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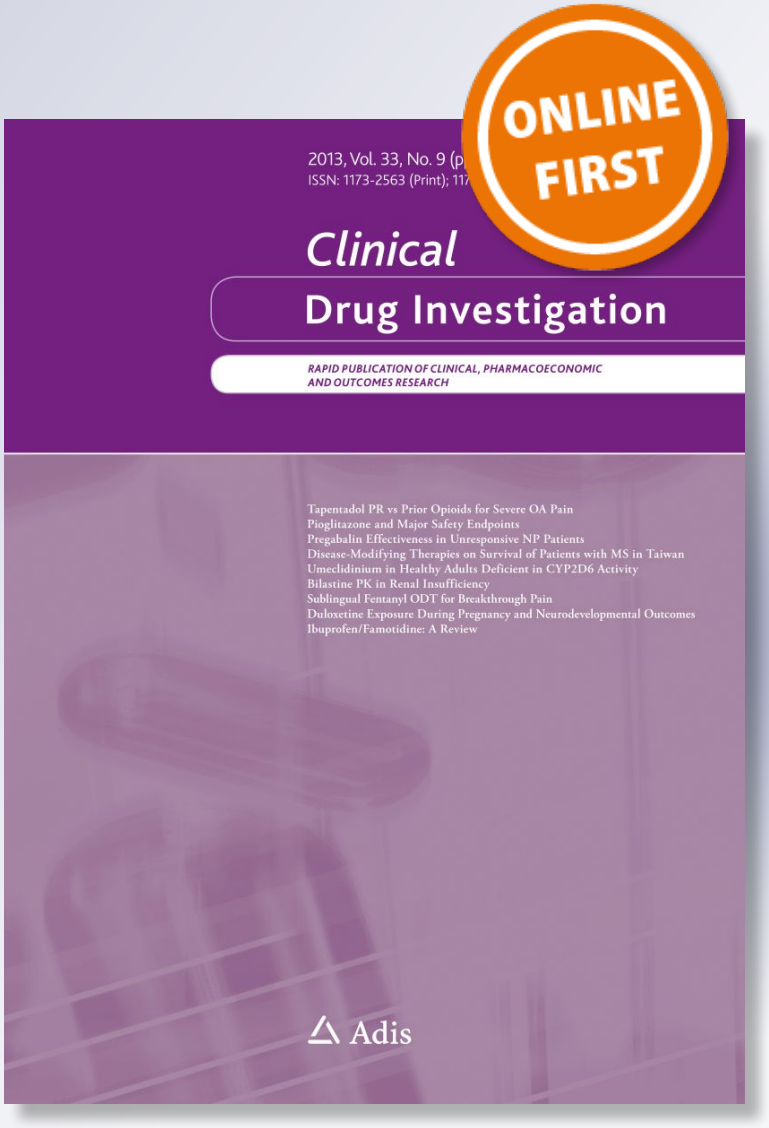

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ORIGINAL RESEARCH ARTICLE

A Comparison of Adverse Drug Reaction Profiles in Patients on Antiretroviral and Antitubercular Treatment in Zimbabwe

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Abstract

Introduction Few studies describe the adverse drug event profiles in patients simultaneously receiving antiretroviral and anti-tubercular medicines in resource-limited countries.

Objectives To describe and compare the adverse drug reaction profiles in patients on highly active antiretroviral therapy only (HAART), HAART and isoniazid preventive therapy (HHART), and HAART and antitubercular treatment (ATTHAART).

Methods We analysed individual case safety reports (ICSRs) for patients on antiretroviral therapy and antitubercular treatment submitted to the national pharmacovigilance centre during the targeted spontaneous reporting (TSR) programme from 1 September 2012 through 31 August 2016. All reports considered certain, probable or possible were included in the analysis.

Results A total of 1076 ICSRs were included in the analysis. Most of the reports were from the HAART only group ($n = 882$; 82.0%), followed by patients on HHART ($n = 132$; 12.3%), and ATTHAART ($n = 62$; 5.7%). The ATTHAART (35.5%) and HHAART (34.1%) had a higher frequency of hepatic disorders than the HAART group (5.0%) ($p < 0.0001$). A higher frequency of rash was reported in the HHAART (35.6%) and HAART groups (29.4%) than the ATTHAART group (14.5%) ($p = 0.011$). Peripheral neuropathy occurred more frequently in the ATTHAART group (19.3%) than other groups ($p = 0.001$) while Stevens-Johnson syndrome (14.7%; $p < 0.001$), gynaecomastia (18.2%; $p < 0.001$), and lipodystrophy (4.5%; $p = 0.012$) occurred more frequently in the HAART group. The HHAART group was associated with a higher frequency of psychosis (4.5%; $p = 0.002$).

Conclusion Antiretroviral therapy was associated with a higher frequency of Stevens-Johnson syndrome, gynaecomastia, and lipodystrophy. Co-administration of antiretroviral and antitubercular medicines was associated with a higher frequency of drug-induced liver injury and peripheral neuropathy. Similarly, co-administration of isoniazid preventive therapy and antiretroviral drugs was associated with a higher risk for psychosis. There is a need to carefully manage TB/HIV co-infected patients, due to the higher risk of adverse drug reactions which may lead to poor treatment adherence and outcomes.

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Key Points

Antiretroviral therapy was associated with a higher frequency of Stevens–Johnson syndrome, gynaecomastia, and lipodystrophy. The higher rates of renal, breast, and dermatological disorders in the study population may be explained by the fact that many patients present with advanced HIV disease. Patients with low CD4 count have been observed to have a higher incidence of rash, Stevens–Johnson syndrome, and hepatotoxicity in previous studies.

Co-administration of antiretroviral and antitubercular medicines was associated with a higher frequency of drug-induced liver injury and peripheral neuropathy. Similarly, co-administration of isoniazid preventive therapy and antiretroviral drugs was associated with a higher risk for psychosis.

Rash was most frequently reported during use of nevirapine, isoniazid, and efavirenz while drug-induced liver injury was most frequently reported during use of isoniazid, rifampicin, and atazanavir.

The most commonly suspected medicines were nevirapine, efavirenz, isoniazid, stavudine, tenofovir, zidovudine, rifampicin, and atazanavir.

The study highlights the need to carefully manage integrated dual chemotherapy for HIV and TB in scope of possible treatment interruptions that could occur with the compounded ADRs.

1 Introduction

Tuberculosis (TB) is a major public health burden globally, especially in resource-limited countries [1]. It remains the leading cause of death among people infected with human immunodeficiency virus syndrome (HIV), accounting for one in four HIV-related deaths [2]. More than 90% of TB cases and TB mortality occurs in developing countries [3]. In Southern Africa, 60%–80% percent of individuals with TB are co-infected with HIV [4]. Consequently, TB incidence and TB-related mortality rates have tripled in the HIV era compared to rates from the pre-HIV era [5]. This can be explained by a twofold increase in the case fatality rate for the TB/HIV syndemic compared to TB alone [6]. The use of highly active antiretroviral therapy (HAART) in HIV-infected patients markedly decreases the incidence of HIV-1-associated TB by up to 80% [7, 8]. In addition, HAART significantly reduces mortality in TB/HIV co-infected patients [9]. However, co-administration of antiretroviral and antitubercular therapy (ATT) increases the risk of pharmacokinetic interactions, immunopathological responses and adverse drug reactions (ADRs) [10]. Therefore, co-administration of HAART and ATT medicines merits special consideration.

The higher frequency of ADRs in HIV/TB co-infected patients concurrently treated with HAART and ATT may reduce treatment success rates of the HIV and TB treatment regimens because of treatment discontinuation [11]. Studies in developed countries have shown an overlap between the ADR profiles attributable to antiretroviral and antitubercular medicines [10, 12]. The common overlapping toxicities include skin reactions, liver toxicity, gastrointestinal intolerance, peripheral neuropathy, renal impairment and blood dyscrasias [10, 13]. A recently reported study from Rwanda observed that patients co-administered HAART and antitubercular drugs were up to five times more likely to develop serious adverse events compared to those on antitubercular medication alone [14].

The World Health Organisation (WHO) recommends isoniazid preventive therapy (IPT) for people living with HIV to prevent the progression of latent to active tuberculosis [15]. This secondary preventive approach presents additional gastrointestinal, liver and neurological toxicity challenges in HIV/TB co-infected patients [16]. For instance, a twofold increase in hepatotoxicity with nevirapine co-administration compared to patients on efavirenz has been reported in IPT programmes [17]. The observed increase in hepatotoxicity could be due to higher nevirapine concentrations resulting from drug to drug interactions involving cytochrome P450 3A4 (CYP3A4) [18].

Patients in developing countries commonly present with malnutrition, advanced HIV disease, comorbid anaemia and differences in nutritional status compared to those from developed countries [10, 12]. Given the differences in clinical presentation and environmental factors, there is need for additional studies in high HIV and TB burden in resource-limited settings to better describe the ADR profile in these patients [10, 19]. The main objective of this study was to describe and compare the profile of individual case safety reports (ICSRs) of suspected ADRs among patients on highly active antiretroviral therapy alone (HAART), patients on highly active antiretroviral therapy and isoniazid preventive therapy (HHAART), and patients receiving both antiretroviral therapy and antitubercular treatment regimen (ATTHAART). The secondary objective was to characterise the reporting characteristics (i.e. reporting professionals and type of health facility) for ICSRs received through the targeted spontaneous reporting programme.

2 Methods

2.1 Study Design

We analysed all anonymised ICSRs for antiretroviral and antitubercular drugs collected from 1 September 2012 through 31 August 2016 using a prospective observational targeted spontaneous reporting (TSR) methodology. The TSR reporting system, modelled on the WHO TSR methodology, was designed to capture all suspected ADRs reported by healthcare professionals from patients on HAART, ATT, and other selected essential medicines from the Essential Drug List of Zimbabwe (EDLIZ) [20]. The data reported in this article are based on ICSRs for HAART and ATT submitted during the study period. The TSR programme is scheduled to end in December 2018.

2.2 TSR Programme Implementation

The TSR programme was implemented in two phases. Phase 1 was the pilot TSR programme in twenty antiretroviral treatment clinics and tuberculosis clinics from five central hospitals (Parirenyatwa Hospital, Harare Hospital, Chitungwiza Hospital, Mpilo Hospital, and United Bulawayo Hospitals), three referral infectious diseases hospitals (Wilkins Hospital, Beatrice Hospital, Thorngrove Hospital), one provincial hospital (Mutare Hospital), and two district hospitals (Nkayi Hospital and Inyathi Hospital). The sites were selected based on the recommendations from the AIDS and TB unit within the Ministry of Health and Child Care. The sites were easily accessible antiretroviral (ART) and TB clinics which facilitated easy implementation of the pilot phase of the TSR programme. The pilot phase ran from 1 September 2012 until 31 March 2013. During phase 2, the TSR programme was rolled out to all antiretroviral and tuberculosis treatment centres in the country because the pilot phase had demonstrated the feasibility of the programme. Phase 2 of the programme started on 1 October 2013 and is scheduled to end in December 2018.

The TSR programme was implemented by the national pharmacovigilance centre of the Medicines Control Authority of Zimbabwe (MCAZ) with the approval and support of the Ministry of Health and Child Care and its relevant departments including the AIDS and TB unit and the Directorate of Pharmacy Services. At provincial and district levels, the TSR programme was supported by the ART and TB public health programmes. All the ICSRs collected from the public and private hospitals were submitted to the national pharmacovigilance centre at the MCAZ for collation, analysis and causality assessment. The ADRs were subsequently uploaded to VigiBase (the WHO's global ICSR database). The WHO-VigiGrade completeness score for most reports from Zimbabwe is in the range of 0.75–1.0.

2.3 Training and Support Supervision for the TSR Programme

The MCAZ staff facilitated the TSR training based on the train a trainer model in collaboration with the AIDS and TB unit, Directorate of Pharmacy Services, and provincial and district ART and TB healthcare teams. Regular scheduled visits were conducted by personnel from the national pharmacovigilance centre of the MCAZ to support the TSR programme. This was achieved by sensitising the healthcare professionals to adverse events occurring with HAART and ATT, training on adverse event reporting, TSR ADR form completion, and the WHO-VigiGrade completeness score. The training module included the WHO-VigiGrade completeness score to ensure that the ADR reports were of good quality to allow meaningful causality assessment. The healthcare professionals involved in the programme comprised medical doctors, clinical officers, nurses, pharmacists and pharmacy technicians working at district, provincial and national referral hospitals. Extra programme support was provided by the distribution of the TSR forms and contact details of the national pharmacovigilance centre. This facilitated communication and submission of the completed TSR forms to the national pharmacovigilance centre and feedback to reporters.

2.4 Data Collection

Booklets with the specially designed TSR adverse drug reaction forms printed in triplicate were distributed to sites. One copy of each completed ADR form was sent to the National AIDS and Tuberculosis Unit in the Ministry of Health and Child Care while the second copy was sent the MCAZ. The third copy of the ADR form remained at the site for verification and for inspection during support, feedback and training visits. The information collected on the ADR form included patient clinic/hospital numbers, patient demographics (age, gender, weight), adverse event(s) (description of event, date of onset, date of cessation, treatment or action taken, outcome), prescribed medications (posology, dates treatment was started and stopped, batch number), suspected medicine, laboratory test results, and details of the healthcare practitioner completing the ADR form.

All ICSRs were reviewed by the Pharmacovigilance and Clinical Trials Committee of the MCAZ, which is composed of specialist physicians, paediatricians, general practitioners, pharmacists, and ethicists. All members of the committee were trained by WHO on causality

assessment. All assessable suspected ADR reports from the ICSRs that were categorized as certain, probable or possible by the committee were included in our analysis. An ADR was defined using the WHO definition as any response to a medicine which is noxious and unintended, and which occurs at doses normally used in humans [21]. Causality assessment was performed using the WHO Uppsala Monitoring Centre (WHO-UMC) criteria [21]. Data cleaning was done to exclude duplicate and incomplete ADR reports. Medication errors were excluded from further analysis. The reports and their causality assessments were then entered and saved on a Microsoft Excel® spreadsheet (Microsoft Corporation, Redmond, WA, USA) and uploaded on the WHO global ICSR database (VigiBase).

2.5 Statistical Analysis

A one-way ANOVA test was used to compare the means between the treatment groups, followed by Tukey's post hoc test. Comparisons of categorical data and event reporting rates between groups were performed using the two-tailed Fisher exact test or the Chi squared test as appropriate. A significance of alpha < 0.05 was set a priori for all statistical analysis. Statistical analyses were done using the Statistical Package for Social Sciences Version 17.0 (Chicago, USA) and Stata Version 12 (College Station, TX, USA).

2.6 Ethical Considerations

An exemption was granted by the national ethics body, the Medical Research Council of Zimbabwe. Monitoring and reporting of adverse drug reactions is a routine activity in the clinical setting. Therefore, informed consent was not individually taken from each patient by the healthcare practitioners who made the reports to the national pharmacovigilance centre. Furthermore, patient confidentiality was preserved as no patient identifiers (e.g. national identification number, patient name) are included in the ADR form used by the national pharmacovigilance centre. However, the ADR form included information on the clinic/hospital number for verification of ADR reports and to detect duplicate reports. Routinely collected, de-identified and anonymized data were used in the study.

3 Results

3.1 Causality Assessment

A total of 1104 targeted spontaneous ICSRs were received during the study period. Of these, 28 ICSRs (2.5%) were excluded from further analysis as they did not have critical information. Of the remaining 1076 ICSRs, 897 (83.4%) were classified as probable, while 179 (16.6%) were classified as possible. None of the adverse drug reaction reports were classified as certain.

3.2 Patient Characteristics

Table 1 shows the demographic and clinical characteristics of patients included in the study. The majority of ICSRs, were for patients on HAART ($n = 882$; 82.0%) followed by patients on HHART ($n = 132$; 12.3%), and ATTHAART ($n = 62$; 5.7%). Most of the ICSRs were for female patients (58.5%) and for patients in the 16- to 44-year age category (62.7%). Paediatric patients were more likely to be on antiretroviral therapy and antitubercular drugs ($p < 0.001$) while patients aged 16–44 years were more likely to be receiving either antiretroviral therapy alone or in combination with isoniazid preventive therapy ($p = 0.004$). There was no statistically significant difference in the female to male gender proportions between the three treatment groups ($p = 0.874$).

3.3 ICSR Characteristics

Patients on HAART only were older ($p = 0.005$) and had a higher weight ($p < 0.0001$) than the other treatment groups. Patients on tenofovir/lamivudine/nevirapine regimens in combination with isoniazid prevention therapy were associated with a higher frequency of ADRs than patients on tenofovir/lamivudine/nevirapine alone or in combination with antitubercular treatment ($p < 0.001$). However, patients on tenofovir/lamivudine/efavirenz regimens only were associated with a higher frequency of ADRs than patients on tenofovir/lamivudine/efavirenz regimens in combination with isoniazid prevention therapy or antitubercular treatment ($p < 0.001$).

3.4 Reporter Characteristics

Most of the reports were submitted by nurses (83.4%) followed by physicians (12.4%), pharmacists and pharmacy technicians (2.3%), clinical officers (0.7%), and TB coordinators (0.5%). More than half of the reports (53.3%) were submitted by primary healthcare facilities (clinics, district and provincial hospitals). The remainder of the reports were submitted by the main national referral hospitals (33.4%) and the national TB referral centres (13.3%).

3.5 Characteristics of Medications and ADRs

The most common nucleoside reverse-transcriptase inhibitor backbone was tenofovir/lamivudine ($n = 705$;

Table 1 Demographic and clinical characteristics of patients

Patient characteristic	Total ICSRs ($N = 1076$) n (%)	HAART ($N = 882$) n (%)	HHAART ($N = 132$) n (%)	ATTHAART ($N = 62$) n (%)	P value
Gender[a]					
Female	620 (58.5)	492 (56.7)	90 (69.2)	38 (61.3)	0.874
Male	440 (41.5)	376 (43.3)	40 (30.8)	24(38.7)	
Age (mean ± SD)	35.6 ± 15.1	36.5 ± 14.3	32.5 ± 17.2	32.8 ± 18.0	0.005
Age categories[a,b]					
≤ 16 years	141 (13.6)	92 (10.5%)	30 (22.7)	19 (30.6)	<0.001
> 16 to ≤ 44 years	648 (62.7%)	550 (62.7)	71 (53.8)	27 (43.5)	0.004
> 45 to ≤ 54 years	255 (23.3)	214 (24.4)	26 (19.7)	15 (24.2)	0.514
≥ 65 years	27 (2.5)	21 (2.4)	5 (3.8)	1 (1.6)	0.564
Weight (mean ± SD)	54.1 ± 16.7	55.8 ± 15.5	50.2 ± 18.8	45.0 ± 18.5	<0.001
HAART regimens					
d4T + 3TC + NVP	170 (15.8)	166 (18.8)	0 (0.0)	4 (6.4)	<0.001
d4T + 3TC + EFV	16 (1.5)	8 (0.9)	0 (0.0)	8 (12.9)	<0.001
TDF + 3TC + NVP	300 (27.9)	215 (24.4)	66 (50.0)	19 (30.6)	<0.001
TDF + 3TC + EFV	389 (36.1)	350 (39.7)	34 (25.7)	5 (8.1)	<0.001
AZT + 3TC + NVP	97 (9.0)	59 (6.7)	24 (18.2)	14 (22.6)	<0.001
AZT + 3TC + EFV	15 (1.4)	11 (1.2)	2 (1.5)	2 (3.2)	0.435
Other combinations	89 (8.3)	73 (8.2)	6 (4.5)	10 (16.1)	0.002

AZT zidovudine, *d4T* stavudine, *EFV* efavirenz, *NVP* nevirapine, *TDF* tenofovir disoproxil fumarate, *3TC* lamivudine, *ADR* adverse drug reaction, *ICSRs* individual case safety reports, *HAART* highly active antiretroviral therapy, *HHAART* isoniazid preventive therapy highly and active antiretroviral therapy, *ATTHAART* antitubercular treatment and highly active antiretroviral therapy

[a]Frequencies exclude reports with missing information on gender and age

[b]Represent paediatric, young adult, middle aged and the elderly age groups, respectively

65.5%). This was followed by stavudine/lamivudine ($n = 189$; 17.6%) and zidovudine/lamivudine ($n = 130$; 12.1%). Of the 194 ICSRs of patients receiving anti-mycobacterial therapy, 132 (68.0%) were on isoniazid prophylaxis while 62 (32.0%) were in the intensive and continuation treatment phases of antitubercular treatment regimens. Patients in the intensive treatment phase were receiving isoniazid, rifampicin, pyrazinamide, and ethambutol, while patients in the continuation phase of treatment were receiving isoniazid and rifampicin.

Table 2 shows a comparison of the frequency of the specific ADRs and the organ system ADRs in the three treatment groups. There were 1309 ADR reports listed on the ICSRs for an average of 1.22 ADRs per ICSR. The ADR to ICSR ratio was highest in the HHAART treatment group. The five most common organ system ADRs were skin and integumentary (42.3%), nervous system (17.1%), breast (15.4%), hepatic and biliary (10.3%), and renal (7.5%) adverse events. Patients on antiretroviral therapy alone or in combination with isoniazid preventive therapy were associated with a higher frequency of skin and integumentary adverse drug reactions than those on antiretroviral therapy in combination with antitubercular treatment ($p < 0.001$). Psychiatric ADRs were reported with a higher frequency among patients on antiretroviral therapy in combination with isoniazid preventive therapy than other treatment groups ($p = 0.007$). Patients on antiretroviral therapy alone were associated with a higher frequency of breast-related ADRs than other treatment groups ($p < 0.001$) while patients on antiretroviral therapy in combination with isoniazid preventive therapy or antitubercular treatment were associated with a higher frequency of gastrointestinal and hepatobiliary ADRs ($p < 0.001$).

The five most common specific ADRs were rash (29.3%), gynaecomastia (15.1%), Stevens-Johnson syndrome (12.5%), drug-induced liver injury (10.3%), and peripheral neuropathy (8.5%). Patients on antiretroviral therapy alone or in combination with isoniazid preventive therapy were associated with a higher frequency of rash ($p < 0.001$), while peripheral neuropathy was reported with a higher frequency among patients on antiretroviral therapy in combination with antitubercular treatment ($p < 0.001$). Stevens-Johnson syndrome and gynaecomastia were reported with a higher frequency in patients on antiretroviral therapy alone ($p < 0.001$). Co-administration

Table 2 Comparison of distribution of ADRs in respective treatment groups

Patient characteristic	Total ICSRs ($n = 1076$) n (%)[a]	HAART ($n = 882$) n (%)[a]	HHAART ($n = 132$) n (%)[a]	ATTHAART ($n = 62$) n (%)[a]	p value
Number of ADRs[b]	1309 (100.0)	1032 (78.8)	187 (14.3)	90 (6.9)	<0.001
Skin and integumentary	455 (42.3)	393 (44.5)	51 (38.6)	11 (17.7)	<0.001
Nervous system	184 (17.1)	150 (17.0)	18 (13.6)	16 (25.8)	0.109
Psychiatric	20 (1.8)	12 (1.4)	7 (5.3)	1 (1.6)	0.007
Gastrointestinal	76 (7.1)	37 (4.2)	25 (18.9)	14 (22.6)	<0.001
Hepatic and biliary	111 (10.3)	44 (5.0)	45 (34.1)	22(35.5)	<0.001
Respiratory	7 (0.6)	4 (0.4)	0 (0.0)	3 (4.8)	0.067
Haematological	24 (2.2)	21 (2.4)	2 (1.5)	1 (1.6)	0.775
Breast	166 (15.4)	164 (18.6)	2 (1.5)	0 (0.0)	<0.001
Renal	81 (7.5)	65 (7.4)	11 (8.3)	5 (8.1)	0.912
General and musculoskeletal	66 (6.1)	38 (4.3)	19 (14.3)	9 (14.5)	<0.001
Metabolic	40 (3.7)	40 (4.5)	0 (0.0)	0 (0.0)	0.010
Other	79 (7.3)	64 (7.2)	7 (5.3)	8 (12.9)	
Specific ADRs					
Rash	315 (29.3)	259 (29.4)	47 (35.6)	9 (14.5)	0.011
DILI	111 (10.3)	44 (5.0)	45 (34.1)	22 (35.5)	<0.001
Peripheral neuropathy	92 (8.5)	76 (8.6)	4 (3.0)	12 (19.3)	0.001
Renal impairment	80 (7.2)	65 (7.4)	10 (7.6)	5 (8.1)	0.978
SJS	135 (12.5)	130 (14.7)	4 (3.0)	1 (1.6)	<0.001
Gynaecomastia	163 (15.1)	161 (18.2)	2 (1.5)	0 (0.0)	<0.001
Anaemia	24 (2.2)	21 (2.4)	2 (1.5)	1 (1.6)	0.392
Lipodystrophy	39 (3.6)	39 (4.4)	0 (0.0)	0 (0.0)	0.012
Psychosis	14 (1.3)	7 (0.8)	6 (4.5)	1 (1.6)	0.002
Dizziness	54 (5.0)	46 (5.2)	6 (4.5)	2 (3.2)	0.759
Other	45 (4.2)	34 (3.8)	2 (1.5)	9 (14.5)	

[a]Percentages represent the proportion of ADRs in each treatment group. Some ICSRs had more than one ADR report, therefore the ADRs do not sum to the total number of ICSRs

[b]Row percentages *DILI* drug-induced liver injury, *SJS* Stevens-Johnson syndrome, *ADR* adverse drug reaction, *ICSRs* individual case safety reports, *HAART* highly active antiretroviral therapy, *HHAART* isoniazid preventive therapy and highly active antiretroviral therapy, *ATTHAART* antitubercular treatment and highly active antiretroviral therapy

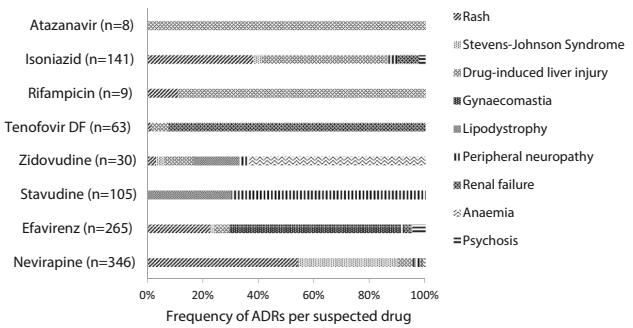

Fig. 1 The distribution of the most frequently reported adverse drug reaction reports per suspected drug. *ADR* adverse drug reaction, *tenofovir DF* tenofovir disoproxil fumarate

of isoniazid preventive therapy with antiretroviral therapy was associated with a higher frequency of psychosis ($p = 0.002$).

The profile of reported ADRs for commonly suspected medicines is shown in Fig. 1. The most commonly suspected medicines were nevirapine ($n = 348$; 32.3%), efavirenz ($n = 313$; 29.1%), isoniazid ($n = 165$; 15.3%), stavudine ($n = 102$; 9.5%), tenofovir ($n = 71$; 6.6%), zidovudine ($n = 36$; 3.3%) and rifampicin ($n = 11$; 1.0%). Rash was most frequently reported during use of nevirapine, isoniazid, and efavirenz while drug-induced liver injury was most frequently reported during use of isoniazid, rifampicin, and atazanavir. Peripheral neuropathy was most frequently reported during use of stavudine while anaemia was most frequently reported in patients on zidovudine. The most frequently reported ADR for tenofovir was renal impairment, while lipodystrophy was most frequently reported during use of stavudine and zidovudine.

4 Discussion

In this study, we set out to describe and compare the adverse drug reaction profiles between patients administered HAART alone, isoniazid and HAART, and ATT and HAART. This study also describes the reporting patterns from the 9th ranked ICSR submitting country in Africa, for one of the most reported product classes in the region—antiretroviral drugs [20]. The majority of ICSRs were collected from the 16- to 44-year age patient category. This possibly reflects the medication use in the study population and not necessarily the age category's risk profile. Furthermore, regardless of treatment regimen, more ADR reports were collected from females compared to males. This could be due to the different treatment seeking behaviour between the two gender categories [21]. A similar pattern of ADR reporting (or ICSR submission) in Africa in terms of age and gender has been observed [20]. A small proportion (1.4%) of ICSRs did not specify the age or the gender of the patient, respectively. For the African dataset in Vigibase (WHO global ICSR database), age and gender were not specified in 16.8% and 6.0%, respectively. Therefore, our data were more complete in the ICSR submissions on these and possibly other parameters.

Most of the submitted ADRs were dermatological adverse drug reactions. These findings are similar to those reported in a recent study based on spontaneous reports in VigiBase where skin-related adverse drug reactions contributed 31.1% of all reports [20]. Most of the cutaneous ADRs were observed in the antiretroviral only treatment group. The reason for this observation is not clear. However, it can be related to the fact that most regimens included nevirapine, which is usually associated with a higher frequency of skin reactions. As expected, hepatic and peripheral neuropathic adverse reactions were reported more commonly in the groups receiving both antiretroviral and antitubercular medicines. The findings for peripheral neuropathy are consistent with those reported in a similar population in South Africa [11]. These observations could be due to summative hepatic and neuronal toxicity from antitubercular medicines, especially in the intensive phase of ATT therapy.

The reporting rates for renal disorders, breast disorders and dermatological disorders listed in the summary of product characteristics (SmPC) for tenofovir, efavirenz and nevirapine, respectively, are not the same as we found in our study. Breast disorders (gynaecomastia and/or mastodynia) and renal disorders are listed as uncommon in the respective SmPCs for the suspected medicines efavirenz and tenofovir. The SmPC classification of uncommon equates to an expected reporting rate of 1–10 users in 1000, but the observed rates for the respective disorders were significantly higher in our study. A similar trend was observed in the reported rates for dermatological disorders (rash and Stevens-Johnson syndrome) for nevirapine. In contrast, the reporting rate of $\geq$ 1 in 10 stated in the SmPC for dermatological disorders (rash and Stevens-Johnson syndrome), we observed a higher reporting rate approximately equal to 1 in 2 for nevirapine. These observed differences can be explained by the different patient clinical characteristics. Rash and Stevens-Johnson syndrome have been noted to occur with a higher frequency in patients with low CD4 count. However, more studies in the African population are required to clarify these findings. This will guide rational prescribing as the drug interaction studies listed in the respective SmPCs do not state the effect of some of the drug combinations used in the study population, thereby limiting the informed use of these medicines as provided in the current treatment guidelines.

In contrast to ADR reporting trends in Europe, Zimbabwean nurses (83.4%) submitted most of the ICSRs, followed by doctors (12.4%). In Portugal (between January 2000 and December 2010) and Turkey (between July 2005 and December 2013), doctors submitted the most ICSRs at 54% and 59.8%, respectively [22, 23]. This difference in the ADR reporting trends can be explained by the fact that more than half of ICSRs were submitted by peripheral clinics and district hospitals where most staff are nurses. HIV and TB treatment centres are decentralized to primary healthcare clinics and district hospitals. Most doctors are based at provincial and referral hospitals. Therefore, the high number of reports received from nurses may be due to the nurse-driven peripheral healthcare delivery system in Zimbabwe where, incidentally, most of the TSR awareness training was carried out.

Our results should be interpreted with caution due to the following limitations. First, this study was based ICSRs submitted during the targeted spontaneous reporting (TSR) programme and therefore lacked denominator data for the calculation of incidence rates. Second, the submitted ICSRs could be a small proportion of the total ADRs occurring in the study population and this limits generalisation of the study findings. However, our study gives insight into the commonly reported ADRs and allows for a comparison of the reported ADRs between the respective treatments groups in a resource-limited setting. In addition, the study highlights the need to carefully manage integrated dual chemotherapy for HIV and TB in scope of possible treatment interruptions that could occur with the compounded ADRs. This is especially important in a population with high rates of multi-drug-resistant TB (MDR TB), extensively drug resistant TB (XDR TB) and limited antiretroviral and antitubercular medication options. Overall, the study delineated and characterised the adverse-event profile and reporting healthcare workers and

facilities. Reporting from referral hospitals and dedicated TB centres should be encouraged to capture the more serious adverse events treated at these institutions.

5 Conclusion

Antiretroviral therapy was associated with a higher frequency of Stevens-Johnson syndrome, gynaecomastia, and lipodystrophy. Co-administration of antiretroviral and antitubercular medicines was associated with a higher frequency of drug-induced liver injury and peripheral neuropathy. Similarly, co-administration of isoniazid preventive therapy and antiretroviral drugs was associated with a higher risk for psychosis. There is a need to carefully manage TB/HIV co-infected patients, due to the higher risk of adverse drug reactions, which may lead to poor treatment adherence and outcomes.

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Authors' contributions JTM was involved in the study design, collection and analysis of the data, and drafted the manuscript. PC was involved in the study design, collection and analysis of the data. PPN and SK were involved in the study design, analysis of the data, revised and critically reviewed the manuscript. AS critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest All the authors declare no conflict of interest.

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Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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