Retrospective Review of ART Regimens in HIV-Positive to HIV-Positive Kidney Transplant Recipients

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Introduction: The management of complex interactions between antiretroviral therapy (ART) and calcineurin inhibitor (CNI) immunosuppression regimens in HIV-positive to HIV-positive renal transplant recipients can be challenging. Literature describing ART regimens and indications for regimen switching in these patients is limited.

Methods: This retrospective review included 53 HIV-positive to HIV-positive renal transplant recipients. Data on ART regimens, reasons for ART switching, and timing of switches were described from day of transplant to study endpoint (end of study date, death, or graft failure). The association between rejection and ART regimen (protease inhibitor [PI] -based vs. non-PI-based regimen) was analyzed using negative binomial regression.

Results: There were a total of 46 switches in 31 of 53 patients (58%). Protocol switches ($n = 17$ of 46, 37%) accounted for most switches, of which the majority were from non-nucleoside reverse transcriptase inhibitors (NNRTIs) to PIs. Other common reasons for switching include cytochrome P450 enzyme induction from efavirenz (EFV) (9 of 46, 20%), tenofovir disoproxil fumarate (TDF) nephrotoxicity (8 of 46, 17%) or side effects (6 of 46, 13%). Of the 46 switches, nearly half ($n = 21$, 46%) occurred during the transplant admission period, and approximately two-thirds ($n = 28$, 62%) were during the first year post-transplantation. There was an association between rejection and being maintained on a PI-based regimen (incidence rate ratio 2.77 (95% confidence interval 1.03–7.48), $P = 0.044$).

Conclusion: Despite frequent switching of ART regimens, HIV viral loads remained supressed and graft function remained stable in most HIV-positive kidney transplant recipients in our cohort. There was however a concerning signal for increased rejection rates in those on a PI-based regimen.

HIV-positive patients with chronic kidney disease were long considered to be poor candidates for organ transplantation. As outlined in Muller *et al.*[1], prior to 2008, South African chronic dialysis programs did not accept HIV-positive patients. At that time, a large number of people with HIV-associated nephropathy and chronic kidney disease had little or no access to kidney replacement therapy. This was in part due to the misconception that immunosuppressing a transplant recipient with an already compromised immune system to prevent rejection would be too risky. It was thought that it would predispose to diseases of over-immunosuppression, including infections and malignancies.[1,2]

In 2008, the first HIV-positive to HIV-positive kidney transplant using deceased donors was performed at the Groote Schuur Hospital. Deceased donors were not required to be on ART, have no history of opportunistic infection or cancer, and have normal renal function.[1] Soon thereafter, this novel transplant program resulted in the acceptance of HIV-positive patients into state dialysis programs in South Africa. The South African Renal Registry (2018) reported that of the 8948 patients receiving kidney replacement therapy, 11% were HIV-positive.[2] Our group and others have shown that HIV *per se* is not a barrier to transplantation and that clinical outcomes are good as long as HIV is controlled on a stable ART regimen.[3–5] The

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entry criteria for HIV-positive patients with chronic kidney disease to be eligible for transplant include HIV viral load suppression on ART, stable HIV disease, and no previous opportunistic disease (besides fully treated tuberculosis).

Another reason for the reluctance to transplant these patients was the complexity of interaction between ART and immunosuppressive medication.[6] There is limited literature on the use of ARTs in HIV-positive kidney transplant recipients who received organs from HIV-positive donors, including the causes that necessitate ART switching. South Africa is a resource-constrained country; therefore in the first 5 years of the study, our protocol included switching patients from NNRTIs to PIs to save cost on immunosuppression. Integrase strand transferase inhibitors are now becoming more widely available; therefore only a few and mainly the more recently transplanted patients are on this class of antiretroviral drugs.

A few studies have found an association between graft loss and rejection, and PI-based regimes.[7–9] CNIs such as tacrolimus are metabolized by cytochrome P-450 3A4 (encoded by the CYP3A4 gene) and are a substrate of P-glycoprotein (encoded by the *ABCB1* gene). Both pathways can be inhibited by PIs.[10] Although combining these drugs allows for a dramatic reduction in the dose of CNIs, this may also paradoxically contribute to subtherapeutic dosing by minimizing the absorption peak even if trough levels are similar to those not on PIs.[11]

The primary aim of this study was to describe ART regimens and reasons for switching in HIV-positive recipients. The secondary aim was to evaluate any associations between ART regimens and rejection over the study period.

METHODS

Patients and Data Collection
Between September 2008 and May 2021, 55 HIV-positve patients were transplanted with kidneys. Data was drawn from the HIV-positive to HIV-positive renal transplant prospective cohort study database hosted by DFexplore (5.4.0, DF/Net Research, Seattle, WA). Data collection was initiated in September 2008 and is ongoing to date. Briefly, HIV-positive patients with chronic kidney disease stage 5 with supressed HIV viral loads on ART and CD4 counts sustained above 200 cells/ul, received kidney transplants from deceased HIV-positive donors, almost all of whom were not on ART at the time of organ procurement. Induction therapy included rabbit antithymocyte globulin and maintenance immunosuppression included mycophenolate mofetil and tacrolimus targeting long term

maintenance trough levels of 6 to 10 ng/ml, regardless of the ART regimen. Additional details on study design and methods can be found in article by Muller *et al* on HIV-postive kidney transplantation.[3]

Inclusion and Exclusion Criteria
Two patients experienced primary graft failure and were excluded from the analysis because they had nephrectomies within 2 days post-transplantation.

ART Regimens and Switch Definitions
ART switches were assigned to categories, including protocol, enzyme induction, nephrotoxicity, side effects, and other.

Protocol Switches
There were 2 main reasons for protocol switches in the study period. The first protocol switch occurred during the early phase of the study. All patients who were not already on a PI-based ART regimen were switched to this regimen as part of the study protocol. This was done in order to utilize the known inhibitory effect of PIs on tacrolimus catabolism in order to reduce costs of immunosuppression post-transplantation.[10] The only PI used during this study period was lopinavir boosted with ritonavir (LPV/r). In 2014, the study protocol was amended in that ART was left unchanged at the time of transplantation due to concerns over safety with the PIs.[12]

The second protocol switch was related to the phasing out of stavudine (d4T) use. Starting in 2010, d4T use was largely phased out in South Africa due to concerns over long-term side effects[13] and alternatives including abacavir and TDF became more widely available to adults.

Nephrotoxicity
Patients with an unexplained, progressive, or sustained rise in creatinine greater than 20% and in whom the allograft biopsy showed acute tubular necrosis without active rejection or any other evident cause for graft dysfunction, were switched away from TDF due to concerns over potential nephrotoxicity. Not all patients with renal impairment had a biopsy-proven diagnosis at time of switching.

NNRTI-Induced CNI Catabolism
EFV is a well-known cytochrome P450 enzyme-inducer.[14] Therefore, patients on EFV usually require a higher dose of tacrolimus due to increased catabolism. Patients were switched from EFV to LPV/r for cost-saving reasons, if they required doses of tacrolimus more than 30 mg per day to reach target tacrolimus levels.

Side Effects
ARTs were switched if a patient developed known short-term or long-term adverse effects on a specific drug.

Other

Reasons for switching that could not be categorized according to the criteria above were included in the "other" category.

For the purposes of the secondary aim of this study, which is to assess the relationship between rejection and ART regimens, ART regimens were grouped into non-PI regimens (combination of NNRTIs and nucleoside reverse transcriptase inhibitors), and PI-based regimens that were maintained from the transplant admission period to end of study. The transplant admission period was defined as the time from the day of transplant to discharge from hospital.

Outcome Definition

All types of biopsy-proven rejection i.e., active T cell-mediated rejection, acute antibody-mediated rejection, chronic and suspicious (borderline) for acute T cell-mediated rejection, were classified using Banff classification of renal allograft pathology (2018).[15] We included borderline (suspicious) for T cell-mediated rejection cases in the rejection category as all borderline rejection cases required treatment adjustment.

Data Analysis

Data was extracted from DFexplore data management software (5.4.0, DF/Net Research). Data was summarized as median with interquartile range for continuous variables, and frequency and percentages for categorical variables. Tacrolimus levels from transplant to end of study were compared by regimen (non-PI−based vs. PI-based) using the Wilcoxon rank-sum test. A negative binomial regression model was generated to analyze the association between rejection episodes and ART regimen maintained from transplant admission period to end of study, and was adjusted for exposure time. Five patients who switched to a PI during late follow-up period (2 due to side effects and 3 due to NNRTI-induced CNI catabolism) were excluded in order to observe the magnitude of association when patients were on a consistent ART regimen. Incidence rate ratios were presented with 95% confidence intervals. All analysis was performed in Stata (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Ethics

The University of Cape Town Human Research Ethics committee granted permission for this study (414/2008), and all the participants provided written informed consent.

Table 1. Baseline demographics and clinical characteristics of recipients at discharge postrenal transplantation

Demographics	Total group $N = 53$
Age (yrs), median (IQR)	41 (34–48)
Male sex, *n* (%)	32 (60%)
Race *n* (%)	
Black African	49 (92%)
Mixed ancestry	4 (8%)
Primary cause of ESRD *n* (%)	
HIVAN (All)	34 (64%)
HIVAN only	22 (42%)
HIVAN & Hypertension	10 (19%)
HIVAN & Glomerulonephritis	2 (4%)
Hypertension	10 (19%)
Glomerulonephritis	6 (11%)
Reflux nephropathy	1 (2%)
ADPKD	1 (2%)
Severe IFTA	1 (2%)
Retransplanted, yes *n* (%)	1 (2%)
CD4 count - cells/ul (*n* = 49), median (IQR)	420 (288–539)

ADPKD, Autosomal dominant polycystic kidney disease; ART, Antiretroviral treatment; ESRD, End-stage renal failure; HIVAN, HIV-associated nephropathy; IFTA, Interstitial fibrosis and tubular atrophy.

RESULTS

Baseline demographics are shown in Table 1. This was a cohort of relatively young, majority African ethnicity kidney transplant recipients, all of whom had an undetectable HIV viral load at the time of transplant. The primary cause of renal failure in most cases was HIV-associated nephropathy.

Baseline ART treatment at admission is shown in Table 2. Most patients were on an NNRTI-based regimen (46 of 53, 86%), which is aligned with national guidelines. Seven patients (13%) were switched to a PI-based regimen at admission as per initial study protocol. Time on ART pretransplantation ranged from

Table 2. ART regimen pretransplant

NNRTI-based	*n* (%)
EFV-based	39/53 (74%)
EFV+ABC+3TC	21 (40%)
EFV+d4T+3TC	8 (15%)
EFV+AZT+3TC	5 (9%)
EFV+TDF+3TC	4 (8%)
EFV+d4T+TDF	1 (2%)
NVP-based	7/53 (13%)
NVP+d4T+3TC	3 (6%)
NVP+AZT+3TC	3 (6%)
NVP+ABC+3TC	1 (2%)
PI-based	7/53 (13%)
LPV/r+TDF+3TC	5 (9%)
LPV/r+ABC+3TC	1 (2%)
LPV/r+AZT+ABC	1 (2%)

ABC, Abacavir; ART, Antiretroviral treatment; AZT, Zidovudine; d4T, Stavudine; EFV, Efavirenz; IQR, interquartile range; 3TC, Lamivudine; LPV/r, Lopinavir/Ritonavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, Nevirapine; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

4 months to 12 years (median 4.2 years, interquartile range 2.5–5.6 years).

Antiretroviral Drug Switches by Indication

There were a total of 46 switches in 31 of 53 (58%) patients (Table 3). In patients who switched, 19 (36%) required 1 switch, 12 (23%) required 2 switches and 1 (2%) required 3 switches. Of the 46 switches, protocol switches ($n = 17$, 37%) accounted for the largest group. Seven patients had early protocol switches during their transplant admission to a PI-based regimen at the time of transplantation. The remaining protocol switches were from d4T or AZT (Zidovudine) to abacavir.

The most frequent nonprotocol reasons for switching was NNRTI-induced CNI catabolism and nephrotoxicity due to TDF. All 6 switches due to ART side effects were due to AZT and EFV. Three recipients received kidney transplants from hepatitis B antigenaemic donors with raised viral load and were switched to TDF at transplant (day 1) as a precaution.

HIV Viral Load

There were isolated HIV viral load blips in 3 patients that resolved within 3 months. One patient experienced recurrent blips 6 years post-transplantation. All HIV viral load blips were investigated and attributed to poor ART adherence. Viral resistance was excluded with deep sequencing methods.[4]

Timing of Switches

Of the 46 switches, nearly half ($n = 21$, 46%) occurred during the transplant admission period, and 28 switches (61%) were during the first year post-transplantation. The frequency of switching over

Table 3. Antiretroviral drug switches by indication[a] during transplantation admission and follow period

Indication for ART switch	Transplant admission period [b] n (%)	Follow up period n (%)	Total switches n (%)	Time to switch (days), Median (IQR)
Protocol switch				
D4T→ABC	1	8	9	
EFV→LPV/r	3		3	
D4T→ LPV/r	3		3	
AZT→ABC	1		1	
NVP→ LPV/r	1		1	
Total	9	8	17 (37%)	7 (1–1244)
NNRTI-induced CNI catabolism				
EFV→ LPV/r	5	3		
EFV→ABC	1	0		
Total	6	3	9 (20%)	9 (5–38)
Nephrotoxicity				
TDF→ABC	2	4	6	
D4T→ABC		1	1	
TDF→3TC		1	1	
TDF→D4T		1	1	
Total	2	7	9 (20%)	273 (28–1269)
Side effects				
Leucopaenia & anemia (AZT→ABC)	1		1	
Leucopaenia & anemia (AZT→D4T)		1	1	
Anemia (AZT→ RTV)		1	1	
Osteoporosis (EFV→ LPV/r)		1	1	
Tinnitus & hearing difficulties (EFV→NVP)		1	1	
HIV encephalopathy secondary to EFV (EFV→ LPV/r)		1	1	
Total	1	5	6 (13%)	131 (16–619)
Other				
Hepatitis B positive donor (NVP→TDF)	2			
Hepatitis B positive donor (ABC→TDF)	1			
Raised hepatitis B viral load (3TC→TDF)		1		
Unknown (ABC→D4T)		1		
Total	3	2	5 (11%)	2 (1–896)
Total switches	21	25	46	

ABC, Abacavir; ART, Antiretroviral treatment; AZT, Zidovudine; D4T, Stavudine; EFV, Efavirenz; IQR, interquartile range; LPV/r, Lopinavir/Ritonavir; NVP, Nevirapine; RTV, Ritonavir; TDF, Tenofovir disoproxil fumarate; 3TC, Lamivudine.
Total column percentages may not equal 100% in some instances due to rounding.
[a]Refer to methods for definitions of indications
[b]Transplant admission period was defined as the day 0 admission for transplant to discharge from hospital.
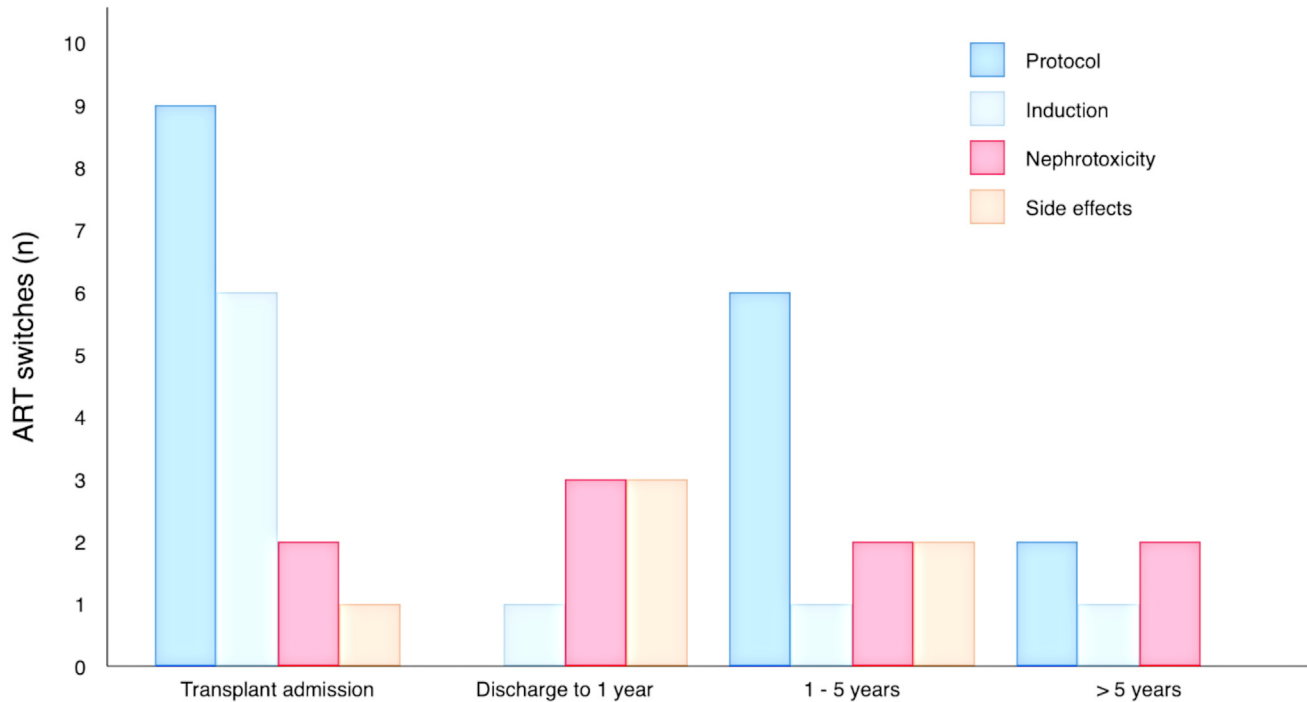
Figure 1. Frequency of switches from transplant by indication and time period.
"Other" category excluded from graphs.
Note: Induction refers to NNRTI-induced CNI catabolism

time by the indication for switching is shown in Figure 1. Most switches during the transplant admission period were protocol switches ($n = 9$) or to account for the effect of liver enzyme induction from EFV ($n = 6$). The later protocol switches were mostly switches to phase out of d4T. Switches from TDF and d4T to abacavir or 3TC (lamivudine) due to nephrotoxicity occurred throughout the time periods. Four of the 6 switches due to side effects were during transplant admission or first year post-transplantation.

Rejection and ART Regimen

A greater number of patients who were maintained on PI-based regimens from transplant admission to end of study experienced rejection or recurrent rejection, compared to those maintained on NNRTI regimes. Of the total of 32 rejection episodes, approximately half were attributed to borderline rejection (15 of 32, 47%) and 17 of 32 (53%) were either active antibody-mediated rejection or acute T cell-mediated rejection.

Twelve patients (63%) maintained on PI-based regimen and 8 patients (28%) maintained on NNRTI-based regimens developed rejection (Table 4). Eight patients in the NNRTI group had 9 episodes of rejection, whereas in the PI group 12 patients experienced 23 episodes. In the regression analysis, there was a positive association between rejection and being maintained on a PI-based regimen incidence rate ratio 2.77 (95% confidence intervals 1.03–7.48).

Tacrolimus Levels

Tacrolimus trough levels from transplant to end of study were compared between PI-based regimen and non-PI based regimens regimes. Both regimens maintained levels within the clinical target range (6–10 ng/ml), however the PI-based regimen (median 8.6 ng/ml, interquartile range (8.0–9.3) was higher than non-PI based regimens (median 7.4 ng/ml, interquartile range 6.4–8.7) ($P = 0.012$).

Table 4. Incidence Rate Ratio for Rejection by ART regimen

All rejection	Patients[a] (*n*)	Patients who had rejection *n* (%)	Total rejection episodes	Adjusted IRR (95% CI)	*P* value
NNRTI regimen[b]	29	8/29 (28%)	9	ref	
PI regimen[c]	19	12/19 (63%)	23	2.77 (1.03–7.48)	0.044
Total	48	20	32		

CI, confidence interval; IRR, Incidence Rate Ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor;
[a]Five patients who switched to a PI in late follow up period (2 due to side effects and 3 NNRTI-induced CNI catabolism) were excluded from this analysis in order to observe the magnitude of association when patients were on a consistent ART regimen from transplant admission.
[b]Patients maintained on NNRTI from transplant admission to end of study.
[c]Patients maintained on PI from transplant admission to end of study.

DISCUSSION

In this cohort of relatively young, majority African HIV-positive kidney transplant recipients, frequent switching of ART was observed during transplant admission and in the first year post-transplantation. Despite this, HIV viral loads remained supressed and graft function remained stable in most of the cohort. Early protocol switches from EFV to LPV/r were the most frequently observed reason for a change in ART, whereas TDF-associated nephrotoxicity accounted for the most frequent reason for nonprotocol switches. NNRTI-induced CNI catabolism that required a switch from EFV to LPV/r occurred more frequently during the transplant admission period. Other reasons for switching were few and heterogenous.

The initial use of PI-based regimens resulted in substantial cost savings due to a reduction in tacrolimus dosing. The cost of CNIs continue to be a major issue in a resource-constrained healthcare system such as South Africa's public health sector. In our experience, concomitant use of a PI and tacrolimus leads to a dose reduction in tacrolimus of over 99% (average tacrolimus dose while on a PI is 0.5 mg/week vs. 10 mg/day for those not on a PI). In patients using NNRTIs, induction of cytochrome P450 3A results in faster catabolism of tacrolimus and increased dose requirements.[10] In view of the high prevalence of *CYP3A5* expression in South African transplant recipients, high tacrolimus dose requirements are often necessary and result in substantially increased immunosuppression costs.[16] Nevertheless, in view of patient safety concerns, the continued mandatory use of PIs was reconsidered in 2014.[12]

TDF has been well described to be associated with tubular nephrotoxicity.[17] Because of the limited availability of tenofovir alafenamide, which has been shown to be less toxic,[18] TDF is still part of first line ART therapy in national guidelines and has been shown to be robust in reducing HIV viral load. For this reason, it remained first line therapy in our HIV transplant cohort until 2014 when abacavir became more widely available.

Suspected nephrotoxicity due to TDF was the most frequent reason for nonprotocol ART switches. PIs containing ritonavir have been shown to influence the risk of TDF-associated nephrotoxicity by increasing exposure to tenofovir through inhibition of apical tubular cell tenofovir transporters.[19,20] When a sustained decline in eGFR was observed in the absence of other known causes, we assumed this to be due to TDF-associated nephrotoxicity and switched away from TDF.

Since AZT has a high side-effect profile,[21] no patients on our study were switched to AZT. Of those who were initially on AZT, all have subsequently been switched to alternatives; 3 were due to bone marrow toxicity.

HIV-positive kidney transplant recipients are at high risk for rejection, but the exact reason for this remains unclear. Possible reasons could include an altered immune response, the effect of the viral reservoir in the transplanted kidney, and drug interactions between immunosuppressive treatments and ART.[22] Recent evidence indicates that PIs may influence graft survival in HIV-positive renal transplant recipients. Sawinski *et al.*[7] reported a 1.8-fold and 1.9-fold increased risk of graft loss and death respectively in 332 HIV-positive kidney transplant recipients in the Scientific Registry of Transplant Recipients database. In a multivariable modified Poisson regression model in that study, there was a trend to a higher risk of acute rejection in those on PIs, although the exact mechanism for poorer outcomes was not clear. Despite the inherent limitations in the interpretation of registry data, calls have been made to eliminate the use of PIs in ART for HIV-positive transplant recipients.[23] One small retrospective study reported higher rejection rates in those on a PI-based regimen.[8] During the study period, tacrolimus levels in the long-term were similar in both groups. Interestingly, another small retrospective study reported lower rejection rates in those on tacrolimus and a PI-based ART regimen.[9] In that study, there were significant baseline differences between the 2 groups and mean tacrolimus levels at 12 months were approximately 40% higher in those receiving PIs. In our study, the use of a PI-based ART regimen was associated with a nearly 3-fold increase in rejection rates. Whereas we targeted the same tacrolimus trough levels in all our patients, we found tacrolimus levels to be higher in those on PI-based regimens compared to NNRTI-based regimens by about 16%. Van Maarseveen *et al.*[11] have shown that in patients on PI-based ART, the lack of 12-hour absorption peaks results in a flat area under the curve and 40% less tacrolimus exposure. This may account for the higher rejection rates seen in our study among those on PI-based ART, where despite higher trough levels, the lack of a postdose peak would still result in less tacrolimus exposure. Fortunately, integrase strand transferase inhibitors such as dolutegravir are now becoming more widely available in South Africa and initial evidence from the use of this class of drugs in HIV-positive transplantation cohorts is encouraging. Importantly, they are not associated with any drug-drug interactions with current immunosuppressive agents and this simplifies the post-transplantation management of such patients.[24]

Four recipients received kidney transplants from hepatitis B antigenaemic donors with raised viral load. All 4 recipients received intravenous hepatitis B immune globulin to maintain titres of more than 200 IU/

ml for a 2-week period. Two of the recipients were immune to hepatitis B at transplantation and never developed any evidence of active hepatitis B infection. The other 2 were hepatitis B nonimmune and developed serological hepatitis B infection following transplantation, but hepatitis B viral loads have remained supressed since transplantation to date and neither patient developed hepatitis *per se*. One patient was already on TDF and the other 3 required a switch to a TDF. All of these patients are still alive and remain hepatitis B surface antigen negative with viral loads that have remained below the detectable threshold.

Our study was limited by small sample size, heterogenous baseline ART regimens which evolved with time, and the lack of supporting immunological data to correlate with the rejection episodes. Nevertheless, the study reports prospectively over a period of 12 years, gives a broad overview of issues experienced with ART in the HIV-positive transplant setting, and is supported by comprehensive biopsy data. Furthermore, there has been no loss of follow-up and only 2 patients were excluded from the analysis because of early graft loss. Based on our preliminary findings in this cohort, further analysis on outcomes in a larger cohort is required to investigate the effect of PIs on rejection and tacrolimus levels.

Despite frequent switching of ART regimens, HIV viral loads remained supressed and graft function remained stable in most HIV-positive kidney transplant recipients in our cohort. Though toxicity did occur, safer alternatives are now available. Clinicians should therefore be reassured that switching ART is a safe strategy when necessary. There was however a concerning signal for increased rejection rates in those on PI-based regimen. Given the increasing availability of newer antiretroviral agents that do not interfere with the pharmacokinetics of CNIs, consideration should be given to avoiding PIs when possible. In the absence of the availability of safe and effective alternative ART treatment, it may be prudent to target higher trough tacrolimus levels in patients on PI-based ART.

DISCLOSURE

ACKNOWLEDGMENTS

TRANSLATIONAL STATEMENT

This study provides reassuring data that despite frequent switching of ART regimens in HIV-positive kidney transplant recipients, viral suppression and graft function remained stable in most patients. There was a concerning signal for increased rejection rates in those on PI-based regimens. Adjusted analysis with inclusion of immunological and additional pharmacokinetic data is required to validate this finding. Newer ART drugs that do not interfere with CNI pharmacokinetics should be preferably used. However, in the absence of the availability of alternative ART treatment, targeting higher trough tacrolimus levels in patients on PI-based ART may be warranted.

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