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ANTIRETROVIRAL THERAPY DOSE ADJUSTMENTS BASED ON CALCULATED CREATININE CLEARANCE
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ABSTRACT

Background: Whereas therapy for HIV is dependent on level of creatinine clearance, most laboratories locally only report an absolute creatinine value. There is likelihood that the patients already on antiretroviral therapy (ART) may have required dosage adjustment at the time of initiation of therapy or sometime during ongoing therapy. This paper explores a group of patients who are already on ART to determine their creatinine clearance and assess the need for ART dose adjustment.

Objective: To determine the proportion of stable HIV outpatients who have a documented creatinine clearance (CrCl) and the proportion requiring antiretroviral drug dose adjustments depending on their creatinine clearance.

Design: Retrospective observational study.

Setting: One stop HIV medical clinic, Aga Khan University Hospital, Nairobi between January and February 2007.

Subjects: Ninety three patients seen.

Results: None of the study subjects had a calculated creatinine clearance in their medical records. Fifteen of the 93 patients (16.1%) had no serum creatinine performed in the twelve months preceding the last clinic visit. Nine of the remaining 78 patients (11.5%) had evidence of renal insufficiency (CrCl <60mls/min) as estimated by the Cockcroft Gault method, with six patients (7.7%) requiring dose adjustments to the one or more drugs in their antiretroviral therapy (ART) regime (CrCl <50mls/min).

Conclusion: It is imperative to have a CrCl prior to and during follow up of patients with HIV disease on ART to reduce potential drug toxicities and interactions, especially with the increased utilisation of newer and potentially more nephrotoxic antiretrovirals.

INTRODUCTION

Although the Infectious Disease Society of America (IDSA) recommends measurement of renal function prior to initiation of antiretroviral therapy (ART) (1) and regular screening of renal chemistry while on ART, majority of the patients in resource constrained settings do not conform to these guidelines largely due to financial constraints. Those that attempt to measure renal chemistries, use serum creatinine as an estimation of the renal function. However, serum creatinine alone is not ideal for the measurement of renal function. Many HIV positive patients present late in our set-up. At presentation, these patients usually have weight loss with significant reduction in muscle mass. Serum creatinine is influenced by muscle mass even without a

change in glomerular filtration rate. The current recommendation is that the glomerular filtration rate (GFR), rather than serum creatinine, be used to assess the degree of renal impairment and to follow the course of renal disease.

Several modalities have been utilised in the general population to determine the GFR. A twenty four hour urine collection and subsequent measurement of creatinine clearance (CrCl) was once commonly used. However, attendant problems of accurate urine collection, timing, convenience and cost have relegated this method predominantly to in-patients where this can be supervised. It is now acceptable to estimate creatinine clearance using either Cockcroft Gault or the modification of diet in renal disease (MDRD) formula (2,3). Based on this, most guidelines on ART recommend antiretroviral

dose adjustment based on calculated GFR rather than serum creatinine levels (1-4).

Although highly active antiretroviral therapy (HAART) has revolutionised the treatment of HIV-infected patients, new problems have emerged, such as viral resistance, drug interactions and drug-related adverse effects. This has therefore made ARV drug prescription increasingly complex, predisposing to prescription errors, both in hospitalised patients and the out-patient setting (5-9). In a review of 209 admissions over a one-year period, Rastegar *et al* (7) reported that in 16.7% of hospitalised HIV-infected patients, ARV medication errors were due to incorrect amount or frequency of dosage; over half of these errors were attributable to failure to appropriately adjust dosage for renal insufficiency.

Several antiretroviral medications may have renal adverse events. Conversely, many patients with already impaired renal function have increased incidence of side effects of ART such as neuropathy, lipodystrophy and Fanconi syndrome (1). There have been several case reports of renal failure in patients on tenofovir (10-14), most of whom had normal renal function prior to initiation of ART. This deterioration of renal function is potentially worse in patients who have an impaired baseline creatinine clearance.

Wools-Kaloustian *et al* (15) performed a cross-sectional study in an ARV-naive Kenyan population and found baseline renal insufficiency defined as a CrCl <60mls/min in 11.5% and CrCl <50mls/min in 4.8% of the study population. With an HIV prevalence rate of 7.8% (16) in the Kenyan population of 37 million, over two million would be HIV-infected of whom, close to 300,000 HIV infected patients may have potential baseline renal insufficiency. When these patients are commenced on HAART, close monitoring of their renal function would be required, both prior to and during therapy.

Whereas therapy of HIV is dependent on level of creatinine clearance, most of the laboratories in our country only report creatinine as an absolute value. There is a likelihood that the patients already on ART may have required dosage adjustment at the time of initiation of therapy or sometime during ongoing therapy. This paper explores this group of patients who are already on ART and determine their creatinine clearance thereby determining those whose treatment should have been adjusted.

MATERIALS AND METHODS

One hundred and twenty seven patient records which met criteria for inclusion and excluded thirty four who either were not on ART or had insufficient data on their age, gender and weight.

Analysis was therefore performed for ninety-three patients' records between January and February 2007. Since these patients re-attended the out-patient clinic after February 2007, the last date of appointment in the year 2007 was noted and the following parameters obtained: Age, gender and race; weight at the last appointment date; outpatient serum creatinine in the preceding 12 months of the last review date. We only utilised serum creatinine done as an out-patient since this parameter may change when patients are acutely unwell; ART regime and dosing as per the last review date; last available CD₄ count and plasma viral load within the preceding 12mo.

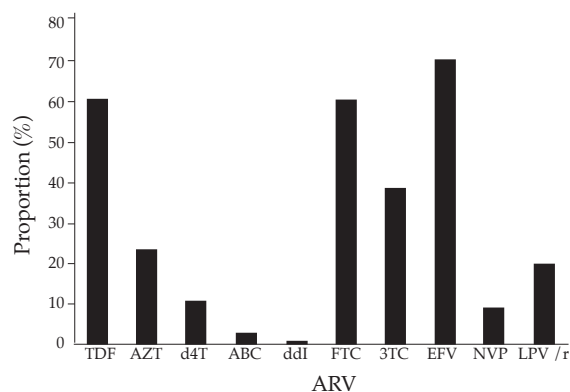
Every eligible patient had a serum creatinine clearance calculated using both the Cockcroft-Gault and simplified MDRD method. Dosing recommendations was utilised as per the guidelines for the use of antiretroviral agents in HIV -infected adults and adolescents (15).

RESULTS

The mean age was 42.8 years (25 - 67 years) and males comprised 61.3% of the study population giving a male: female ratio of 1.6: 1. All our patients were black Africans.

Figure 1

ART use was distributed as follows



TDF = Tenofovir
AZT = Zidovudine
d4T = Stavudine
ABC = Abacavir
ddI = Didanosine
FTC = Emtricitabine
3TC = Lamivudine
EFV = Efavirenz
NVP = Nevirapine
LPV /r = Lopinavir/
Ritonavir

Seventy eight point two per cent of patients had CD₄ counts \geq 200 with the mean CD₄ count of 385 cells/mm³ (2-1304 cells/mm³). On analysis of the plasma viral load data available for 85 (91.4%) patients, 63 (74.1%) patients had undetectable viral loads (<50 copies/ml).

None of the study patients either had a calculated creatinine clearance recorded in

their medical records or had had ART dosages adjusted. Fifteen of the 93 patients evaluated (16.1%) had not had a serum creatinine done in the 12 months preceding the last clinic visit. Of the 78 patients who had data on their serum creatinine, nine (11.5%) had a CrCl <60mls/min and six (7.7%) had a CrCl <50mls/min as per the Cockcroft Gault method while 7.6% and 3.8% had CrCl <60mls/min and <50mls/min respectively, as per the simplified MDRD formula.

DISCUSSION

None of the study patients had a documented calculated creatinine clearance on which their ART dosing was based on. This is not in keeping with the recommendations either from the guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents (17) or the IDSA guidelines (1) which recommend ART dosing based on the CrCl. It is also not in tandem with the WHO guidelines (18) for ARV monitoring in regional referral centres where full serum chemistries have been advocated as opposed to resource-limited settings at primary health care and district levels.

From our study cohort, we also found 7.7% of the patients had a CrCl <50mls/min, reflecting the proportion of patients who require dose adjustment in their ART, mainly in the nucleoside and nucleotide reverse transcriptase inhibitor dosing. Although not our primary aim, it would have been interesting to identify the proportion and nature of adverse events in this cohort of patients who actually had renal insufficiency and required ART dose adjustment. The predominant agents requiring dose modification from our study included: tenofovir, emtricitabine, stavudine and lamivudine. An additional 3.8% of the study patients had a CrCl between 51-60mls/min and will therefore require close monitoring of their renal function. The need for dose adjustment of ART in patients with chronic kidney disease is under-appreciated by physicians offering care to patients with HIV disease.

Over 60% of the patients in our study were on a tenofovir based ARV regime. However, the guidelines for antiretroviral therapy in Kenya (19) recommend the use of either stavudine or zidovudine as the nucleoside backbone. The difference is likely to be due to the simplicity of use and safety profile of tenofovir, hence physician and patient preferences in using this drug.

With increasing use of potentially nephrotoxic antiretrovirals, this calls for physicians taking care of patients with HIV disease to be vigilant in monitoring renal function and calculate the CrCl both prior and during

treatment. It also adds to the growing momentum that CrCl rather than absolute creatinine values be reported by all laboratories to facilitate drug dosing and reduce toxicity profiles due to inadvertent drug overdosing.

The IDSA guideline recommends use of the Cockcroft-Gault formula for calculation of the CrCl to base drug dosing on. In our study, the Cockcroft-Gault formula was able to identify twice as many patients with an estimated CrCl <50mls/min, compared to the modified MDRD method. Due to this superiority and the ease of calculation of the CrCl using the Cockcroft-Gault equation, this should probably be the recommended method in our population. However, this formula has neither been validated in our population nor in patients with HIV disease. Therefore, more local and regional data comparing the calculated methods of creatinine clearance to urinary clearance of exogenous filtration markers is required in patients with HIV disease.

Although not a primary goal of our study, we also noted that none of our patients had routine urinalysis done to test for proteinuria. Proteinuria is one of the presentations of HIV related kidney disease. This would have provided further supporting evidence to identify patients with kidney injury.

In keeping with our study, available local and regional evidence suggest that approximately 11.5% of ARV-naive HIV infected patients have baseline renal insufficiency (CrCl <60mls/min) (15). However, our study demonstrated a higher proportion of patients 7.7% versus 4.8% (5) with hitherto undetected significant renal dysfunction of CrCl <50ml/min requiring dosage adjustment of the ARV prescription. This implies these patients are exposed to higher drug toxicity and nephrotoxic effects of the medication.

In conclusion, the results of this study provides regional evidence, in addition to other loco-regional studies (12), on the estimates of HIV infected patients requiring adjustments to their ARV regime based on their CrCl. It also cautions all treating physicians to calculate an estimated GFR both prior to, and after initiation of ART to ensure appropriate antiretroviral dosage and hence prevent attendant ARV toxicity. In addition, it calls for laboratories to report CrCl using the Cockcroft Gault method rather than absolute creatinine values to facilitate improvement in care for patients with HIV disease.

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