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Full Length Research Paper

Adherence to renal function monitoring guidelines in HIV-infected patients starting tenofovir disoproxil fumarate-based antiretroviral therapy in rural Rwanda

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Tenofovir disoproxil fumarate (TDF) **is a component of several first-line HIV antiretroviral regimens. However, TDF causes nephrotoxicity and guidelines for creatinine monitoring are in place. This study evaluated creatinine testing practices in a retrospective cohort of antiretroviral-naive adult HIV patients initiated on a TDF-containing regimen between January 1, 2012 and December 31, 2012, in 23 outpatient health centers in rural Rwanda. Electronic medical records (EMR) were used to identify eligible subjects. Demographic data and creatinine testing orders and results at baseline, 1, 3, and 6 months, were collected from paper charts. 496 patients were included. At baseline, 252 (51%) patients had a creatinine test ordered and 239 (48%) received a test result. At the 1-, 3-, and 6-month visits, 2.3%-9.3% of the patients had their creatinine monitored. Documentation of creatinine clearance (CrCl) was reported in only 3 patients. 210 patients had sufficient data to calculate CrCl by the Cockcroft-Gault equation, with 24 (11%) patients started on TDF despite a CrCl < 50 mL/min. Adherence to TDF-specific laboratory testing guidelines proved challenging. Automated EMR-generated testing reminders, studies to understand reasons for non-adherence, local adaptation of guidelines, and advocacy for safer medications more easily administered in a resource-limited setting are recommended.**

Key words: Africa, creatinine, guideline adherence, HIV, renal insufficiency, tenofovir.

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor that is frequently included in HIV treatment regimens due to its favorable side effect profile and the availability of once-daily fixed-dose formulations (WHO, 2013). TDF is excreted through the kidney by glomerular filtration and tubular secretion (Rodríguez-Nóvoa *et al*., 2009) and it has been associated with nephrotoxicity, which may manifest as decreased glomeru-

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lar filtration rate and/or proximal tubular dysfunction with proteinuria, glycosuria and hypophosphatemia (Cooper *et al.*, 2005; Njuguna *et al*., 2013; Malik *et al*., 2005). To enhance the safety of TDF use, the World Health Organization (WHO) and other HIV treatment programs recommend baseline assessment and regular monitoring of renal function with dose adjustments, change of regimen, or avoidance of TDF for patients with renal insufficiency (WHO, 2013; Hoen *et al*., 2014).

Data from sub-Saharan Africa on the prevalence of renal dysfunction in HIV-infected patients are sparse and variable, with rates ranging between 6% and 46% (Brennan *et al*., 2011; Emem *et al*., 2008; Han *et al*., 2006; Peters *et al*., 2008; Wools-Kaloustian *et al*., 2007; Msango *et al*., 2011; Reid *et al*., 2008; Odongo *et al*., 2015; Kamkuemah *et al*., 2015). Despite the increased use of TDF in sub-Saharan Africa, following the introduction of the 2010 WHO treatment guidelines (Daisuke *et al*., 2013; RMoH, 2011), few studies have examined the rates of pre-antiretroviral therapy (ART) renal function monitoring (Mulenga *et al*., 2008).

In Rwanda, HIV prevalence is estimated at 3% (RMoH, 2012). Over the last decade the delivery of HIV care has been decentralized from the district hospital level to the health center level, allowing for increased access to HIV testing and treatment services. The country achieved the United Nations ART coverage threshold of 80% by 2009 (WHO *et al*., 2010). More than 90% of patients started on ART were retained in care at 24 months, and 82.7% of patients with viral load testing achieved virologic suppression (Rich *et al*., 2012).

Rwanda HIV treatment guidelines recommend creatinine testing prior to ART initiation, and TDF is contraindicated for patients with creatinine clearance (CrCl) < 50 mL/min. On treatment, monitoring of creatinine is recommended after 1, 3, and 6 months of therapy and then annually (RMoH, 2011). Despite remarkable efforts to improve HIV care in Rwanda, the country still faces infrastructure and human resource challenges similar to other countries in sub-Saharan Africa and thus the level of adherence to these guidelines is unknown. This study evaluated adherence to guidelines regarding renal function baseline assessment and monitoring for HIV-infected adults initiated on TDF-based therapy at rural health centers in Rwanda.

MATERIALS AND METHODS

Study Setting

The study included patients receiving care from outpatient HIV clinics at 23 health centers in two rural districts of Eastern province in Rwanda. These nurse-staffed health centers receive support from a US-based non-governmental organization, Partners In Health/Inshuti Mu Buzima. At the end of 2012, these health centers had 6790 HIV patients enrolled in care, 4603 of whom were on ART. Since 2009, TDF has been a recommended component of two of the four first-line ART regimens, along with lamivudine and a non-nucleoside reverse transcriptase inhibitor (either nevirapine or efavirenz).

Study design and population

This is a retrospective cohort study of ART-naive HIV patients who were initiated on a TDF-based ART regimen between January 1 and December 31, 2012 in 23 health centers. Patients aged≥18 years and started on TDF-based therapy in 2012 were eligible for inclusion. Pregnant women were excluded from the study.

Data source

Electronic medical records (EMR) were used to identify patients for inclusion. After all eligible patients were determined, individual level data were extracted from both patient charts and laboratory registers. Baseline CD4 count, WHO HIV stage, weight, and height were collected. Additionally, data were collected regarding creatinine orders and results at baseline, 1,3, and 6 months.

Analysis and statistics

Creatinine values obtained within 2 weeks prior to ART initiation were considered as baseline values, with follow-up values at 1, 3, and 6 months post treatment accepted if obtained +/-15 days of the scheduled visit. CrCl was calculated using the Cockcroft-Gault equation for patients whose creatinine, age, weight, and sex were available (Cockcroft, 1976). Patients with CrCl < 50 mL/min were categorized as having renal insufficiency. Stata version 12 (College Station, TX: StataCorp LP) was used for analysis.

Ethics

The study used routinely collected data that were anonymized. Ethical approval was granted from the Rwanda National Ethics Committee and Institutional Review Board waivers from Harvard Medical School and Weill Cornell Medical College were also received.

RESULTS

During the study period, 760 patients were started on ART, with 532 initiated on a TDF-based regimen. Of these, 496 patients met the inclusion criteria. The median age was 35 years (IQR:28-42) and the majority of patients were female (65.7%) (Table1). WHO HIV clinical stage was documented in 466 patients (94.0%) and 353 (75.7%) of them were stage 1. CD4 count was documented for 456 patients (92.0%) and 21.9% had CD4 count<200 cells/mm^3 at treatment initiation.

At baseline, 252 (50.8%) patients had creatinine tests ordered by their clinician and creatinine results for 239 (48.2%) patients were reported (Table 2). Subsequently, 339, 347, and 396 patients returned for their 1-, 3-, and 6-month follow-up visits, respectively. Clinicians ordered creatinine tests for 8 patients at 1 month, 16 patients at 3 months, and 37 patients at 6 months of follow-up.

Documentation of the calculated CrCl was low. Of the 239 patients with baseline creatinine results, 3 had their CrCl reported. There were 210 patients with creatinine results, weight, sex, and age documented, which allowed calculation of CrCl. Of the patients started on TDF with sufficient data to calculate CrCl, 24 (11%) had CrCl < 50 mL/min (Table 3).

DISCUSSION

Despite Rwanda's success in expanding and decentralizing HIV care, this study demonstrates difficulties in providing comprehensive guideline-driven HIV management in resource-limited settings. Roughly half of all patients who were started on TDF-based ART had a creatinine ordered before initiating therapy, while 11% of patients with a calculable CrCl had CrCl values at levels that contraindicated TDF use. The etiology of these sub-optimal findings is likely multi-factorial and may include limited provider awareness and understanding, limited laboratory capabilities at treatment sites, and unreliable laboratory services including staffing, material stock or transport of specimen to off-site laboratory facility. Other potential challenges stem specifically from the complexity of CrCl calculation in this setting where HIV care is primarily provided by nurses (Shumbusho *et al*., 2009; O'Brien *et al*., 2008).

Studies on renal function monitoring in national HIV treatment programs in sub-Saharan Africa are sparse and have had variable results, with the percentage of patients who had a baseline creatinine value documented ranging from 32.5% to 71.0% (Mulenga *et al*., 2008; Fawibe *et al*., 2010; By grave *et al*., 2011). Studies on creatinine monitoring in HIV patients in sub-Saharan Africa have taken place in and around urban areas where laboratory facilities may be more accessible (Brennan *et al*., 2011;Kamkuemah*et al*., 2014; Chadwick *et al*., 2015). This study looks at the real-world practice of creatinine monitoring of patients on TDF in resource-constrained rural health centers that provide HIV treatment.

Limitations of our study include possible incomplete documentation of creatinine test results. We attempted to limit this impact by acquiring data from both the patient chart and laboratory database records. A second limitation is the assumption that lack of documented CrCl equates to lack of calculated CrCl. The national HIV clinical charts lacked a space for specifically recording CrCl, and clinicians may have calculated CrCl and used the results for decision making without recording a value. Finally, we did not examine patients not started on TDF, and thus are unable to estimate the frequency at which providers correctly diagnosed renal insufficiency and avoided TDF-based therapy.

CONCLUSION

Adherence to creatinine testing guidelines was less than optimal in our study. While patient safety is paramount, the reality in resource poor settings is that 100% adherence to creatinine testing is not at present achievable given the resource related barriers that exist.

Adherence could potentially be improved by including auto-mated testing reminders in electronic medical records systems (EMR) where they exist. Prompts for creatinine clearance calculation and alerts for renal insufficiency could be beneficial in increasing adherence to guidelines and improving patient safety. A more pragmatic and realistic solution would be to place emphasis on regular training and mentorship of clinicians working in HIV clinics.

This has proved to a valuable approach in scaling up HIV treatment in limited resource settings (Gilks et al, 2006).

Revision of the guidelines to reflect local resources and feasibility would see a reduction in the number of follow up tests required. However, a balance must be sought with patient safety in this instance. Given that the life expectancy of HIV-infected individuals in the antiretroviral therapy era continues to approach that of the general population (Johnson *et al*., 2013; Nsanzimana *et al*., 2015),

Table 1. Patients' Baseline Characteristics.

Variable	Total N=496
Age, median years, (IQR)	35 (28-43)
BMI, mean (SD)	21.2 (3.3)
Gender (n, %)	
Female	326 (65.7)
Male	170 (34.3)
WHO HIV stage (n, %)	n=466
Stage 1	353 (75.7)
Stage 2	68 (14.5)
Stage 3	36 (7.7)
Stage 4	9 (1.9)
CD4cell count (n, %)	n=456
<200 cells/mm^3	100 (21.9)
200-350 cells/mm^3	192 (42.1)
>350 cells/mm^3	164 (35.9)

IQR, Interquartile range; BMI, Body mass index; SD, Standard deviation; WHO, World Health Organization; HIV, Human immunodeficiency virus

Table 2. Renal Function Monitoring during First 6 Months of ART**.**

		Number of patients with documented:		
Clinic visit date	**Total number of patients**	**Creatinine orders**	**Creatinineresults**	**Creatinine clearance**
	N	**n (%)**	**n (%)**	**n**
Baseline	496	252 (50.8)	239 (48.2)	3
1 month	339	8 (2.3)	8 (2.3)	1
3 months	347	16 (4.6)	13 (3.7)	0
6 months	396	37 (9.3)	34 (8.6)	1

the long term effects of antiretroviral therapy need to be considered to provide the highest quality of HIV care and ensure good quality of life as time on treatment lengthens. Finally, newer drugs with less renal toxicity thus requiring less frequent renal monitoring is another possible solution, especially of benefit in resource-limited settings.

Tenofovir alafenamide (TAF), a recently approved antiretroviral by Food and Drug Administration in the United States is a possible TDF replacement that should be evaluated for resource-limited settings in the near future (Sax *et al*., 2015).

Until the introduction of safer antiretroviral therapy, standard

Table 3. Creatinine Clearance (CrCl) at Baseline and Follow-up Visits.

Clinic visit date	Calculable CrCl N	CrCl≥50 mL/min n (%)	CrCl<50 mL/min n (%)
Baseline	210	186 (88.6)	24 (11.4)
1 month	8	7 (87.5)	1 (12.5)
3 months	11	8 (72.8)	3 (27.2)
6 months	32	31 (96.9)	1 (3.1)

systems and treatment algorithms should be in place and more importantly, should be adhered to in so far as is possible, to protect at-risk patients from prolonged exposure to drug toxicity (Jose *et al*., 2014, Barnhart and Shelton, 2015). We have highlighted the extent of adherence to renal function monitoring guidelines and provided suggestions which may help to improve rates of adherence, and ultimately patient safety.

Competing interests

All authors declare that they have no competing interests

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Author's contributions

JCU led the study including the design, data collection, analysis, and manuscript writing. BJE, BLHG and CLA supported the study design, analysis, and manuscript writing. BLHG and CLA also provided mentorship for all aspects of the research and CLA supervised the study. JO supported the data analysis and manuscript writing. AU and EK supported data collection, and manuscript writing. MR, SN and JWN supported study design, manuscript writing, and helped with the interpretation of results for program and policy implications. All authors critically reviewed and approved the final manuscript.

List of Abbreviations

ART: Antiretroviral therapy
CrCl: Creatinine Clearance
EMR: Electronic Medical Records
HIV: Human Immunodeficiency Virus
PIH/IMB: Partners In Health/Inshuti Mu Buzima
RMoH: Rwanda Ministry of Health
TAF: Tenofovir alafenamide
TDF: Tenofovir disoproxil fumarate
WHO: World Health Organization

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