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ORIGINAL RESEARCH ARTICLE

Targeted Spontaneous Reporting of Suspected Renal Toxicity in Patients Undergoing Highly Active Anti-Retroviral Therapy in Two Public Health Facilities in Uganda

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Abstract

Background Although the national HIV control programme in Uganda has a well-established system for monitoring disease progression and treatment outcomes, monitoring of adverse drug reactions (ADRs) is inadequate. In order to address under-reporting of ADRs, the National Pharmacovigilance Centre, in collaboration with the HIV control programme, piloted a targeted spontaneous reporting (TSR) system as a complementary method to traditional spontaneous reporting.

Methods From April 2012 to March 2014, all cases of suspected renal toxicity in 10,225 patients on tenofovir-based regimens were monitored in the regional pharmacovigilance

centres of Masaka and Mbale. The identification of renal toxicity was performed using serum creatinine, urinalysis, and other signs and symptoms of kidney injury.

Results There was one suspected renal toxicity reported for every 200 patients on a tenofovir-based regimen. Some of the serious reactions reported were death in two cases and bone demineralisation in five patients. Most of patients had been on treatment for 2 years. Those that had been on tenofovir for more than 4 years had raised serum creatinine levels, emphasising the importance of monitoring for the risk of renal damage for longer. We also found that the reporting rate of suspected ADRs for all medicines in the two sites increased almost fivefold during the implementation period.

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Key Points

The targeted spontaneous reporting methodology can increase reporting of suspected adverse reactions to a drug.

Although the occurrence of renal toxicity associated with tenofovir is low, in a resource-limited setting where there is rapid scale-up of treatment and patients are initiated on a tenofovir regimen without initial screening, a monitoring programme for those that may develop renal toxicity should be put in place to encourage evidence-based decision making for improved patient safety.

Having adopted and leveraged on existing structures in the STD/AIDS Control Program, a platform for collaboration with the National Pharmacovigilance Centre was created, hence strengthening pharmacovigilance activities.

Conclusion Although the occurrence of suspected tenofovir renal toxicity of HIV patients is low, there is need to monitor those at risk so as to prevent irreversible kidney injury. TSR can complement spontaneous reporting for collecting safety data on particular drugs and increase ADR reporting rates.

1 Introduction

Uganda is a resource-limited country with a high disease burden. Communicable diseases namely malaria, tuberculosis (TB) and HIV/AIDS account for 54 % of the total burden of disease [1]. Access to essential medicines for treating common diseases such as malaria, pneumonia, HIV, and diabetes mellitus at facility level is reported at 50–68 % according to a survey conducted by the Ministry of Health in 2008 [2]. In order to address the high disease burden, the Ministry of Health is focused on rapidly expanding access to essential medicines through implementation of public health programmes and targeting the major communicable and non-communicable diseases. This increased access to medicines is expected to increase the number of people at risk of developing adverse drug reactions (ADRs).

The World Health Organization (WHO) Programme for International Drug Monitoring, recognises a reporting rate of over 200 suspected ADRs per million inhabitants/year, sent at least once a quarter from a national pharmacovigilance centre as good performance [3]. With more than 10 million Individual Case Safety Reports (ICSR) submitted from member countries of this WHO programme, VigiBase[®] is one of the sources of international safety data [4]. Analysis of the spontaneous reports in VigiBase[®] over a decade between the year 2000 and 2009 revealed that high-income countries had high reporting rates ranging from between 3 and 613 reports per million inhabitants per year while low-income countries had the lowest range at 0–21 [5]. Despite recognition of the occurrence and burden of ADRs and the need to report them, several studies show that there is widespread under-reporting of ADRs to spontaneous reporting systems, including serious or severe ADRs [6–9]. The 2014 reporting rate from Uganda in VigiBase[®] corresponds to 20 reports per million inhabitants [10, 11]. A study conducted to assess pharmacovigilance systems in sub-Saharan Africa indicated that in Uganda, public health programmes do not routinely collect and share ADR data with the National Pharmacovigilance Centre (NPC) [12].

As of September 2013, the national STD/AIDS Control Program (ACP) had distributed antiretroviral (ARV) medicines to over 570,573 HIV-infected persons [13]. The

HIV/AIDS 2013 Progress Report [13] showed that cotrimoxazole was dispensed to over 800,000 persons living with HIV whether ARV active or naive. Although, this program has a well-established system for monitoring HIV prevalence, incidence, numbers on treatment and treatment outcomes, monitoring of ADRs due to ARVs is still inadequate.

In order to address under-reporting of ADRs due to ARVs, the NPC, in collaboration with the national ACP piloted the targeted spontaneous reporting (TSR) approach as a complementary method to the traditional spontaneous reporting method. TSR (sometimes called stimulated reporting) is a variant of spontaneous reporting that focuses on capturing ADRs in a well-defined group of patients on treatment [14]. The WHO developed this TSR methodology in 2010 in three countries including Uganda with support from the Monitoring Medicines Project under the seventh framework programme (FP-7) of the European Commission. Following a training workshop on this new methodology, Uganda adapted TSR to monitor renal toxicity among HIV patients on tenofovir-based regimens. TSR was the method chosen because it held the promise of a comprehensive monitoring method that was affordable and feasible in healthcare settings with limited human and financial resources. TSR was considered likely to build on the gains that had already been achieved by the existing efforts in promoting the role of pharmacovigilance as a best practice that improves the quality of care.

Although tenofovir had formerly been recommended as part of the alternative first-line ARV therapy (ART) regimen in the national guidelines and is now the preferred first-line regimen, little was known about its toxicity profile in the Ugandan population. Several studies on the use of tenofovir by patients with mild renal dysfunction or for longer durations indicated that it might be associated with renal toxicity [15–18]. In vitro studies also suggested a higher risk than has been observed in patients [19]. Patient populations are heterogeneous and treatment is complicated by the coadministration of tenofovir with other drugs that may enhance renal toxicity. Monitoring patients on a tenofovir-based regimen for a possible increased risk of renal dysfunction is therefore crucial. However, this is not always done due to a lack of laboratory facilities, inadequate knowledge for monitoring and work overload, especially in resource-limited settings. Failure to monitor patients to identify those who may be at risk of developing renal toxicity may result in significant deterioration in kidney function over a number of years as well as other complications.

The TSR method was adapted and piloted in the ACP among patients on tenofovir-based ART regimens seeking care from the two regional pharmacovigilance centres of Masaka and Mbale Regional Referral hospitals and their

catchment health facilities. The purpose of this study was to pilot TSR using the example of renal toxicity to tenofovir in adults and to enhance pharmacovigilance within the ACP.

2 Methodology

2.1 Implementation Design

This was a pilot using TSR methodology to capture ADRs for HIV-positive clients who were initiated on tenofovir-based regimens. The Uganda health delivery system is comprised of the following levels:

- national referral
- regional referral
- district or general hospital
- health centre IV (Serves a county, should be able to admit patients having a senior medical officer and another doctor as well as a theatre for carrying out emergency operations)
- health centre III (Found in sub-county, runs an out-patient clinic, treating common diseases and offering antenatal care. Its led by a senior clinical officer and has a functioning laboratory)
- health centre II (serves a few thousand people, led by a registered nurse, runs an out-patient clinic treating common diseases and offering antenatal care)
- health centre I (structured as village health teams and working as a link between the community and the health facilities).

Health services are also provided in the private sector by for-profit health providers, not-for-profit healthcare facilities and traditional/complimentary medicine providers. As of June 2014, the Ministry of Health had accredited 1,572 public and private health facilities countrywide to offer ART services. The health workers involved in ART service delivery range from doctors, clinical officers, registered nurses and midwives to nursing assistants. The NPC has leveraged on the expertise in the national and regional referral hospitals and has designated these as regional pharmacovigilance centres. Two focal persons were appointed by the hospitals to coordinate activities in the region including the lower public health facilities.

2.2 Site Selection

From April 2012 to March 2014, all cases of suspected renal toxicity in patients on tenofovir-based regimens were monitored in the two regional pharmacovigilance centres of Masaka and Mbale. The population in the study sites had

been estimated at about 20,000 HIV-positive patients on ART.

2.3 Monitoring of the Tenofovir-Based Regimen

For the pilot study, cases of suspected renal toxicity in patients on tenofovir-based regimens were targeted and monitored. Health workers in the pilot facilities were trained to monitor for signs and symptoms of tenofovir renal toxicity in all patients that were initiating or were already on tenofovir-based regimens. The laboratory tests carried out were serum creatinine and urinalysis (including proteinuria and glycosuria) as per the recommendations in the national guidelines for monitoring tenofovir at the various levels of health service delivery [20–22]. The 2014 national ART guidelines recommend carrying out urinalysis for monitoring of patients initiated on ART at baseline and thereafter every 6 months or as required [20]. They further recommend carrying out serum creatinine and/or blood urea to monitor renal function for patients on tenofovir every 6 months at district and regional referral hospitals.

The measurement parameters were the basis for the case definition and any patient that presented with any one out-of-range parameter was considered for suspected renal toxicity. To simplify monitoring of patients at the pilot sites, a job aid was developed to guide health workers on the frequency of carrying out laboratory tests and on how to identify and report suspected cases. Signs and symptoms suggesting renal toxicity were described in the job aid (see Electronic Supplementary Material 1). Changes from the baseline parameters even in the absence of cardinal symptoms of renal insufficiency would trigger adverse reaction reporting.

2.4 Training and Support Supervision for the Targeted Spontaneous Reporting (TSR) Methodology

The health professionals managing patients were trained on the TSR methodology and renal toxicity monitoring as well as any other safety concerns. To supplement the training, support supervision was conducted regularly and involved personnel from both the NPC and the ACP. During support supervision, review meetings with the pharmacovigilance centre focal persons were held and strategies for strengthening pharmacovigilance in the hospitals were reviewed. Mentoring in ART care with focal facility personnel was also done.

2.5 Data Collection

Based on the case definition and the national guidelines, health workers reported suspected ADRs using the national

form (see Electronic Supplementary Material 2). Completed reports were then relayed to the regional pharmacovigilance coordinator who entered them into the web-based case management system VigiFlow™ [23]. The NPC staff and the ACP focal person held regular meetings to assess causal relationships. The assessors assigned a score to the components and factors considered in establishing the causal relationships between tenofovir and the adverse events such as temporal sequence, alternative causes, confirmation by objective evidence and challenge and re-challenge with the drug. Each question was answered positive (yes), negative (no), or unknown or inapplicable (do not know). The likelihood of tenofovir being related to renal toxicity was assessed using the Naranjo algorithm [24]. The suspected ADR was then assigned to a category from the total score as follows: definite ≥ 9 , probable 5–8, possible 1–4, doubtful ≤ 0 . A descriptive summary of data on renal toxicity was created and is presented in Sect. 3.3.

2.6 Ethical Considerations

ADR monitoring and reporting is a routine clinical care activity. Health workers were required to report the reactions that they observe and those reported by the patients. Informed consent was not individually taken from each patient as the ADR form is confidential and was treated as such by the NPC. Ethical clearance was sought from the Uganda National Council for Science and Technology (Ref: HS 1136), which provides ethics research clearance

at the national level in accordance to the World Medical Association Helsinki Declaration. Approval for the pilot was obtained from National Drug Authority and the ACP to conduct this pilot study.

3 Results

3.1 Background to the Sites

A total of 10,225 patients were on tenofovir-based regimens in the two pilot sites in the 24 months of the pilot implementation. A majority of these patients were from the Masaka region as presented in Table 1.

3.2 Demographics of the Suspected Renal Toxicity Cases

Fifty-three (0.52 % of the exposed cases) of the suspected renal toxicities were reported to the NPC, of which 23 (43.4 %) were males. The median age of these patients was 43 years [interquartile range (IQR) 33–51] and the median body weight was 55 kg (IQR 47–62). Patients had been on tenofovir-based regimen for a median duration of 24 months (IQR 12–36). All patients that had been on a tenofovir regimen for more than 4 years had raised creatinine levels.

The majority (60 %) of this cohort of patients were on the tenofovir/lamivudine/nevirapine (TDF/3TC/NVP) combination, while 35 % were on tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) and the remaining 5 % were on the ritonavir-boosted lopinavir in combination with TDF/3TC.

3.3 Presenting Signs and Symptoms for the Suspected Renal Toxicity

Of the 53 cases with suspected renal toxicities, six (11 %) presented with bilateral pedal oedema, four with facial

Table 1 Patients on the tenofovir-based regimen among the study sites

Study site	Number of patients on tenofovir
Masaka Region	
Masaka Regional Referral hospital	2,637
TASO Masaka	1,759
Villa Maria hospital	1,700
Lyantonde hospital	740
Kalungu Health Centre IV	63
Kitovu hospital	40
Bukulula Health Centre IV	348
Subtotal	7,287
Mbale Region	
Mbale Regional Referral hospital	950
TASO Tororo	1,615
St. Antony hospital Tororo	158
Bududa hospital	215
Sub-total	2,938
Total	10,225

Table 2 Summary of presenting signs and symptoms of suspected renal toxicity

Parameter	Number of patients (%)	Total (N)
Increased creatinine (>1.2 g/dL)	43 (81)	53
Creatinine clearance >90 mL/min	43 (100)	43
Creatinine levels not provided	10 (19)	53
Proteinuria	25 (66)	38
Glycosuria and proteinuria	11 (44)	25
Bone demineralisation	5 (9)	53
Bilateral pitting pedal oedema	6 (11)	53
Facial puffiness	4 (8)	53

puffiness and five with bone demineralisation, which was confirmed by X-ray. Eleven (21 %) cases had out-of-range urinalysis, and the results are summarised in Table 2 along with other observed signs and symptoms of suspected renal toxicity. All of the patients that presented with glycosuria also had proteinuria. Two out of every three patients on a tenofovir-based regimen whose protein levels were tested ($n = 38$) had a positive result. Haematuria found in one patient out of the 53 reported cases was not expected. None of the patients in this study presented with hyperglycaemia.

Twenty-one patients were changed to a non-tenofovir-based regimen and their urine parameters and creatinine clearance improved thereafter. Tenofovir was substituted with zidovudine in six of these cases and the other 15 cases were substituted with abacavir. Two of those cases changed to abacavir had co-morbidities of both hypertension and diabetes, whereas two of the cases changed to zidovudine also had hypertension. A 45-year-old male, who had been on a tenofovir-based regimen for 5 years and presented with increased serum creatinine, glycosuria and proteinuria, was the only case with hypertension that was monitored without a regimen change as the signs and symptoms of renal damage resolved thereafter. Other co-morbidities reported included one case of lipodystrophy and one case of Kaposi's sarcoma. The laboratory findings for one case were consistent with Fanconi syndrome (i.e. hypouricaemia, hypokalaemia, generalised aminoaciduria and proteinuria).

About 80 % of the cases tested had a raised serum creatinine level. A raised serum creatinine and calculated creatinine clearance of <90 mL/min (calculated with the Cockcroft and Gault formula) was reported in all 43 patients that had a serum creatinine test performed and this is presented in detail in Table 3.

One in every five cases of suspected renal toxicity did not have a result for serum creatinine. The characteristics of the ten patients whose serum creatinine results could not be established are listed in Table 4. Six of the ten cases had their regimen changed, mainly because of bone demineralisation, and two patients died.

3.4 Causality Assessment

The majority (80 %) of the suspected renal toxicity cases were classified as probable and the rest were possibly related to tenofovir. None of the causality assessment grading belonged to the extreme categories of doubtful and definite.

3.5 Reporting Trends for Suspected Adverse Drug Reactions

During the time of the pilot, there was an increase in the overall number of ADR reports that VigiBase[®] submitted to

the national pharmacovigilance system compared with the previous years (shown in Fig. 1) and also specifically from the annual number of reports collected in the two study sites of Mbale and Masaka (seen in Table 5 with comparisons before and after the TSR pilot period). The reports collected is about five times more than the pre-study period.

4 Discussion

4.1 Background to the Study

This pilot was implemented to establish the feasibility and positive effects that may accrue from a targeted spontaneous reporting methodology in resource-limited settings. In the ACP, the TSR was adapted to monitor the safety of patients on HIV treatment by focusing on suspected renal toxicity related to the use of tenofovir.

4.2 Summary of Findings

In our study, there was one suspected renal toxicity reported in every 200 patients on a tenofovir-based regimen. Among the serious reactions reported were the death of two patients and bone demineralisation, also known as osteomalacia, which occurred in five patients. Further assessment of the causality relationship revealed that these reports were probably or possibly but not definitely related to tenofovir. The median duration of treatment for the patients in this cohort was 2 years. However, all 13 (100 %) patients that had been on the tenofovir regimen for more than 4 years had raised creatinine levels. This group of patients emphasises the importance of monitoring for the risk of renal damage the longer patients are on tenofovir. We also found out that the reporting rate of suspected ADRs to all medicines in the two selected sites increased almost five-fold during the implementation of the TSR methodology.

4.3 Suspected Adverse Reactions Associated with Tenofovir

Tenofovir is a drug that is widely used for treatment of HIV infections in Uganda as more than half of the patients on ART in the two targeted study sites had it as part of their regimen [20].

Based on the case definition, the findings from this pilot support the presenting signs and symptoms of renal toxicity associated with tenofovir that are not different from that reported in the literature [16, 17]. According to the manufacturer, adverse reactions with a suspected relationship with tenofovir are classified as either uncommon ($\geq 1/1,000$ to $<1/100$) or rare ($\geq 1/10,000$ to $<1/1,000$) [25].

Table 3 Characteristics of the patients with suspected renal toxicity

Age	Sex	Duration on ART (months)	Regimen	Concomitant drugs	Presenting symptom/signs	Outcome and remarks	Serum creatinine (mg/dL)	Creatinine clearance (mL/min)	Regimen change
43	F	5	TDF/3TC/NVP	Cotrimoxazole	Raised serum creatinine	Expected but not serious	1.36	52.0	No
30	F	12	TDF/3TC/NVP	Cotrimoxazole	Increased serum creatinine glucose: nil Proteins: +	Life-threatening but expected	1.47	58.2	No
51	M	5	TDF/3TC/NVP	Cotrimoxazole	Raised serum creatinine Proteins: +	Expected but not serious; urinalysis has been normal since May 2014	1.47	47	No
62	M	12	TDF/3TC/NVP	None reported	Urine RBCs: nil Pus cells: + Epithelial cells: ++ Urine protein: ++ Glucose: nil.	Reaction expected and was life-threatening. Improved	1.52	32.8	Changed from TDF to AZT
64	M	6	TDF/3TC/EFV	Cotrimoxazole	Raised serum creatinine Urine protein: + Urea: 8.3 mg/dL	Cotrimoxazole stopped due to neutropenia. Patient improved. Reaction expected	1.35	54.4	Changed from TDF to ABC
62	F	84	TDF/3TC/NVP	None reported	Raised serum creatinine Urine protein: +++ Glucose: +	Reaction was serious but expected	1.36	37.2	No
30	F	4	TDF/3TC/NVP	Cotrimoxazole	Increased creatinine levels Glucose: nil Proteins: nil	Reaction was expected but not life-threatening. Patient recovered	1.75	37.5	No
45	M	19	TDF/3TC/NVP	Cotrimoxazole	Raised serum creatinine	Reaction was expected but not life-threatening. Patient recovered	1.42	60	No
42	F	6	TDF/3TC/NVP	Cotrimoxazole	Raised serum creatinine	No co-morbidities reported, patient died	1.80	71.0	No
68	M	10	TDF/3TC/NVP	Cotrimoxazole	Raised serum creatinine	Reaction was expected but not life-threatening. Patient recovered	1.57	57.0	No
52	M	9	TDF/3TC/EFV	Cotrimoxazole	Raised serum creatinine	Reaction was expected and life-threatening but resolved	1.47	53.0	No
41	F		TDF/3TC/lopinavir	Dapsone	Generalised oedema, progressive anuria	Dapsone has an effect on renal function. The patient was allergic to cotrimoxazole. The reaction was expected and life-threatening but it resolved	2.3	21.0	TDF changed to AZT
28	M	24	TDF/3TC/EFV	None reported	Renal tubular necrosis, raised serum creatinine Urine glucose: nil Proteins: +	Good viral suppression at 381 copies Patient recovered. Reaction was expected	Actual results not seen		TDF changed to ABC

Table 3 continued

Age	Sex	Duration on ART (months)	Regimen	Concomitant drugs	Presenting symptom/signs	Outcome and remarks	Serum creatinine (mg/dL)	Creatinine clearance (mL/min)	Regimen change
33	M	12	TDF/3TC/NVP	Cotrimoxazole	Increased creatinine	Reaction was expected. Patient has normal urinalysis	Results not seen		No
38	F	48	TDF/3TC/EFV	Cotrimoxazole	Raised serum creatinine	AZT had been changed to TDF after 2 months of treatment. Follow-up urinalysis on TDF regimen indicated protein +. The reaction was expected and serious	2.57	27.0	No
29	F	24	TDF/3TC/NVP	Ibuprofen for 5 days and vitamin B complex for 2 weeks	Increased creatinine: 1.65 mg/dL. Follow-up value was 1.3 mg/dL	The patient was reported to also have lumbago. Reaction was serious and expected but resolved	1.65	58.0	No
37	M	84	TDF/3TC/NVP	Cotrimoxazole	Increased creatinine	Very poor adherence with very poor immunological outcome. The suspected renal abnormality is also resolving	10.91	6.2	No
45	M	36	TDF/3TC/NVP	Carvedilol, spironolactone	Oedema, polyuria, raised serum creatinine protein 3+ and a known hypertensive	Reaction expected and patient is recovering	4.6	24.4	TDF changed to AZT
42	F	84	TDF/3TC/NVP	Cotrimoxazole	Increased creatinine: 1.3 then 1.1 mg/dL	Reaction expected and patient is recovering	1.3	51.6	No
49	F	48	TDF/3TC/NVP	Cotrimoxazole	Neuropathy and increased creatinine	Reaction expected and patient recovered	10.0	7.2	TDF changed to ABC
61	M	36	TDF/3TC/NVP	Cotrimoxazole	Glucose: nil Proteins: + Increased creatinine	Reaction expected and patient recovered	Results not seen		No
33	M	12	TDF/3TC	Atazanavir	Increase creatinine, facial puffiness, high urea level Glucose: nil Protein: nil	Reaction expected and patient recovered	10.9	10.6	No
55	M		TDF/3TC/NVP	None reported	Raised serum creatinine Glucose: nil Proteins: nil	Reaction expected and patient recovered	1.5	44.2	No
47	F	24	TDF/3TC/NVP	Insulin	Increased serum creatinine Glucose: + Proteins: +	Known to be hypertensive and have diabetes mellitus. Reaction expected and patient recovering	Results not seen		TDF changed to ABC

Table 3 continued

Age	Sex	Duration on ART (months)	Regimen	Concomitant drugs	Presenting symptom/signs	Outcome and remarks	Serum creatinine (mg/dL)	Creatinine clearance (mL/min)	Regimen change
49	M	12	TDF/3TC	Alluvia and cotrimoxazole	Increased creatinine levels Glucose: nil Proteins: nil	History of TB treatment immediately before starting ART. Reaction expected and patient recovering	1.66	27.8	No
53	M	12	TDF/3TC/NVP	Cotrimoxazole	Facial puffiness, increased serum creatinine Proteinuria: +++ Glucose: +	Signs of treatment failure. The reaction was expected	Results not seen		TDF withdrawn, changed to ABC
50	F	24	TDF/3TC/NVP	None reported	Increased creatinine Glucose: nil Proteins: +	Had lactic acidosis with high LDH levels. Reaction expected	Results not seen		No
48	F	5	TDF/3TC	EFV	Increased creatinine levels	Reaction expected and patient recovering	1.76	30.7	No
29	F	36	TDF/3TC/NVP	Cotrimoxazole	Increased creatinine levels Urea: 51 mg/dL	Reaction expected and patient recovering	1.74	47.8	No
28	F	24	TDF/3TC/NVP	Cotrimoxazole	Raised serum creatinine, proteinuria Urine protein: 3+++ Glucose: nil	Reaction expected and patient recovered	1.43	58.3	Changed from TDF to AZT regimen
25	F	12	TDF/3TC/NVP	Cotrimoxazole	Fanconi syndrome Urine protein: 3+++ Urine glucose: + Random blood sugar: 6.1 mmol	Raised amylase, raised AST. Outcome is not yet known, patient still being monitored	1.79	34.0	ART stopped
22	F	48	TDF/3TC/EFV	Cotrimoxazole	Raised serum creatinine	Urinalysis was normal during follow-up. Reaction expected and patient recovering	1.45	36.0	No
52	M	2	TDF/3TC/EFV	Cotrimoxazole	Raised creatinine Glucose: nil Proteins: nil	Had a Kaposi's sarcoma lesion as well. Urinalysis results returned to normal. Reaction expected and patient recovering	1.30	54.3	From NVP to EFV
45	M	60	TDF/3TC/NVP	Captopril, mifedipine	Increased creatinine, known hypertension Glucose: + Proteins: +	Known hypertensive. Reaction expected and patient recovering	1.79	61.9	No

Table 3 continued

Age	Sex	Duration on ART (months)	Regimen	Concomitant drugs	Presenting symptom/signs	Outcome and remarks	Serum creatinine (mg/dL)	Creatinine clearance (mL/min)	Regimen change
38	F	24	TDF/3TC/EFV	Atorvastatin	Increased serum creatinine	Started ART (AZT/3TC/EFV) in 2006, substituted AZT with TDF due to lipodystrophy	1.43	53.4	No
31	F	24	TDF/3TC/NVP	Nifedipine, atenolol	Renal tubular necrosis, raised serum creatinine Glucose: nil Protein: +	Reaction expected and patient recovered. Serum creatinine reduced to 1.39 mg/dL Right-sided hemiparesis of a known hypertensive Reaction expected and patient recovered	4.28	14.1	From TDF to ABC
56	F	66	TDF/3TC/NVP	Cotrimoxazole	Facial puffiness, easy fatigue, raised creatinine levels Urea: 240 mg/dL	Reaction expected and patient recovering	7.26	7.7	Changed TDF to ABC
56	M	24	TDF/3TC/NVP	Cotrimoxazole	Raised creatinine, urea (92 mg/dL) Glucose: + Proteins: ++	Patient had pancytopenia and he died	3.15	17.2	No
44	F	24	TDF/3TC	NVP	Facial puffiness, increased creatinine levels	Not known	Results not seen		No
40	M	2	TDF/3TC/NVP	None reported	Renal toxicity with bilateral pedal oedema Glucose: + Proteins: +	Had a history of TB of the kidneys. Reaction was expected	16.52	3.9	Drug stopped
39	M	48	TDF/3TC/NVP	Cotrimoxazole	Increased creatinine	Reaction was expected and the patient recovered	Results not seen		TDF substituted for ABC

+ (30–100 mg/dl), ++ (100–300 mg/dl), +++ (300–1000 mg/dl), ++++ (>1000 mg/dl) define measured level of protein/glucose

3TC lamivudine, ABC abacavir, ART antiretroviral therapy, AZT zidovudine, EFV efavirenz, F female, HTN hypertension, LDH lactate dehydrogenase, M male, NVP nevirapine, RBCs red blood cells, TB tuberculosis, TDF tenofovir

Table 4 Characteristics of patients for whom serum creatinine was not performed

Age	Sex	ART regimen	Duration on ART (months)	Concomitant drugs	Presenting symptom/signs	Outcome and remarks
30	F	TDF/3TC/EFV	48	Ciprofloxacin 500 mg	Blood in urine Urine protein: + (30 g/dL) White blood cells: 2+ Glucose: nil Urinary tract infection that did not improve on ciprofloxacin 500 mg twice daily for 1 week	Regimen changed from TDF to ABC and the patient recovered
29	M	TDF/3TC/NVP	1.2	Dapsone, prednisone	Bilateral pedal oedema Urine protein: 3+ Red blood cells: 2+ Pus cells: 2+	Patient died
52	F	TDF/3TC/NVP	28	Cotrimoxazole, ciprofloxacin 500 mg	Urine protein: 2++ Pus cells: ++ Epithelial cells: ++ CD4: 15	Patient improved on ciprofloxacin 500 mg. Regimen was maintained
47	F	TDF/3TC/NVP	36	Anti-TB drugs for 6 months	Paraesthesia of both limbs Glucose: ++ Protein: ++ Pale	Had just completed TB treatment 1 week ago, TDF was changed to ABC and recovered
38	M	TDF/3TC/EFV	1	None	Bilateral pedal oedema Anaemia (haemoglobin 6.6 g/dL) Protein: +	Patient died
34	M	First on AZT/3TC/NVP, then TDF/3TC/NVP	24	Cotrimoxazole	Ultrasound revealed bilateral hydronephrosis Bone demineralisation on left head of femur Glucose: nil Proteins: nil	Developed hyperpigmentation of the nails and was substituted to TDF on request
43	F	TDF/NVP/3TC	36	None	Bone demineralisation Glucose: + Proteins: ++	TDF substituted with ABC and recovered
46	F	TDF/3TC/NVP	24	None	Severe bone pains and unstable gait	Outcome and new regimen could not be readily established

Table 4 continued

Age	Sex	ART regimen	Duration on ART (months)	Concomitant drugs	Presenting symptom/signs	Outcome and remarks
60	F	TDF/3TC/NVP	5	Cotrimoxazole	Osteomalacia, reduced bone density of femur Glucose: nil Proteins: +	TDF substituted with AZT
39	F	TDF/3TC/EFV	12	Cotrimoxazole	Bone demineralisation Reduced bone density of the right and left femur Glucose: nil Proteins: nil	TDF substituted to ABC and recovered

+ (30–100 mg/dl), ++ or 2+ (100–300 mg/dl), 3+ (300–1000 mg/dl), 4+ (>1000 mg/dl) define measured level of protein/glucose

3TC lamivudine, ABC abacavir, ART antiretroviral therapy, AZT zidovudine, EFV efavirenz, F female, M male, NVP nevirapine, TB tuberculosis, TDF tenofovir

Increased serum creatinine was uncommon and renal failure, osteomalacia, lipodystrophy and angioedema were considered to be rare in the European Summary of Product Characteristics.

From our cases, proteinuria, glycosuria, raised serum creatinine and bone demineralisation are characteristics of tenofovir-induced kidney injury. Use of proteinuria and glycosuria to screen for tenofovir-induced kidney injury seems to be a very useful approach that should be emphasised and for which cost effectiveness ought to be studied further, especially for long-term monitoring of patients in resource-limited settings. Patients who had proteinuria diagnosed with dipstick, their regimens subsequently changed had a positive treatment outcome similar to other studies [16].

Since the main target for tenofovir toxicity is the proximal tubule, the presence of tubular proteinuria would be the most sensitive test for detecting proximal tubular dysfunction. However, it was not possible to measure tubular proteinuria in this pilot. The dipstick analysis used in this pilot primarily detected albuminuria, which is insensitive for low molecular weight proteinuria characteristic of tenofovir toxicity. The alternative tests for assessing proximal tubular function were to measure fractional excretion of phosphates and glycosuria, which are also established markers of proximal tubule dysfunction and are easy to screen for but are less sensitive tests than tubular protein excretion. Glycosuria was found in 11 of the patients, who also had proteinuria, while bone demineralization was found in five patients, which points to proximal tubular dysfunction [16, 25, 26].

In studies [27, 28], serum creatinine >1.2 g/dL with calculated creatinine clearance <90 mL/min was reported in more than 80 % of the cases. This is consistent with findings of a study of more than 1,000 HIV-infected patients on tenofovir which identified 1 % whose serum creatinine increased to >120 g/dL [29]. The SCOLTA (Surveillance Cohort Long-Term Toxicity Antiretroviral) study of 754 HIV-infected, tenofovir-treated patients found a 2.5 % incidence of creatinine elevations more than 1.5 times the upper limit of normal in a mean follow-up of 19.5 months, similar to the monitoring period of the patients in this pilot [29].

4.4 Achievement of the TSR Pilot

The project piloted TSR as a methodology for enhancing ADR reporting in the ACP in Uganda. It was specifically targeting patients who developed renal toxicity after taking tenofovir. This initiative was the first of its kind in Uganda and in sub-Saharan Africa.

The pilot was established on the basis of collaboration with a public health programme and the NPC, which

Fig. 1 Number of individual case safety reports (ICSRs) from Uganda in VigiBase® per year

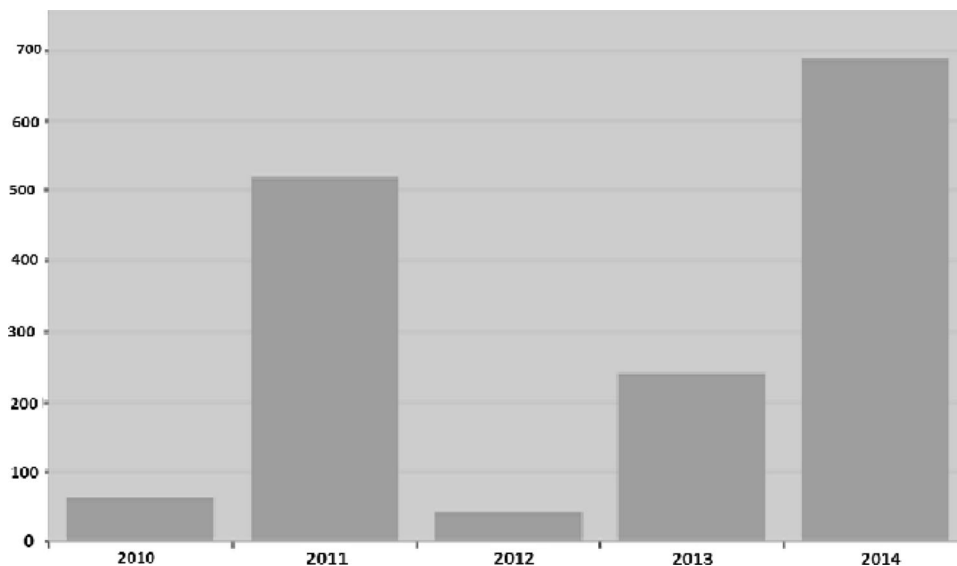


Table 5 Comparison of suspected adverse drug reaction reports collected from the study sites with the overall adverse drug reaction reports

Source of reports	Period						
	Before TSR pilot study			After start of TSR			
	2010	2011	Total	2012	2013	2014	Total
Study sites	17	27	44	142	46	181	369
Uganda VigiBase® reports	60	518	578	42	239	687	968
Percentage	8 % (44/578)			38 % (369/968)			

TSR targeted spontaneous reporting

ensured ownership and division of activities according to the comparative advantage of each participating entity. The healthcare providers identified with the activity mostly because of the involvement of the ACP.

As a result of this collaboration, the ACP incorporated ADR reporting in its training manuals for ART. Also, pharmacovigilance reports from ART sites are incorporated into the national quarterly ART report. This has increased the number of spontaneous reports from public health facilities. It has increased visibility of the NPC activities by opening communication lines with all public health system programmes through sharing of reports, feedback meetings, case review meetings and joint training of healthcare providers.

The pilot was observational with no exclusion and inclusion criteria for those monitored. Patients were monitored in the routine clinical setting where risk factors and gaps in care were observed and studied. In the case of lifelong treatment such as ART, reporting lasts a lifetime as well [14]. The fivefold increase in the reporting rate compared to the pre-study period suggests that the TSR methodology addresses the problem of under-reporting that is seen with the traditional Ugandan spontaneous reporting.

Through joint support supervision activities, the NDA and NPC were able to identify gaps in health service

provision. The point in case is the Ministry of Health ART guidelines which were not clear to health workers regarding monitoring patients on tenofovir. The NPC noted that health workers were opting for more expensive tests such as serum creatinine for monitoring tenofovir instead of a urine dipstick which is a cheaper alternative.

This pilot had a capacity-building component in terms of training, mentorship and feedback on the quality of care provided at the health facilities. This motivated health workers to provide better services and also to report suspected adverse reactions. At the pilot close-out dissemination meeting, stakeholders were particularly impressed by the feedback presented to them about the quality of reports as analysed by the NPC. Stakeholders requested that the TSR method of monitoring safety be rolled out to other parts of the country.

4.5 Challenges and Limitations of the TSR Pilot

HIV treatment is a rapidly evolving field whose guidelines keep changing. The recommendations for ART and preventing mother to child transmission (PMTCT) kept changing as the policies and guidelines changed. As a result, the planned TSR roll-out for PMTCT services has not yet been carried out.

Assessment of the cases was difficult because some reports did not have baseline tests for renal function at the start of therapy. The dipstick analysis used in this pilot detected primarily albuminuria and is insensitive for low molecular weight proteinuria characteristic of tenofovir toxicity. Ideally, proteinuria should be assessed by formal measurement of the urine protein-to-creatinine ratio (P:C) or albumin-to-creatinine ratio (A:C). This was not possible in this study because the pilot used dipstick testing for detecting proteinuria and hence absolute urine protein values were not obtained. The lack of baseline laboratory tests in some reported cases makes it difficult to attribute the findings to tenofovir renal toxicity since it was not possible to rule out the existence of renal disease before tenofovir regimens had been started.

Monitoring for ADRs was initially viewed as an extra activity stretching the programme's logistics and resources. The NPC at one point provided some supplies and gave incentives to those involved in the project. Health workers viewed the programme as research that comes with added work since they already have a heavy workload from their usual work and so expected allowances. The joint support supervision encouraged the health workers and contributed to their change of attitude and the quality of patient care started improving.

4.6 Recommendations

Use of targeted surveillance monitoring strategies increases the number of reports and can help to identify risks that are associated with specific treatment in public health programmes. This plays an important role in signal detection. The role of co-morbidities such as hypertension and diabetes in this case also needs to be further studied as the TSR is rolled out. The numbers in this study were too small to come to a meaningful conclusion regarding their relationship to tenofovir-associated renal toxicity. The cost effectiveness of using these simple tests should also be further studied, especially in resource-limited settings.

Pharmacovigilance should be integrated into public health systems as a routine activity. However, there is still the need to plan for pharmacovigilance activities and resources such as having a focal person at the health facility level, especially where there are high patient loads, and a regional focal person to coordinate pharmacovigilance activities within the regions. In order to improve ADR reporting, the reporting of pharmacovigilance activities in Uganda needs to be simplified and harmonised with the current electronic reporting systems for the public health programmes and the health management information systems. Advocacy for integration should be enhanced by the relevant stakeholders and continuous information sharing. For successful implementation, involvement of different

stakeholders is key because the issues encountered are better handled by a multi-disciplinary approach.

5 Conclusion

This pilot revealed that the incidence of suspected adverse events that are possibly related to the use of tenofovir-based regimens in HIV treatment is one report in 200 patients. We also found that the reporting rate of suspected ADRs to all medicines in the two selected sites increased almost fivefold during the implementation of the TSR methodology.

Targeted spontaneous reporting as a surveillance method can complement spontaneous reporting since it comes with the advantages of an increased reporting rate and the possibility of calculating the incidence of the ADR in question. In resource-limited settings, a successful monitoring programme for the safety of medicines used in public health programmes can be implemented and a specific question of interest can be answered in a specific population. This encourages use of evidence-based decision making for a better-quality patient care programme.

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