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Kidney dysfunction does not contribute significantly to antiretroviral therapy (ART) modification in Treatment Naïve PLWH receiving initial ART

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Abstract

Background—Antiretroviral therapy (ART) durability, time to modification or cessation, has declined. The study objective was to determine if kidney dysfunction is contributing to reduced durability.

Methods—This retrospective follow-up study of CNICS evaluated treatment-naive PLWH initiating ART between 2007 and 2014. Regimen modification was defined as cessation/modification of any part of the 3-drug ART regimen. We evaluated the role of kidney dysfunction in initial regimen modification as both a mediator and effect measure modifier. Associations of the variables with the ART modification was examined using univariable and multivariable Cox proportional hazards models.

Results—Out of 4,515 PLWH included in the analysis, 1,967 modified their ART. Of those receiving TDF-based ART (n=3,888), 1,580 (41%) modified their regimen compared with 387 (62%) receiving other regimens. Overall the median eGFR decreased by 5 mL/min/1.73m^2 (Quartiles: 1st= −16, 3rd = 0) from baseline to follow-up. Of the 128 patients with low baseline eGFR (<60 mL/min/1.73m^2), the final eGFR remained low in 73% while it increased to above 60 ml/min/1.73m^2 in 27%. Of the 4,387 with normal baseline eGFR, only 135 (3%) had a final eGFR <60 ml/min/1.73m^2. Those with low eGFR at the baseline and/or final visits were more likely to modify ART than others (HR=1.75, 95% CI: 1.39 – 2.19, p<0.001)). Relative to other regimens,

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TDF-based ART was less likely to be modified when accounting for numerous clinical and demographic traits.

Conclusions—For patients in our study initiated on ART, including TDF-based ART, in the last decade, kidney dysfunction is not a major factor leading to regimen modification.

Background

Since 2007, the number of available single-tablet antiretroviral regimens (ART) regimens has increased from one to five, yet the durability of ART (time to modification or discontinuation) has declined.[1] It remains unclear if durability trends are due to ART simplification and/or subclinical side effects which lead to regimen discontinuation. When it comes to ART, persons living with HIV (PLWH) prioritize kidney health and an avoidance of toxicity.[2] Despite this, a number of commonly- prescribed ART medications are potentially nephrotoxic. In a large multisite cohort, tenofovir disoproxil fumarate (TDF) was prescribed to 87% of treatment naïve PLWH.[1] In another large U.S. cohort, TDF was associated with a 34% increased risk of proteinuria, 11% increased risk of rapid decline ($>=3$ ml/min per 1.73 m^2 annual decline), and 33% increased risk of CKD for each year of exposure.[3] Other common antiretrovirals, including protease inhibitors[4,5] and pharmacoenhancers (e.g., cobicistat),[6] may increase that risk. Specifically, protease inhibitors are independently associated with CKD risk and cobicistat likely just enhances the risk associated with TDF. The objective of this study was to determine if kidney dysfunction contributes to ART modifications, perhaps explaining declining durability observed in recent years.

Methods

This retrospective follow-up study of the CNICS (CFAR Network of Integrated Clinical Systems) cohort integrates data from 8 Center for AIDS Research (CFAR) sites in the U.S.[7] Treatment-naive PLWH initiating 3-drug ART between January 2007 and December 2014 were included if creatinine values were available at ART start and at a subsequent date prior to study end. Regimen modification ("event"), the outcome of interest, was defined as cessation/modification of any part of the 3-drug ART regimen. Simplifications from multi-tablet regimens to single tablet regimens of the same antiretroviral drugs did not meet criteria for modification. Patients without an event were considered to have "continued." ART regimens were categorized based on the presence of TDF. Patients who did not modify ART were censored at their last contact with the health system (e.g. clinic, lab visit); 90 days were added to the duration from that date as prescriptions are routinely given with 3-month supplies. For patients who continued ART and contact with the health system throughout the entire study, administrative censoring occurred between January 2013 and July 2015, depending on data collection at each CNICS site. Glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.[8] Baseline eGFR was identified at ART initiation. A final eGFR most proximate (but within

180 days) to date of ART modification was identified for those with an event and before the censoring date for those who did not modify ART over the study. Kidney dysfunction was defined as eGFR <60 mL/min/1.73m^2. All measures including eGFR, sociodemographic, and laboratory measures were obtained on or up to 180 days prior to the date of interest.

The primary study examining ART durability and its association with various characteristics has been published elsewhere.[1] In this secondary analysis, we evaluated the role of kidney dysfunction (using final eGFR) in initial regimen modification as both a potential mediator and effect measure modifier. Associations of the variables with the ART modification were examined using univariable and multivariable Cox proportional hazards models estimating crude and adjusted hazards ratios (HRs) with 95% confidence intervals (CIs). Proportionality assumption was tested by Schoenfeld residuals. In multivariable analyses with kidney dysfunction as a mediator, the following clinically significant confounders were selected a-priori: baseline (at regimen initiation) values of age, sex, race, viral load, CD4 count, and eGFR. An additional model also included transmission mode (homsexual, heterosexual, IVDU) and initiation era. Due to a common outcome, mediation analysis was conducted using Accelerated Failure Time (exponential) models with boot-strapping (1,000 samples).[9] Effect measure modification of the association between the regimen and modification was examined by stratifying by final eGFR. We categorized eGFR of <60 mL/min/1.73m^2 as "low eGFR" and 60 mL/min/1.73m^2 as "normal eGFR." Due to channeling bias for receiving TDF-based vs other regimens, multivariable models were also examined using propensity score analyses by the inverse probability weighting (based on confounders) method. Analysis was conducted using SAS statistical software, version 9.4 (Cary, NC). Statistical significance was set at 0.05 (two-tailed).

Results

Of an initial 5,373 PLWH in the primary study,[1] the present analysis included 4,515 who had data available for both baseline and final eGFR assessment. Compared with study participants, those excluded (N=858) had similar age, sex, race, CD4, and VL. Overall, 1,967 (44%) modified their ART. A plurality were 30-45 years old (47%), Caucasian (49%), male (84%), and men who have sex with men (MSM)(63%). Most had a CD4 cell count 200 cells (70%) and a pre-treatment viral load <10^4 copies/mL (78%). Most (86%) were receiving a TDF-based ART regimen. Most common regimens were: efavirenz/ emtricitabine/TDF (39%), atazanavir/emtricitabine/ TDF/ritonavir (13%), and elvitegravir/ emtricitabine/ TDF (11%). One percent of those who received TDF had a baseline low eGFR (N=37) relative to 15% of those who received "other" (N=91), indicating channeling bias. There was no difference in the percentage receiving cobicistat in the TDF based (1%) and "other" regimens (1%).

Of those receiving TDF, 1,580 (41%) modified their regimen compared with 387 (62%) receiving "other" (Table 1). The most common "other" regimens among those discontinuing were abacavir/ atazanavir /lamivudine/ritonavir (N=37) and abacavir/efavirenz/lamivudine (N=28). Of the 228 (5%) with final low eGFR, 136 (TDF=82, Other=54) modified their regimen (Table 1). In this study, the median time to modification (Kaplan-Meir survival curve) for TDF-based regimen was 51 months and 18 months for other regimens. Over the

study period, overall the median eGFR reduced by 5 mL/min/1.73m^2; the median (descriptive statistics) follow-up period was 17.9 months (mean=26.0 months). Of the 128 (3%) patients with low baseline eGFR, in 93 (73%) final eGFR remained low while in 35 (27%) it improved to normal; 16/35 were receiving TDF-based ART. Of the 4,387 with normal baseline eGFR, only 135 (3%) had low final eGFR. Most eGFR reductions were small (Supplementary Table 1): only 14/135 (10%) patients transitioned from an eGFR of 60 mL/min/1.73 m^2 to <30 mL/min/1.73 m^2 while the remaining 121 (90%) had small fluctuation between 30-60 mL/min/1.73 m^2.

In univariable analysis, those with a baseline low eGFR were more likely to modify ART (HR=1.75, 95% CI: 1.39 – 2.19, p<0.001) than those with baseline normal eGFR. Similar risk was observed for those with final low eGFR (HR=1.53; 95% CI: 1.28-1.82) (Table 1). TDF-based regimens were significantly less likely to be modified (HR=0.47, 95% CI: 0.42-0.52) relative to "other" regimens. When final eGFR was added (Model 1), the association of regimen remained almost the same indicating that the mediation by kidney dysfunction was negligible (3.84%). Adding multiplicative interaction term of regimen and final eGFR to this model increased the mediation effect to 7.80%; the interaction term was statistically significant (Model 2). However, when confounders were added in multivariable analyses (Models 3 and 4), kidney dysfunction was found to mediate <1% of the effect; the results remained the same when transmission mode and initiation era were added (models not shown). Furthermore, the results of these models remained the same with propensity score analyses (models not shown)

Effect measure modification by kidney dysfunction was observed in the stratified analyses. Within the strata of low final eGFR, no significant difference was observed between the regimens with regard to modification (Crude HR=0.79, 95% CI: 0.56 – 1.12; Adjusted HR=0.99, 95% CI: 0.62 – 1.56) (not shown in table); additional stratification is shown in Supplementary Table 2. However, within the strata of normal final eGFR, those receiving TDF were significantly less likely to modify the regimen as compared to those receiving other regimens (Crude HR=0.45, 95% CI: 0.40 – 0.51; Adjusted HR=0.47, 95% CI: 0.41 – 0.53). This effect modification was further evident when the data were analyzed by combining regimen and final eGFR forming a four-category variable (Table 1, Model 5).

Discussion

In this large, multisite study of treatment naïve PLWH, a majority of patients were initiated on TDF-based ART, but only 5% had kidney dysfunction as defined by a eGFR <60 mL/min/1.73m^2 at the final measurement. Most eGFR reductions were mild, and it was unusual for patients to transition from an eGFR 60 mL/min/1.73 m^2 to <30 mL/min/1.73 m^2. Furthermore, several receiving TDF actually experienced improvements in eGFR. Overall, <1% of the effect (regimen being modified) was mediated through final eGFR. Further, almost one-fourth of participants who initiated ART with an eGFR <60 mL/min/1.73m^2 had improved renal function (60 mL/min/1.73m^2) by the study end including 16 who initiated TDF-based ART. Not surprisingly, those with lower eGFR at baseline and/or final measurement were more likely to modify ART than others. Furthermore, most eGFR fluctuations were small. Relative to other regimens, TDF-based ART was less likely to be

modified when accounting for a range of clinical and demographic traits. We found no evidence that kidney dysfunction significantly contributes to treatment modification.

Among patients with low final eGFR, no significant difference was observed between the regimens with regard to modification. While among those with normal final eGFR, those receiving TDF were significantly less likely to modify the regimen as compared to those receiving other regimens. In other words, although those receiving TDF were less likely to switch regimens, this "protective" effect was not observed for those with low eGFR at follow-up. Thus, kidney dysfunction was not a significant mediator but was an effect modifier. These findings support the notion that many ART changes in recent years, including TDF and non-TDF containing regimens, are related to convenience and simplicity rather than nephrotoxicity and other adverse ART effects.

The results of this study should be considered in light of the following limitations. As the study included those initiating therapy from 2007 to 2014, it does not incorporate the effects of tenofovir alafenamide (TAF) on treatment naïve PLWH. Not surprisingly, TDF was prescribed less commonly in those with baseline kidney dysfunction (channeling bias), minimizing the potential impact of TDF in this important subgroup. However, even with additional analyses using propensity score method, the results remained the same. The CNICS database is a large and robust database, but it does not collect information on reasons for ART discontinuation, making it challenging to identify the myriad reasons for modification: simplification, preference, toxicity, adverse effects, and/or viral failure.[10] It is possible that these reasons in combination with declining eGFR may contribute to ART modifications. Although we specifically analyzed eGFR <60 mL/min/1.73m^2 as a reason for ART discontinuation, it is possible that more subtle changes in creatinine and/or eGFR prompt ART modifications. Although experts recommend that TDF be modified at an eGFR < 50mL/min /1.73m^2, it is likely that many TDF-based regimens are modified earlier with more subtle GFR declines because there are numerous TDF-free regimens available.[11,12] In addition, it is possible that some patients were misclassified by eGFR strata as we included only a single measure of eGFR. Finally, we did not have information on urine protein excretion, which may have been another factor leading to ART modification.

Conclusions

Despite patient concerns,[2] kidney dysfunction likely contributes to a minority of ART modifications in the last decade. Our findings also suggest that patients initiated on ART, including TDF-based ART, in the last decade are unlikely to develop treatment limiting kidney dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.

Descriptive statistics and hazard ratios examining regimen modification in the presence of kidney dysfunction[a] in treatment naïve PLWH, CNICS cohort (2007-2014)

Variable	Descriptive Statistics		Cox proportional hazard analyses						
	Total	Modified	Univariable	Bivariable[b]		Multivariable[c]			
				Model 1	Model 2	Model 3	Model 4	Model 5	
	N	n (%)	Crude HR p-value	Adjusted HR p-value	Adjusted HR p-value	Adjusted HR p-value	Adjusted HR p-value	Adjusted HR p-value	
	N=4,515	N=1,967							
Regimen: TDF	3888	1580 (41)	0.47 (0.42 – 0.52) <0.001	0.48 (0.43 – 0.54) <0.001	0.45 (0.40 – 0.51) <0.001	0.49 (0.44 – 0.55) <0.001	0.47 (0.42 – 0.53) <0.001	-	
Other*	627	387 (62)	Ref.	Ref	Ref.	Ref	Ref.	-	
Final eGFR[a,d]: <60	228	136 (60)	1.53 (1.28 – 1.82) <0.001	1.22 (1.02 – 1.46) 0.03	0.89 (0.67 – 1.18) 0.42	1.19 (0.96 – 1.47) 0.11	0.80 (0.56 – 1.15) 0.22	-	
≥60*	4287	1831 (43)	Ref.	Ref	Ref.	Ref	Ref.	-	
Regimen*Final eGFR[e]	-	-	-	-	1.75 (1.22 – 2.52) 0.003	-	1.76 (1.17 – 2.64) 0.007	-	
Regimen and Final eGFR									
TDF and <60	130	82 (63)	0.70 (0.55 – 0.89) 0.004	--	--	--	--	0.65 (0.51 – 0.83) 0.002	
TDF and ≥60	3758	1498 (40)	0.45 (0.40 – 0.51) <0.001	--	--	--	--	0.47 (0.42 – 0.53) <0.001	
Other and <60	98	54 (55)	0.89 (0.67 – 1.18) 0.42	--	--	--	--	0.78 (0.56 – 1.09) 0.14	
Other and ≥60*	529	333 (63)	Ref.	--	--	--	--	Ref.	
Mediation[f] (%)	--	--	--	3.84	7.80	0.46	0.87	--	

CI=Confidence interval; CNICS=CFAR Network of Integrated Clinical Systems; HR=Hazard ratio; PLWH=People living with HIV; Ref=Reference category; TDF=Tenofovir disoproxil fumarate.

*
Reference category.

[a]
Kidney dysfunction expressed as an estimated Glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation[6] and categorized as <60 vs. ≥60 mL/min/1.73m^2.

[b]
Models 1 and 2: No additional variables than reported in the table.

[c]
Models 3, 4, 5: Also adjusted for confounders: baseline (at regimen initiation) values of GFR at regimen initiation, age, sex, race, viral load (at regimen initiation), and CD4 count (regimen initiation).

[d]
Identified prior (within 180 days) to modifying regimen and the censoring date for those who continued their initial ART regimen over the study period.

[e]Multiplicative interaction term.

[f]Percentage calculated by dividing the "total" effect by "indirect" effect mediated by Final eGFR in the association of regimen and (regimen) modification.