



Original article



## Adult medical emergency unit presentations due to adverse drug reactions in a setting of high HIV prevalence

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### ABSTRACT

**Introduction:** South Africa has the world's largest antiretroviral treatment programme, which may contribute to the adverse drug reaction (ADR) burden. We aimed to determine the proportion of adult non-trauma emergency unit (EU) presentations attributable to ADRs and to characterise ADR-related EU presentations, stratified according to HIV status, to determine the contribution of drugs used in management of HIV and its complications to ADR-related EU presentations, and identify factors associated with ADR-related EU presentation.

**Methods:** We conducted a retrospective folder review on a random 1.7% sample of presentations over a 12-month period in 2014/2015 to the EUs of two hospitals in Cape Town, South Africa. We identified potential ADRs with the help of a trigger tool. A multidisciplinary panel assessed potential ADRs for causality, severity, and preventability.

**Results:** We included 1010 EU presentations and assessed 80/1010 (7.9%) as ADR-related, including 20/239 (8.4%) presentations among HIV-positive attendees. Among HIV-positive EU attendees with ADRs 17/20 (85%) were admitted, versus 22/60 (37%) of HIV-negative/unknown EU attendees. Only 5/21 (24%) ADRs in HIV-positive EU attendees were preventable, versus 24/63 (38%) in HIV-negative/unknown EU attendees. On multivariate analysis, only increasing drug count was associated with ADR-related EU presentation (adjusted odds ratio 1.10 per additional drug, 95% confidence interval 1.03 to 1.18), adjusted for age, sex, HIV status, comorbidity, and hospital.

**Conclusions:** ADRs caused a significant proportion of EU presentations, similar to findings from other resource-limited settings. The spectrum of ADR manifestations in our EUs reflects South Africa's colliding epidemics of infectious and non-communicable diseases. ADRs among HIV-positive EU attendees were more severe and less likely to be preventable.

### Introduction

In South Africa, rapid scale-up of the HIV treatment programme is occurring within already overstretched and frequently understaffed health care facilities [1]. While the antiretrovirals currently included in South African guidelines are generally safe, and serious adverse drug reactions (ADRs) only occur in a small proportion of patients, the size of

the treatment programme means that the absolute ADR burden may be considerable [2]. Strategies to minimize preventable harm should form a crucial part of such large-scale public health programmes; yet, in our setting, the burden of ADRs in general, and the burden of ADRs attributable to antiretroviral therapy (ART) specifically, is still largely unknown [3].

The emergency unit (EU) provides an opportune environment in

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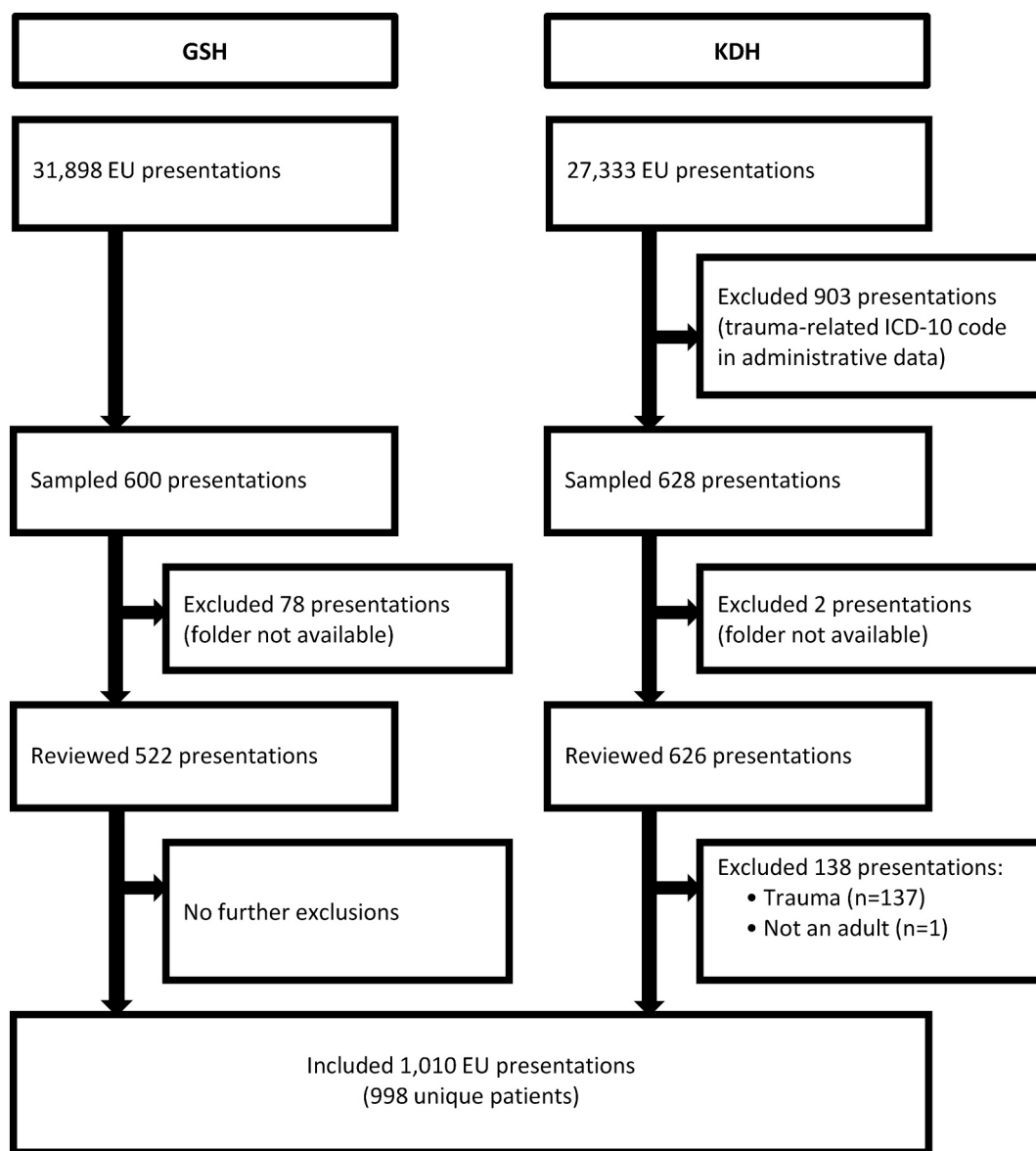
which to study this burden: in South Africa, the EU forms the entry point into hospital for most patients, and resource limitations may result in even severely ill patients being managed fully in the EU, and not being admitted [4,5]. Hospital admission has been used to define an ADR as serious [6], but we considered that in a resource-limited setting EU presentation may also reflect serious ADRs.

We aimed to determine the proportion of EU presentations at two hospitals in Cape Town, South Africa that were due to ADRs, stratified by HIV status. Secondary objectives were to describe the common ADR manifestations, their preventability, and the drugs most commonly implicated, stratified by HIV infection status; to describe the contribution of drugs used in the management of HIV infection and its complications to the burden of ADR-related EU presentations; and to identify factors associated with ADR-related EU presentations.

**Methods**

*Study design and setting*

We retrospectively reviewed a random sample of adult (≥19 years) medical presentations to the EUs of two hospitals in Cape Town, South Africa over a twelve-month period. Groote Schuur Hospital (GSH) provides tertiary and secondary level care, and Khayelitsha District Hospital (KDH) is a district-level hospital, serving as a first point of referral for primary health care facilities in the district and providing a generalist level of care. Trends at the emergency unit of KDH have previously been published [4,5,7]. In 2015, the HIV prevalence among adults 15–49 years old was 10.0% (95% confidence interval (CI) 7.9% to 11.9%) in the Western Cape province, of which Cape Town is the capital and largest city [8]. Programmatic guidelines implemented in December 2014 recommended ART initiation at CD4 counts below 500 cells/μL with a fixed-dose-combination of tenofovir disoproxil fumarate (TDF), emtricitabine, and efavirenz the preferred first line therapy [9].



**Fig. 1.** Sampling strategy and exclusions applied.

EU: emergency unit; GSH: Groote Schuur Hospital; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; KDH: Khayelitsha District Hospital.

### Sample size calculation

A previous study from a resource-limited setting, in Mumbai, India, found the proportion of ADR-related EU presentations to be 3.8% [10]. We calculated our sample size based on this proportion, using the z-score test for proportions in single populations: to detect a 3.8% proportion with 95% CI 1.8% to 5.8% a sample of 824 would be required. We planned to include  $\geq 1000$  presentations (500 per site), and over-sampled to allow for exclusions and missing records.

### Sampling and eligibility criteria

We obtained an administrative data extract from each hospital of all adult presentations to the EU over the period 1 December 2014 to 30 November 2015 (Fig. 1). At GSH, there were 31,898 presentations to the non-trauma EU over this period (the hospital has a separate trauma EU). At KDH, which has a single multidisciplinary EU, there were 27,333 EU presentations. From these we excluded 903 trauma-related presentations on the basis of the presence of ICD-10 codes S00-T35, T51-T79, T90-95, or V01-Y98 in the data, and included the remaining 26,430 presentations in the KDH sampling frame. ICD-10 codes were frequently missing in the administrative data, and therefore we allowed presentations without ICD-10 codes into the sampling frame.

We drew a simple random sample of 600 presentations at GSH, and a simple random sample of 628 presentations at KDH. We requested the medical records of the 1228 sampled presentations for folder review. We excluded sampled presentations if during folder review we found the patient was not an adult (i.e., incorrectly registered in the hospital information system) or if the patient presented to KDH EU for a trauma-related reason (i.e., trauma-related ICD-10 code was missing or incorrect). We also excluded presentations if the patient's folder could not be found.

### Data sources and data collection methodology

Each folder was reviewed collaboratively by a doctor-pharmacist pair. Data sources included clinical and nursing notes, discharge summaries, bedside and laboratory investigation results, and prescription sheets. Electronic dispensing records were available for some patients; we used these to verify and augment the drug history contained in the folder. Doctor-pharmacist pairs used a trigger tool (Supplementary Table S1) adapted from Rozich [11] and previously used in our setting [12] to assist in identifying potential ADRs. Triggers were events, drug orders, or laboratory results suggestive of potential ADRs.

### Assessments and case definition

A multidisciplinary panel (a clinical pharmacologist, a clinical pharmacist, a general physician, an EU physician, and the two doctors and two pharmacists who conducted the folder reviews) assessed each potential ADR for causality, severity, and preventability through consensus discussion. We used the Aronson and Ferner ADR definition [13], the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) system for standardised case causality assessment [14], Schumock and Thornton preventability criteria [15], and severity classification guidelines which we slightly modified from Temple [16] in these assessments. Severity was classified (modification italicised) as (1) increased patient monitoring, but no patient harm; (2) treatment intervention, with temporary patient harm; (3) causing or contributing to the EU presentation, temporary patient harm; (4) permanent harm; (5) near-death; and (6) death.

An ADR-related EU presentation was defined as a presentation with an ADR of severity level 3 or higher and causality assessment of 'possible', 'probable', or 'certain'.

We classified ADRs as type A (predictable from the pharmacological action of the drug) or type B (idiosyncratic) according to the Rawlins and

Thompson classification [17].

### Analysis

We calculated the drug count as the number of unique drugs used over the 30-day period before the EU presentation. Where we used electronic dispensing records (which contained the dispensed quantity without details on dose, dosing frequency, or duration) we considered any drug dispensed within 45 days before the presentation as being used during the 30-day window.

We calculated a modified Charlson comorbidity score [18] for each presentation. Our modification excluded a diagnosis of HIV/AIDS from the calculation as the original score allocated to HIV/AIDS is inappropriately high in the ART era [19] and as we wanted to explore associations between HIV status and ADR-related presentation independently.

We used cross-tabulation and chi-square statistics to explore associations between binary and categorical variables. We summarized continuous variables using medians and interquartile ranges, as they were not normally distributed, and used the Wilcoxon rank-sum test to compare the groups. We considered a *P* value of  $< 0.05$  to indicate significant difference.

We constructed a multivariate logistic regression model to explore associations between ADR-related EU presentation and age, sex, hospital, HIV infection status, ART status, drug count, and comorbidity score. We only included patients exposed to at least one drug in the model, and for those with multiple presentations, we only included first presentations. We stratified HIV infection and ART as follows: (1) HIV negative; (2) HIV status unknown; (3) HIV-positive, not on ART (or no documented evidence of ART); and (4) HIV-positive, on ART. Variables were selected for inclusion in the multivariate model a priori, at the time of study design, based on associations described previously [12,20,21].

We captured data into a purpose-built MS Access database (Microsoft, Redmond, WA). We analysed data using Stata version 13 (College Station, Texas, USA).

### Ethical considerations

We retrospectively collected data through record review and did not approach patients, caregivers, prescribers, or physicians for any information. We obtained ethics approval for this study from the University of Cape Town's Human Research Ethics Committee (reference number 845/2015), and received permission to conduct the study from the hospitals' management.

We shared anonymised data with the National Adverse Drug Event Monitoring Centre, which collects ADR reports on behalf of the South African medicines regulator.

### Results

We included 1,010 EU presentations by 998 unique patients (Fig. 1), approximately 1.7% of the total number of presentations to the two EUs over the one-year period. Patient and presentation characteristics are summarised in Table 1; a stratification by site is given in Supplementary Table S2. Nearly one quarter of patients were known to be HIV-positive. Other common comorbidities were hypertension in 292/1,010 (29%), type 2 diabetes mellitus in 146/1,010 (14%), chronic kidney disease in 63/1,010 (6.2%) and pulmonary tuberculosis in 45/1,010 (4.5%). Most presentations (645/1,010, 64%) were associated with a zero score on the modified Charlson comorbidity index, while only 84/1,010 (8.3%) scored 3 or higher. There was documented use of  $\geq 1$  drug(s) before 606/1,010 (60%) presentations. Drug count ranged from 0 to 23. The most commonly used drugs are presented in Supplementary Table S3. Most EU presentations were for infectious diseases, including 52 (5.1%) for lower respiratory tract infections, 42 (4.2%) for tuberculosis, 31 (3.1%) for urinary tract infections, and 30 (3.0%) for infectious gastroenteritis. Epilepsy/seizures (31 presentations, 3.1%), heart failure

(23, 2.3%), non-specific abdominal / pelvic pain (21, 2.1%), chronic obstructive pulmonary disease (20, 2.0%), chest pain (20, 2.0%), headache (16, 1.6%), and backache (14, 1.4%) were other common reasons for presenting.

The multidisciplinary panel confirmed 80/1010 (7.9%) EU presentations to be ADR-related (95% CI 6.3% to 9.8%). The five most common ADRs are described in Fig. 2. Patients with ADR-related presentations appeared to be more often admitted than others (Table 1) although this did not reach statistical significance ( $p = 0.067$ ). ADR-related EU presentations did result in longer hospital stays than other presentations (Table 1,  $p = 0.030$ ).

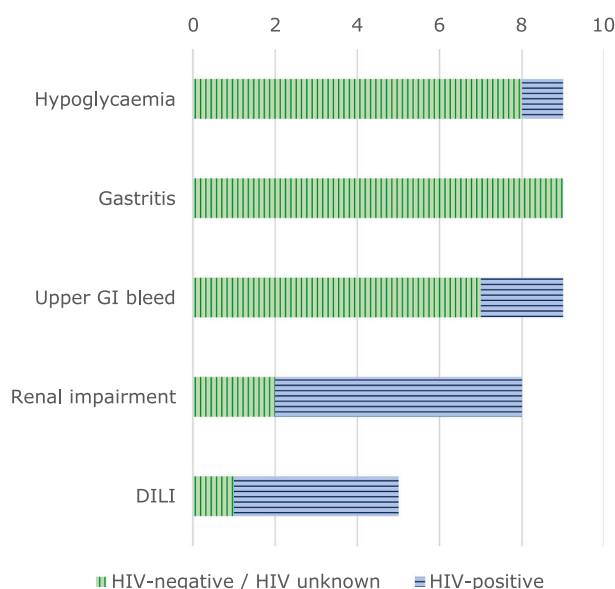
**ADRs in HIV-positive EU attendees**

Among HIV-positive EU attendees there were 20/239 (8.4%) ADR-related EU presentations (Table 2). Drugs used in the management of HIV and its complications were implicated in 13 of these presentations: six for drug-induced renal impairment with TDF and/or rifampicin, four for drug-induced liver injury with efavirenz and/or antituberculosis treatment, three for diarrhoea with ritonavir-boosted lopinavir, and one for efavirenz-associated headache.

The median age of HIV-positive EU attendees with ADR-related presentations was 39 years [IQR 33 to 46 years]. Thirteen of 21 (62%) ADRs were classified as type A (predictable from the pharmacological action of the drug) and 8/21 (38%) as type B (idiosyncratic). None of the ADRs in this patient group was fatal or near-fatal. Five of 21 (24%) were preventable: in all 5 cases, the implicated drugs were inappropriate for the patients' condition (Supplementary Table S4). Regarding outcomes, we found that one patient (1/20, 5%) was discharged home from the EU, 2/20 (10%) were transferred out to other facilities, and 17/20 (85%) were admitted to longer-stay hospital wards for a median [IQR] duration 8 [3 to 15] days.

**ADRs in HIV-negative EU attendees and attendees with unknown HIV status**

There were 60/771 (7.8%) ADR-related presentations in this patient



**Fig. 2.** Frequency of the five most common adverse drug reaction-related presentations to two emergency units in Cape Town, South Africa, 2014–2015. DILI: drug-induced liver injury; GI: gastrointestinal.

group (Supplementary Table S5). Nine presentations were for gastritis with non-steroidal anti-inflammatories, eight for hypoglycaemia with insulin and/or oral hypoglycaemic agents, and seven for upper gastrointestinal bleeds with non-steroidal anti-inflammatories.

The median age of this group of EU attendees with ADR-related presentations was 62 years [IQR 47 to 74 years]. Fifty-nine of 63 (94%) ADRs were classified as type A and 4/63 (6.3%) as type B. One ADR was fatal (an elderly man who presented with cardiac failure exacerbation following a large increase in carvedilol dose) and another was nearly fatal. Twenty-four of 63 (38%) were preventable, most often (17/24, 71%) because the implicated drugs were inappropriate for the patients' condition (Supplementary Table S4). Thirty-six patients in this

**Table 1**

Characteristics of patients and first presentations (n = 998) to two EUs in Cape Town, South Africa, 2014–2015.

	n	All patients	Patients with first EU presentation ADR-related (n = 78)	Patients with first EU presentation not ADR-related (n = 920)
Age – median [IQR] (years)	998	44 [31 to 61]	55 [40 to 72]	43 [30 to 59]
Age 19–39 years		434/998 (43%)	18/78 (23%)	416/920 (45%)
Age 40–59 years		307/998 (31%)	26/78 (33%)	281/920 (31%)
Age 60–79 years	998	219/998 (22%)	30/78 (38%)	189/920 (21%)
Age ≥80 years		38/998 (3.8%)	4/78 (5.1%)	34/920 (3.7%)
Sex – proportion female	992 <sup>a</sup>	562/992 (57%)	49/78 (63%)	513/914 (56%)
HIV-positive		234/998 (23%)	19/78 (24%)	215/920 (23%)
HIV-negative	998	283/998 (28%)	14/78 (18%)	269/920 (29%)
HIV status unknown		481/998 (48%)	45/78 (58%)	436/920 (47%)
Presentations resulting in admission	998	377/998 (38%)	37/78 (47%)	340/920 (37%)
Presentations ending in death	998	43/998 (4.3%)	3/78 (3.8%)	40/920 (4.3%)
Duration of EU stay – median [IQR] (days)	967 <sup>b</sup>	1 [1 to 2]	1 [1 to 2]	1 [1 to 2]
Duration of total hospital stay – median [IQR] (days)	910 <sup>c</sup>	2 [1 to 5]	2 [1 to 7]	2 [1 to 5]
Drug count before presentation – median [IQR] (n drugs)	998	1 [0 to 4]	5 [3 to 9]	1 [0 to 4]
Modified Charlson score – median [IQR]	998	0 [0 to 1]	1 [0 to 2]	0 [0 to 1]

ADR: adverse drug reaction; EU: emergency unit; IQR: interquartile range.

<sup>a</sup> Sex missing for 6 patients.

<sup>b</sup> Duration of EU stay missing for 31 presentations.

<sup>c</sup> Duration of total hospital stay missing for 88 presentations.

**Table 2**

Details of adverse drug reaction-related presentations to two emergency units in Cape Town, South Africa, 2014–2015, among 20 HIV-positive emergency unit attendees.

Age (y)	Sex	ADR description	Type	Causality	Implicated drug/s	Preventable				
45	M	Hypoglycaemia	A	Certain	Gliclazide	Yes				
30	F	<i>Clostridium difficile</i> enteritis	A	Possible	Ceftriaxone	No				
					Ciprofloxacin	No				
					Metronidazole	No				
40	M	Diarrhoea	A	Possible	Lopinavir/ritonavir	Yes				
40	M	Diarrhoea	A	Probable	Lopinavir/ritonavir	No				
45	F	Diarrhoea	A	Probable	Lopinavir/ritonavir	No				
60	F	Constipation	A	Certain	Tramadol	Yes				
33	F	Constipation	A	Certain	Tramadol	No				
47	M	Upper gastrointestinal haemorrhage	A	Probable	Acetylsalicylic acid	No				
34	F	Upper gastrointestinal haemorrhage	A	Probable	Ibuprofen	Yes				
28	M	Headache	A	Possible	Efavirenz	No				
33	F	Hepatocellular DILI	B	Possible	Efavirenz	No				
38	F	Hepatocellular DILI	B	Certain	Efavirenz	No				
32	F	Cholestatic DILI	B	Certain	Efavirenz	No				
					Mixed DILI	B	Probable	Cotrimoxazole	No	
								Possible	Efavirenz	No
									Isoniazid	No
									Pyrazinamide	No
									Rifampicin	No
Acute kidney injury	B	Possible	Cotrimoxazole	No						
			Rifampicin	No						
58	F	Renal failure	A	Possible	Tenofovir disoproxil	No				
					Tenofovir disoproxil	No				
36	M	Acute kidney injury	A	Possible	Tenofovir disoproxil	No				
					B	Possible	Ciprofloxacin	No		
							Diclofenac	Yes		
39	M	Acute-on-chronic kidney injury	B	Possible	Ibuprofen	No				
					B	Possible	Rifampicin	No		
							Rifampicin	No		
28	M	Acute kidney injury	B	Possible	Rifampicin	No				
49	M	Acute kidney injury	B	Possible	Rifampicin	No				
38	F	Abnormal uterine bleeding	A	Probable	Norethisterone	No				

ADR: adverse drug reaction; DILI: drug-induced liver injury; EU: emergency unit; F: female; M: male; y: years.

group (36/60, 60%) were discharged home from the EU, 22/60 (37%) were admitted to longer-stay hospital wards, 1/60 (1.7%) left the EU of their own volition, and 1/60 (1.7%) had missing exit information. The 22 admissions were of median [IQR] duration 7 [4 to 10] days.

*Factors associated with ADR-related presentation to the EU*

In the bivariate analysis we found associations between ADR-related EU presentation and age, hospital, drug count, and HIV/ART status.

In the multivariate model we included 596 presentations: in 404/1,010 EU presentations (40%) there was no documented drug exposure before the presentation, and ten remaining presentations were repeat presentations. In the multivariate analysis only an increasing drug count was independently associated with ADR-related presentation (Table 3). A sensitivity analysis, considering only HIV status and not ART status, showed similar results (Supplementary Table S6).

**Discussion**

ADRs constituted a significant proportion of the non-trauma burden in two EUs in our setting: there were more ADR-related presentations (7.9% of EU presentations) than presentations for lower respiratory tract infections, or for tuberculosis. Considering our resource limitations, it is important to note that patients presenting to the EU for ADRs stayed in hospital longer than patients presenting for other medical reasons, and that about one-third of these ADR-related EU presentations may have been avoided through more appropriate prescribing. With HIV a major public health problem in South Africa, we wanted to determine the relative contribution of drugs used in the management of HIV and its complications to the burden of ADR-related EU presentations, and found that these drugs were implicated in 13/80 (16%) ADR-related EU presentations.

The proportion of ADR-related EU presentations was similar among HIV-positive and HIV-negative/unknown EU attendees (8.4% and 7.8%) and in our multivariate logistic regression analysis, HIV infection was not independently associated with ADR-related EU presentation.



**Table 3**

Results of logistic regression model (n = 596 presentations) exploring associations with ADR-related EU presentation in Cape Town, South Africa, 2014–2015.

Variable	n	Crude		Adjusted <sup>a</sup>	
		Odds ratio (95% CI)	p-Value	Odds ratio (95% CI)	p-Value
Sex					
Female	352	Referent		Referent	
Male	244	0.834 (0.510 to 1.36)	0.46	0.889 (0.534 to 1.48)	0.65
Age					
Per additional decade	596	1.25 (1.09 to 1.43)	0.001	1.18 (0.992 to 1.41)	0.06
HIV and ART status					
Negative	170	Referent		Referent	
Unknown	261	2.32 (1.23 to 4.38)	0.009	1.87 (0.934 to 3.76)	0.08
Positive, no ART	33	1.11 (0.302 to 4.12)	0.87	1.68 (0.433 to 6.49)	0.46
Positive and on ART	132	1.54 (0.721 to 3.27)	0.27	2.17 (0.934 to 5.02)	0.07
Hospital					
GSH	339	Referent		Referent	
KDH	257	0.508 (0.303 to 0.851)	0.010	0.690 (0.357 to 1.33)	0.27
Drug count					
Per additional drug	596	1.13 (1.06 to 1.19)	<0.001	1.10 (1.03 to 1.18)	0.005
Modified Charlson comorbidity score					
Per additional point	596	1.22 (1.02 to 1.46)	0.03	0.990 (0.786 to 1.25)	0.93

ADR: adverse drug reaction; ART: antiretroviral therapy; CI: confidence interval; EU: emergency unit; GSH: Groote Schuur Hospital; KDH: Khayelitsha District Hospital.

<sup>a</sup> Adjusted for other predictor variables in the model.

However, our study was not powered to detect such an association, and we nevertheless found substantial differences in the presentation, severity, and preventability of ADRs when comparing these two groups of patients. HIV-positive individuals were younger, and were more likely to present with type B (idiosyncratic) ADRs, which were less likely to be preventable. These frequently included kidney and liver injuries attributable to ART and antituberculosis treatment. In contrast, individuals who were HIV-negative or had unknown HIV status were older, and more likely to present with type A ADRs, predictable from the pharmacological action of the drugs involved, and therefore often preventable. Typical ADRs in this group of patients included gastritis and upper gastrointestinal bleeds attributable to non-steroidal anti-inflammatories, and hypoglycaemia attributed to insulin and oral hypoglycaemic agents. It is also notable that ADRs affecting the HIV-positive group were seemingly more severe, as 85% of this patient group were admitted into longer-stay wards versus only 37% of the HIV-negative/unknown EU attendees presenting with ADRs.

The proportion of non-trauma EU presentations that were attributed to ADRs in our study (7.9%) was higher than those from two studies from India (which found 3.8% [10] and 2.6% [22] respectively) but agrees with findings from similar studies in other resource-limited settings: around 10% in Brazil [23], Malaysia [24], and Thailand [25], and 5.9% in Turkey [26]. The Thai study [25] assessed preventability by the same criteria we did, and found a higher proportion of preventable ADRs (49%) than our study (35%). This difference may be due to differences in methodology: the Thai investigators interviewed patients whereas we conducted a folder review, which may have missed some preventability factors. There is little data on burden of ADRs resulting in EU presentation in South Africa. A prospective study of elderly patients ( $\geq 65$  years) presenting to the GSH EU was conducted in 2005: an adverse drug event (ADE) contributed to the EU presentation of one in five patients in that study [27]. In that elderly study population, higher drug count was the only factor associated with ADE-related EU presentation on multivariate analysis, similar to our finding [27].

Our study has limitations. We were unable to obtain the folders of 80/1228 (6.5%) randomly sampled presentations, especially at GSH, which might have introduced bias. Furthermore, information on clinical presentation and drug history came from contemporaneous notes made by clinicians in the patient folder. We attempted to reduce this limitation by supplementing data with electronic laboratory and dispensing data

where possible. Nevertheless, we may have missed some ADR-related EU presentations due to missing information. HIV status was unknown in nearly half of all EU presentations, and only 136/239 (57%) HIV-positive EU attendees had ART documented in the folder. For the remaining 43%, our study design did not allow distinguishing between those truly not engaged in care, those who did not qualify for ART under guidelines then in use, and those whose ART was just not documented during the EU presentation. Better ART documentation may have increased the number of ADRs identified. In addition to misclassification of outcomes, missing HIV and ART data may have influenced the estimates in our multivariate model, and limit the robustness of our findings related to HIV. As our study was limited to medical EU presentations, we missed trauma presentations precipitated by ADRs such as arrhythmia, syncope, altered mental status, etc. While data extractors may have been inaccurate or biased in their ascertainment of potential ADRs, data extraction was done by multidisciplinary pairs, and we used a trigger tool to aid potential ADR identification to minimize these inaccuracies and bias. We acknowledge that causality, severity, and preventability assessment of ADRs is inherently subjective; we attempted to reduce this subjectivity by conducting these reviews through a multidisciplinary panel discussion of each case. Future prospective studies which incorporate patients' views and their social data would greatly enrich the understanding of factors predisposing to the development of ADRs.

Our results may be generalizable to other district to tertiary level settings with similar disease burden and drug use patterns, and have important implications for clinicians and policymakers. First, we have clearly demonstrated an independent strong association between drug count and the occurrence of adverse drug reactions. Clinicians working in emergency units should always have a high index of suspicion for ADRs, but particularly so as the number of drugs a patient takes increases. Second, for all prescribers and dispensing pharmacists, we highlight that the most common preventability factor was injudicious prescribing of the drug in question: either an inappropriate drug was prescribed, or a dose that was inappropriate was prescribed. Closer adherence to drugs' regulated indications, contraindications, and dosing information is required, and serious consideration should be given to implementing intelligent prescription decision support systems to avoid errors. Moreover, improving patient education on ADRs and improving routine monitoring for ADRs within the HIV programme is important for earlier detection of ADRs, should they occur.

While drugs used in the management of HIV and its complications contributed only a small number of ADRs in this study, the ADRs seen with these drugs were often severe and unavoidable. Quantifying these severe harms is important and our study demonstrates that it is feasible to collect this type of pharmacovigilance data in resource-constrained settings. The methodology developed is suitable for scaling in order to improve surveillance coverage, and can be periodically repeated. Repeated studies using this methodology may facilitate detection of changes in the pattern or burden of ADR-related harm associated with expansion of or changes to public health treatment programmes.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.afjem.2020.10.010>.

### Dissemination of results

These findings have not yet been shared with the community from which it originated.

### Authors' contribution

Authors contributed as follow to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content: JPM and NJ contributed 25% each; KC contributed 13%; HG, AS, and GM contributed 7% each; CN contributed 5%; UM, SL, and RC contributed 3% each; IE contributed 2%. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

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### Declaration of competing interest

The authors declared no conflicts of interest.

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