education were two times at higher risk of developing ADR compared to those with tertiary education, which is consistent with the studies conducted in Bahir Dar City,¹⁵ Northwest Ethiopia, Northern Nigeria,¹⁴ and Jodhpur-India.¹⁹ A good understanding of ARV compliance, good nutrition, and caring for them can be thought to have provided some protection against drug reactions.¹⁵

Table 3 Cox Regression Analysis of the Relationship Between Explanatory Variables and the Time to ADR Development

Variables		Survival Status		CHR (95%CI)	AHR (95%CI)
		Event	Censored		
Age	15–24	24 (15.9%)	60 (19.9%)	I	I
	25–34	37 (24.5%)	97 (32.2%)	0.93 (0.55–1.55)	0.97 (0.57–1.67)
	35–44	45 (29.8%)	88 (29.2%)	0.96 (0.58–1.58)	1.03 (0.59–1.76)
	≥45	45 (29.8%)	56 (18.6%)	1.38 (0.84–2.27)	1.62 (0.98–2.69)
Marital status	Never married	43 (28.5%)	87 (28.9%)	I	I
	Divorced	28 (18.5%)	43 (14.3%)	0.77 (0.47–1.24)	0.63 (0.36–1.12)
	Married	66 (43.7%)	142 (47.2%)	0.96 (0.65–1.41)	0.78 (0.49–1.25)
	Widowed	14 (9.3%)	29 (9.6%)	0.98 (0.54–1.79)	0.78 (0.39–1.56)
Education status	No formal education	36 (23.8%)	93 (30.9%)	1.04 (1.01–2.41)	1.58 (1.03–2.41)*
	Primary education	56 (37.1%)	83 (27.6%)	1.78 (0.78–1.85)	1.29 (0.83–2.04)
	Secondary education	48 (31.8%)	96 (31.9%)	1.32 (0.57–2.20)	1.19 (0.58–2.45)
	Tertiary education	11 (7.3%)	29 (9.6%)	I	I
Experience of OI	Yes	25 (16.6%)	58 (19.3%)	0.73 (0.47–1.12)	0.72 (0.45–1.14)
	No	126 (83.4%)	243 (80.7%)	I	I
Experience of regimen changed	Yes	60 (39.7%)	70 (23.3%)	2.18 (1.92–2.89)	1.59 (1.12–2.91)**
	No	91 (60.3%)	231 (76.7%)	I	I
Ever took anti-TB prophylaxis	Yes	114 (75.5%)	222 (73.8%)	I	I
	No	37 (24.5%)	79 (26.2%)	0.81 (0.56–1.18)	0.81 (0.54–1.21)
Ever took other medication	Yes	48 (31.8%)	85 (28.2%)	1.18 (1.01–1.84)	1.49 (1.05–2.15)*
	No	103 (68.2%)	216 (71.7%)	I	I
BMI	Underweight	151 (65.9%)	71 (31.8%)	2.84 (1.12–3.51)	3.24 (1.18–4.91)**
	Normal	72 (31.4%)	144 (64.6%)	1.29 (0.14–1.61)	1.37 (0.14–1.39)
	Overweight	6 (2.7%)	8 (3.6%)	I	I

Note: *P-value <0.05, **P-value <0.001.

Abbreviations: BMI, body mass index; TB, tuberculosis; OI, opportunistic infection.

The risk of ADRs among patients with experience of regimen change was two times higher at any time compared to those with a patient with no experience of regimen change. This finding is in line with a study done in Debre Markos Referral Hospital, Gondar Referral Hospital,²⁰ Jimma Southwest Ethiopia,²¹ and Kenya.²² Patients who ever took other medication were 1.5 times more likely to develop adverse drug reactions at any time in the follow-up compared to those with no such experience. This is in line with previous literature revealing HIV-infected patients receiving TB treatment commonly experience drug toxicity,^{23,24} some findings even recommended deferring of ARVs during the intensive phase of TB treatment.^{24,25} Patients with BMI underweight were three times at higher risk of developing ADR at any time. This is supported by a prospective cohort study conducted in Ethiopia which shows severe ADRs were associated with a decreased gain in BMI.²⁶ Studies indicated

that patients with lower BMI (underweight) have a high rate of hospitalization, and exposure to opportunistic infections and subsequent pill burden to treat them, and these may lead to ADR.²⁷

The current study put effort into comprehensively assessing the incidence of ADRs and related factors. However, there are some limitations. First, there was data incompleteness (with incomplete information, loss of patient cards, and illegible handwriting on patients' cards) given the record based nature of the source of data. We were, therefore, unable to assess the details of sociodemographic variables and some important variables. Second, we have not been able to describe and discuss the details of each specific type of adverse drug reaction.

Conclusions

The incidence of ADRs seems lower than the studies conducted in other parts of Ethiopia and some developing

countries but the burden was still considerable. HIV-patients with a lower level of educational status, the experience of regime change, ever took other medication and low BMI attributed to an adverse drug reaction. This group of HIV patients should seek special attention to minimize the adverse drug reaction. We also recommend improving the data handling of hospitals. The health-care providers should document detailed patients' information clearly on their cards.

Abbreviations

3TC, lamivudine; ART/ARV, antiretroviral therapy; AZT/ZDV, zidovudine; BMI, body mass index; CD4, cluster of differentiation 4; CPT, co-trimoxazole preventive therapy; D4T, stavudine; IPT, ionized preventive therapy; LMM, linear mixed model; PLHIV, people living with HIV; TDF, tenofovir.

Data Sharing Statement

All relevant data are within the paper. The SPSS data of individual patients are not permitted to be provided to other bodies, as outlined by the ethics committee who approved the study. However, Teferi (teferigebru12@gmail.com) can provide an anonymized data set for researchers who need further clarification.

Ethics Approval and Consent to Participate

Ethical clearance was obtained from the Aksum University College of Health Science (CHS) ethical review committee and permission letter was obtained from the St Mary General Hospital before data collection. A formal letter was written to the ART clinic and a responsible official was communicated with. Due to difficulty to reach patients to obtain informed consent, data were extracted anonymously ensuring patient data confidentiality, and all data collection was conducted in compliance with the Declaration of Helsinki.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of

data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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References

1. UNAIDS. *UNAIDS Terminology Guidelines Midterm Additions* 2011/009. October, 2011.
2. HIV/AIDS, J.U.N.P.o. *Global HIV & AIDS Statistics—2018 Fact Sheet*. Geneva, Switzerland: World Health Organization; 2019.
3. Nygren-Krug H. *The Joint United Nations Programme on HIV/AIDS*. Human Rights in Global Health: Rights-Based Governance for a Globalizing World; 2018:281.
4. Office, F.H.A.P.a.C. *HIV Prevention in Ethiopia National Road Map 2018–2020*. November, 2018.
5. Organization(WHO), W.H. *Clinical Aspects of ADRs in HIV and ARV Toxicity Monitoring Approaches*. Gaborone, Botswana. June 26, 2018.
6. Shet A, Antony J, Arumugam K, et al. Influence of adverse drug reactions on treatment success: prospective cohort analysis of HIV-infected individuals initiating first-line antiretroviral therapy in India. *PLoS One*. 2014;9(3):e91028. doi:10.1371/journal.pone.0091028
7. Eluwa GI, Badru T, Akpoigbe KJ. Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria. *BMC Clin Pharmacol*. 2012;12(1):1–9. doi:10.1186/1472-6904-12-1
8. Gudina EK, Teklu AM, Berhan A, et al. Magnitude of antiretroviral drug toxicity in adult HIV patients in Ethiopia: a cohort study at seven teaching hospitals. *Ethiop J Health Sci*. 2017;27(1):39–52. doi:10.4314/ejhs.v27i1.5S
9. Lartey M, Asante-Quashie A, Essel A, Kenu E, Ganu V. Adverse drug reactions to antiretroviral therapy during the early art period at a tertiary hospital in Ghana. *Pan Afr Med J*. 2014;18.
10. Chaisson RE, Schecter GF, Theuer CP, et al. Tuberculosis in patients with the acquired immunodeficiency syndrome: clinical features, response to therapy, and survival. *Am Rev Respir Dis*. 1987;136(3):570–574. doi:10.1164/ajrccm/136.3.570
11. Alomar MJ. Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharm J*. 2014;22(2):83–94. doi:10.1016/j.jsps.2013.02.003
12. Organization, W.H. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. World Health Organization; 2016.
13. Kibret GD, Ayele TA, Tesfahun A. *Incidence and Predictors of Severe Adverse Drug Reactions Among Patients on Antiretroviral Therapy at Debre Markos Referral Hospital, Northwest Ethiopia*. Research square; 2019.
14. Obiako OR, Muktar HM, Garko SB, et al. Adverse reactions associated with antiretroviral regimens in adult patients of a university teaching hospital HIV program in Zaria, Northern Nigeria: an observational cohort study. *J Antivir Antiretrovir*. 2012;4:6–13.
15. Kindie E, Alamrew Anteneh Z, Worku E, Maga G. Time to development of adverse drug reactions and associated factors among adult HIV positive patients on antiretroviral treatment in Bahir Dar City, Northwest Ethiopia. *PLoS One*. 2017;12(12):e0189322. doi:10.1371/journal.pone.0189322

16. Rajesh R, Sonika S, Sudha V, et al. Association between medication adherence outcomes and adverse drug reactions to highly active antiretroviral therapy in Indian human immunodeficiency virus-positive patients. *J Young Pharm.* **2012**;4(4):250–260. doi:10.4103/0975-1483.104369
17. Coleman JJ, Pontefract SK. Adverse drug reactions. *Clin Med.* **2016**;16(5):481. doi:10.7861/clinmedicine.16-5-481
18. Wolfe D, Yazdi F, Kanji S, et al. Incidence, causes, and consequences of preventable adverse drug reactions occurring in inpatients: a systematic review of systematic reviews. *PLoS One.* **2018**;13(10):e0205426. doi:10.1371/journal.pone.0205426
19. Sood A, Prajapati H, Bhagra S, et al. Characterization and comparative analysis of ADRs of various ART regimens: experience of our medical college from Western Himalayan region. *Int J Res Med Sci.* **2017**;5(2):659–665. doi:10.18203/2320-6012.ijrms20170170
20. Anlay DZ, Alemayehu ZA, Dachew BA. Rate of initial highly active anti-retroviral therapy regimen change and its predictors among adult HIV patients at University of Gondar Referral Hospital, Northwest Ethiopia: a retrospective follow up study. *AIDS Res Ther.* **2016**;13(1):1–8. doi:10.1186/s12981-016-0095-x
21. Birlie B, Braekers R, Awoke T, et al. Multi-state models for the analysis of time-to-treatment modification among HIV patients under highly active antiretroviral therapy in Southwest Ethiopia. *BMC Infect Dis.* **2017**;17(1):1–13. doi:10.1186/s12879-017-2533-3
22. Inzaule S, Otieno J, Kalyango J, et al. Incidence and predictors of first line antiretroviral regimen modification in western Kenya. *PLoS One.* **2014**;9(4):e93106. doi:10.1371/journal.pone.0093106
23. Patel A, Patel K, Patel J, et al. Safety and antiretroviral effectiveness of concomitant use of rifampicin and efavirenz for antiretroviral-naïve patients in India who are coinfecting with tuberculosis and HIV-1. *J Acquir Immune Defic Syndr.* **2004**;37(1):1166–1169. doi:10.1097/01.qai.0000135956.96166.f0
24. Dean GL, Edwards SG, Ives NJ, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *Aids.* **2002**;16(1):75–83. doi:10.1097/00002030-200201040-00010
25. Yee D, Valiquette C, Pelletier M, et al. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med.* **2003**;167(11):1472–1477. doi:10.1164/rccm.200206-626OC
26. Bezabhe WM, Bereznicki LR, Chalmers L, et al. Adverse drug reactions and clinical outcomes in patients initiated on antiretroviral therapy: a prospective cohort study from Ethiopia. *Drug Saf.* **2015**;38(7):629–639. doi:10.1007/s40264-015-0295-7
27. Ottesen TD, Hsiang WR, Malpani R, et al. Underweight patients are the greatest risk body mass index group for 30-day perioperative adverse events after total shoulder arthroplasty. *J Am Acad Orthop Surg.* **2021**;29(3):e132–e142. doi:10.5435/JAAOS-D-20-00049

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