THE IMPACT OF TENOFOVIR DISOPROXIL FUMARATE ON ESTIMATED GLOMERULAR FILTRATION RATE CHANGE AND PROGRESSION TO END-STAGE RENAL DISEASE AMONG HIV-INFECTED ADULTS IN NORTH AMERICA

by
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Abstract

Background: Tenofovir disoproxil fumarate (TDF) was associated with an increased risk of renal toxicity, resulting in proximal tubular dysfunction, proteinuria, and chronic kidney disease (CKD). However, TDF-related nephrotoxicity has not been studied in the context of end-state renal disease (ESRD). We hypothesized that TDF-induced toxicity mainly affected a subset of susceptible HIV-infected patients that led to faster progression to ESRD.

Methods: Data was extracted from 12 clinical cohorts under the North American AIDS Cohort Collaboration for Research and Design study that carried out systematic ESRD validation from January 2000 to December 2009. Piece-wise log-linear mixed effects models were used to compare and contrast estimated glomerular filtration rate (eGFR) trajectories in TDF and other nucleoside reverse transcriptase inhibitor (NRTI) therapy groups. A nested design was employed to identify risk factors associated with increased ESRD risk after TDF exposure.

Results: Among the 19,653 patients, over 20% of high-risk individuals received less than two serum creatinine-based assessments of kidney function per year. For TDF users with baseline eGFR≥90, 60-89.9 and 45-59.9 mL/min/1.73m^2, the annualized eGFR change decreased at -10.1% (p<-0.001), -9.9% (p<-0.001) and -27.2% (p<-0.001), respectively during the first 6 months after therapy initiation. In contrast, eGFR decreased at a slower rate or stabilized among alternative NRTI initiators during this period at rates of -5.9% (p<0.001), 0.7% (p=0.596) and 9.8% (p=0.027) for the same eGFR categories. For patients with baseline eGFR in ranges of 30-44.9 and <30 mL/min/1.73m^2, eGFR change was non-significant at -14.0% (p=0.068) and -9.3% (p=0.617) per year, respectively among TDF initiators, whereas among alternative NRTI users, eGFR declined at -27.7% (p<0.001) and -31.2% (p<0.001) per year. Among TDF-exposed patients, black race was independently associated with 3.4 [95% CI: 1.2-9.6] times higher ESRD risk.

Conclusion: Insufficient screening and monitoring of kidney function remains as an issue for clinical care of kidney diseases among HIV-infected patients. TDF-based therapies are associated with higher ESRD risks. TDF-induced toxicity mainly affects a small subset of susceptible individuals.

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Preface

This thesis is submitted in partial fulfillment of the requirements for the Master of Health Science Degree in epidemiology. It contains work done from September 2014 to April 2015 during the author's master education at Johns Hopkins Bloomberg School of Public Health.

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Introduction

The introduction of highly active retroviral therapy (HAART) in 1996 has dramatically transformed the course of HIV infection (1). Though HAART has significantly alleviated the burden of AIDS-defining illnesses, non-AIDS related conditions like chronic kidney disease have seen an increase in disease prevalence and associated mortality (2-5). HIV-associated nephropathy (HIVAN) was the primary renal complication in the pre-HAART era (6).Viral suppression due to potent combination antiretroviral therapy has reduced the occurrence of HIVAN in the HAART era; further use of HAART is associated with improved kidney function (6-10). Nonetheless, a higher incidence of CKD and other renal disorders continues to be observed in virologically suppressed individuals compared with age-matched general population (11). Aside from the direct role of HIV infection in the risk of kidney dysfunction, many other factors have been demonstrated to influence the development of renal disorders through various mechanisms. Similar to HIV-negative population, HIV-infected patients of older age, female sex and black race are at greater risk of progression to CKD (9, 10, 12, 13). Prevalence of traditional risk factors of kidney diseases (e.g. hypertension, diabetes, chronic hepatitis C coinfection and history of acute kidney injury) are on the rise in an aging population of HIV-infected patients (11), which likely contributes to the increased disease burden of CKD despite the availability of effective antiretroviral therapy (ART) (9, 10, 12-15). The impact of ART on kidney function in HIV-infected population can be double-edged. Though incidence of HIVAN declined dramatically in the post-HAART era, many studies have demonstrated toxicity leading to renal dysfunction in association with the use of HIV medications. Several nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) are excreted primarily through the kidney and have the potential to be nephrotoxic. In addition, longer survival of HIV-infected patients ultimately results in prolonged exposure to HAART, which leads to higher incidence of long-term toxic events such as metabolic disorders, elevated blood

pressures and more severe cardiovascular events (16, 17). Given the above considerations, management of kidney disease in HIV-infected populations remains a complex issue and an area of active research.

Tenofovir disoproxil fumartate (TDF) is a member of the NRTI class of antiretroviral drug (ARV). TDF-containing regimens are the first-line therapy recommended by the US Department of Health and Human Services (DHHS) and the International Antiviral Society-USA for HIV treatment, which makes TDF one of the most widely prescribed ARV drugs in the United States (18, 19). The potential association between TDF and kidney injury has been rigorously researched. Even though TDF-associated renal toxicity was rarely identified in early randomized trials (20, 21), cohort studies have demonstrated an increased risk of proximal tubular dysfunction (22, 23), proteinuria (10, 24) and CKD following TDF exposure (12, 24-26). A meta-analysis of 17 studies found that the use of TDF-containing regimens was associated with a loss of -3.9ml/min in mean calculated creatinine clearance over a median of 48 weeks (27). Drug interactions between TDF and atazanavir (ATV) or a ritonavir-boosted protease inhibitor (rPI) increases drug plasma levels by approximately 20-30% and may result in additive toxicity, which was associated with enhanced loss of kidney function in some but not all studies (8, 28-32).

Glomerular filtration rate (GFR) is a key indicator of kidney function and can be estimated from serum creatinine measurements. Therefore, many studies looked at the temporal trends of estimated GFR change to assess the renal impact of TDF-based therapy. In a small cohort of HIV-infected men who experienced renal impairment after receiving TDF-based ART, the median eGFR decreased by 23 mL/min/1.73m^2 from the baseline level at the time of therapy cessation (33). The Swiss HIV Cohort study also found a modest but persistent decline of median eGFRs within the first two years after initial TDF exposure. eGFR slopes in the pre- and post-exposure periods have been described in several large cohort studies. In the Center for

AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, non-significant change in eGFR slopes was observed after initiating a regimen containing TDF and a non-nucleotide reverse transcriptase inhibitor (NNRTI) in treatment-naïve subjects (8). Significant improvement of eGFR was found in the group that received TDF combined with an rPI (8). Campell et al found that among patients who were diagnosed with CKD, initiation of TDF-containing therapy was associated with 3.7-fold increase in the rate of eGFR decline (34). Fafin et al also identified a dose-response relationship between duration of TDF exposure and decrease in eGFR among HIV-infected patients with CKD (35). Among patients with greater than six months of exposure to TDF who discontinued therapy during observation, an accelerated decline of eGFR (-3.1 mL/min/1.73m^2) was observed during TDF exposure, compared with -0.9 mL/min/1.73m^2 before therapy initiation (36). Loss of kidney function during TDF exposure was not completely reversible in about 40% of patients who discontinued the therapy for any reason (24, 36). Acute decline of eGFR in the early phase of TDF exposure was noted in a few studies (36, 37).

Disagreement over the association between TDF exposure and eGFR outcomes suggested that renal toxic effects of TDF treatment could only affect a subset of HIV-infected population. Additionally, a linear relationship between longitudinal eGFR measurements and time was a convenient assumption adopted in many studies. However, it may be an oversimplified model for describing eGFR patterns of TDF-exposed patients who might experience periods of rapid declines in kidney function. In fact, nonlinear behavior of eGFR change has been discussed in several longitudinal cohorts of HIV-negative individuals, in particular among patients with CKD or at greater risk of renal impairment (38-40). Therefore, using linear models to describe the evolution of eGFR could be a naïve approach that masks distinct eGFR patterns in the heterogeneous HIV-infected populations.

The purpose of this study was to evaluate the eGFR trajectories of HIV-infected adults who initiated TDF-containing regimens and compare them to those of adults who initiated regimens containing alternative NRTIs using a non-linear assumption for eGFR change over time. To fully explore the heterogeneity of eGFR patterns, we stratified this analysis by risk groups determined based on different eGFR thresholds at the time of TDF or alternative NRTI therapy initiation. In addition, to assess the impact of TDF exposure leading to a terminal renal outcome, we examined eGFR changes among individuals who developed incident end-stage renal disease (ESRD). Finally, we used a nested case-control design to address the hypothesis that individuals might respond differently to a TDF exposure. For this, we evaluated the eGFR patterns in TDF-exposed ESRD cases and non-cases to identify risk factors independently associated with faster progression to ESRD.

Methods

Study population

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a multisite collaboration of clinical and interval HIV cohorts from Canada and the United States (41). It contributes HIV patient data from North America to the International Epidemiologic Databases to Evaluate AIDS consortium sponsored by National Institute of Health (41). The study design and characteristics of participating cohorts have been described previously (41). In brief, each participating cohort submits data on demographics, medications, laboratory tests, clinical diagnoses and vital status at scheduled intervals to NA-ACCORD's Central Data Management Core (University of Washington). Quality control is performed before data are combined into summary files for analysis. Review and approval of human subject activities of NA-ACCORD are carried out by local institutional review boards. Twelve clinic-based cohorts carried out systematic verification of ESRD cases using medical record evidence between January 1, 2000 and December 31, 2009. (42) Our study included HIV-infected adults (≥18 years old) who received routine HIV care in these 12 cohorts and initiated a TDF or alternative NRTI-containing therapy between study enrollment on or after January 1, 2000 and study exit on or before December 31, 2009. An alternative NRTI-containing therapy was defined as any HAART regimen containing one or more of the following antiretroviral drugs (ARV): abacavir (ABC), zidovudine (AZT), stavudine (d4T) and didanosine (ddI). Participants from these cohorts who were diagnosed with ESRD prior to study enrollment or had no serum creatinine measurement during observation were excluded from the study.

Study Design

We used two study designs to assess patterns of eGFR change associated with TDF initiation and risk factors associated with rapid decline following TDF initiation:

Prospective Design. To explore post-exposure eGFR patterns, participants were followed from the date of initiation of TDF or alternative NRTI-containing therapy (defined as baseline) to the onset of ESRD, death, cohort-specific end date for ESRD verification, or administrative censoring (December 31, 2009). Negative times from study enrollment to the initiation of TDF or alternative NRTI-containing therapy contributed to the pre-initiation eGFR trajectory estimates. The eGFR trajectories were compared between the two therapy groups without regard for subsequent therapy changes prior to the endpoint. A sub-analysis was conducted only among incident ESRD patients to assess eGFR trajectories leading to a terminal renal event.

Nested Case-Control Design. Among patients who were exposed to TDF, a nested case-control study was conducted to further characterize and contrast pre- and post-exposure eGFR trajectories in individuals who did and did not develop ESRD. For this analysis, only incident ESRD cases who initiated a TDF-based regimen during observation and before the diagnosis of ESRD were included. Two controls were selected without replacement at each event time from patients who were exposed to TDF and remained event-free up to that point. They could, however, become cases later during or after observation. We also matched controls on CKD stage at the time of therapy initiation.

ESRD case validation

A standardized protocol was developed to identify ESRD cases in the NA-ACCORD study. Glomerular filtration rate (GFR) was estimated from serum creatinine level, race and sex using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation (43). Initial screening identified individuals who had two or more consecutive estimated GFR (eGFR) measurements of <30/ml/min/1.73m^2 taken at least 90 days apart. To validate ESRD diagnosis, a complete

review of medical records was performed for each potential ESRD case. The diagnosis was confirmed if evidence was found for 1) hemo- or peritoneal dialysis; 2) kidney transplantation or 3) arteriovenous fistula (AVF) placement with additional evidence of dialysis. Patients on temporary dialysis lasting less than 6 months to treat acute renal failure during hospitalization were not considered ESRD cases. Date of ESRD onset was defined as the earliest confirmed date of dialysis or, when not available, the date of AVF placement (42).

Variable definitions

Initiation of a TDF-based therapy was defined as the first time an individual was placed on a TDF-containing regimen without concomitant use of ABC, AZT, d4T or ddI during observation. Initiation of an alternative NRTI-based therapy was defined as starting a TDF-sparing regimen that contains at least one of following NRTIs: ABC, AZT, d4T and ddI. Individuals who had TDF exposure prior to study enrollment or at any point during observation (between study enrollment and endpoint) were excluded from the alternative NRTI-base therapy group to prevent potential residual TDF exposure effects from influencing results. Self-reported race was collected at the first clinical visit and categorized as Black and non-Black. Baseline CD4+ cell count, HIV RNA level and eGFR were determined using the median value measured within six months of TDF or alternative NRTI initiation. Missing baseline values for these variables were imputed using last observation carried forward. Viral suppression was defined as having a baseline plasma HIV RNA level lower than 400 copies/mL. eGFR categories were determined using the classifications for chronic kidney disease (CKD) from The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline (44). Hypertension was defined as having a clinical diagnosis of hypertension with concomitant use of anti-hypertensive medication. Diabetes was defined as any of the following: taking insulin medication, having a diagnosis of diabetes with concomitant use of hypoglycemic

medication, two random fasting glucose test ≥200 mg/dL or glycated hemoglobin ≥6.5%. Hepatitis C virus seropositive status was determined based on positive HCV antibody assay or detectable HCV RNA level. Current or recent use of ritonavir-boosted protease inhibitors, indinavir, atazanavir and lopinavir were defined as receiving the respective ARV at or within 6 months prior to the initiation of the TDF or NRTI-containing regimen.

Statistical analyses

Statistical analyses included descriptive statistics for demographic and clinical characteristics at the time of TDF or alternative NRTI-containing therapy initiation. Prior exposure to HAART, current or recent use of other antiretroviral drugs, time to therapy discontinuation and time to ESRD diagnosis were calculated and compared for TDF and alternative NRTI therapy initiators. To compare eGFR trajectories before and after therapy initiation in the two treatment groups, we used a piece-wise log-linear mixed effects model with random intercepts and slopes. A knot was positioned at the time of therapy initiation. All available creatinine measurements were used for the analysis. In addition, two spline terms were placed at 6 months and 1 year after the start of therapy to assess and compare the acute (0 to 6 month), delayed (6 month to 1 year) and long-term (>1 year) impact of ART initiation on kidney function.

Analysis of eGFR trajectories was stratified into five groups based on baseline eGFR categories: ≥90, 60-89.9, 45-59.9, 30-44.9 and <30 mL/min/1.73m^2. Covariates that were adjusted for in these models included age, race, CD4+ cell count, HIV RNA level, diagnosis of diabetes, hypertension and hepatitis C co-infection at baseline. Two formal sensitivity analyses were conducted to quantify the degree of emigrative selection bias due to death or ESRD-related early dropouts. In the first one, we excluded patients who had less than one year of follow-up after ART initiation from both treatment groups. We also assessed eGFR change

among those individuals who exited the study within one year from the baseline. A multivariable conditional logistic regression model was used to identify risk factors associated with faster progression to ESRD among TDF-exposed subjects.

Comparisons of baseline demographic and clinical characteristics between the two treatment groups were made using the student t-test for continuous variables and the Pearson's chi-squared test for categorical variables. Wilcoxon signed-rank test was employed to compare characteristics for matched pairs in the nested case control study. All tests were 2-tailed and p-values of 0.05 were used for statistical significance testing. Akaike Information Criterion was used to assess model fit in all analyses. Statistical analyses were performed using Stata/SE 12.0; (StataCorp, College Station, Tx) and R version 3.1.2.

Results

Study population characteristics

A total of 19,653 patients met study inclusion criteria; 13,676 patients initiated a TDF-based regimen without concomitant use of ABC, AZT, d4T or ddI and 5,977 patients initiated an alternative NRTI-containing (ABC, AZT, d4T or ddI) regimen with no known TDF exposure prior to study entry or at any point during observation. The median duration of study follow-up was 5.0 (IQR = 2.8 – 7.4) years for the TDF therapy group and 3.9 (IQR = 2.1 – 6.0) years for the alternative-NRTI therapy group.

The median counts of serum creatinine measurements were 15 (IQR = 8-26) and 11 (IQR = 5-22) for TDF and alternative-NRTI therapy group, respectively. About 25.4% of all patients received less than two creatinine tests per year during observation. In addition, insufficient monitoring of kidney function was found in several high-risk groups. The proportions of patients who did not receive biennial testing of serum creatinine were 24.5%, 20.9%, 20.9%, 21.7% and 28.6%, respectively, for blacks, baseline eGFR <90 mL/min/1.73m^2, concomitant use of ARV drugs with potential nephrotoxicity, CD4+ cell count <200 cells/μL and HIV RNA level >4000 copies/mL.

Patients who initiated a TDF-based regimen were more likely to be non-black ($p<0.001$), virologically suppressed ($p<0.001$) and have higher CD4+ cell count ($p<0.001$) at the time of therapy initiation (Table 1). Regarding the history of ARV exposure, 58.3% TDF therapy initiators were treated with other combination ART for a median of 4.7 (IQR = 2.5-6.8) years before they switched to a TDF-based therapy. Significantly lower proportion of alternative NRTI therapy initiators (44.8%, $p<0.001$) were HAART-experienced for a median of 3.4 (IQR = 1.9-5.3) years before initiating the specific therapies considered for our study. TDF therapy initiators were more likely exposed to an rPI-based HAART compared with other-NRTI therapy initiators (42.9% vs 29.9%, $p<0.001$). The proportions of patients with current or

recent use of atazanavir and lopinavir were, respectively, 36.4% and 23.8% in the TDF therapy group, compared with 16.6% and 21.2% in the alternative NRTI therapy group. Among TDF therapy initiators, 40.4% discontinued therapy within a median of 1.4 (IQR = 0.7-2.9) years compared with 57.9% of alternative NRTI therapy initiators with a median time to discontinuation of 1.2 (IQR = 0.6-2.6) years. The proportions of patients who had traditional risk factors for CKD – diabetes, hypertension and hepatitis C co-infection – were comparable in the two therapy groups (Table 1).

ESRD validation

Among patients included in this study, there were 54 and 106 validated incident ESRD cases from the TDF and other-NRTI therapy groups, respectively. The median time from therapy initiation to ESRD diagnosis were 1.9 (IQR = 0.7-3.3) for TDF initiators and 1.7 (IQR = 0.6-2.7) years for other-NRTI initiators. The median eGFR at the start of therapy were 52.5 and 36.6 mL/min/1.73m^2 for TDF and alternative-NRTI therapy groups, respectively. A significantly higher proportion of the TDF therapy group had normal glomerular function (eGFR≥90 mL/min/1.73m^2) at baseline compared with the control therapy group (26.8% vs 12.1%, p=0.019). The median CD4+ cell counts were 163 (IQR = 66-279) and 229 (IQR=116-340) cells/μL for TDF therapy initiators and other NRTI therapy initiators, respectively. Incident ESRD cases who initiated TDF-containing regimens were more likely to be HAART-experienced relative to the control treatment group (76.8% vs 50.5%, p=0.001). The percentages of patients with current or recent use of atazanavir and lopinavir were also higher among TDF therapy-initiating patients (Table 1).

Pre-exposure eGFR change

Baseline eGFR ≥90 mL/min/1.73m^2: Estimates from the piece-wise log-linear mixed effects model showed that eGFR slopes were approximately flat for these patients during the pre-exposure period, without regard of the regimen types. The rates of eGFR change were not different by therapy groups.

Baseline eGFR <90 mL/min/1.73m^2: Patients with baseline eGFR lower than 90 mL/min/1.73m^2 experienced significant loss of kidney function during this period (Table 2). For patients whose baseline eGFR were in the range of 60-89.9 and 45-59.9 mL/min/1.73m^2, the annual declines in eGFR were significantly faster among patients in the alternative-NRTI group, compared to those in the TDF group. The difference in annualized rate of eGFR decline was 1.3% (p=0.007) and 9.1% (p<0.001) per year, respectively, for these two eGFR strata. The differences in annualized eGFR slopes were not statistically significant by therapy groups in patients whose eGFR were lower than 45 mL/min/1.73m^2 (Table 2).

Incident ESRD: Among patients who developed incident ESRD, the pre-exposure rates of eGFR decline were -24.4% (p<0.001) and -34.2% (p<0.001) per year, respectively, for TDF and alternative NRTI therapy groups.

Acute eGFR change after therapy initiation: 0 to 6 months

Baseline eGFR≥90 mL/min/1.73m^2: The annualized eGFR slope in the first 6 months after therapy initiation was -10.1% and -6.2% in the TDF and alternative NRTI groups, respectively (p<0.001 for both). Compare to the pre-exposure period, both regimen groups had worse eGFR outcomes. However, TDF therapy initiators were more likely to have greater loss of eGFR relative to the pre-initiation period than alternative NRTI initiators (-10.2% vs -6.5%, difference = 3.7%, p <0.001).

Baseline eGFR 45-89.9 mL/min/1.73m^2: For TDF therapy initiators, estimates from piece-wise log-linear mixed effects models indicated an accelerated rate of eGFR decline during this period. The annual loss of eGFR increased from 3.0% to 9.9% (p for difference <0.001) and from 8.0% to 27.2% (p for difference <0.001), respectively, for individuals whose eGFRs were in the range of 60-89.9 and 45-59.9 mL/min/1.73m^2 at therapy initiation.

In contrast, among alternative-NRTI therapy initiators whose baseline eGFR fell in these two strata, we observed stabilization of kidney function during the acute phase. The annualized eGFR change improved from -4.3% to 1.6% (p for difference <0.001) and from -17.1% to 11.5% (p for difference<0.001), respectively, for subjects in baseline eGFR categories 60-89.9 and 45-59.9 mL/min/1.73m^2.

Similar to the eGFR≥90 mL/min/1.73m^2 group, TDF therapy initiators experienced greater loss of kidney function relative to the pre-initiation period than alternative-NRTI therapy initiators in the same eGFR level. For eGFR categories 60-89.9 and 45-59.9 mL/min/1.73m^2, respectively, the decrease in annualized eGFR slope from pre-exposure levels was 12.8% (p<0.001) and 38.7% (p<0.001) greater among TDF users than other NRTI users.

Baseline eGFR<45 mL/min/1.73m^2: Stabilization of eGFR was observed among TDF therapy initiators with moderate to severe (eGFR 30-44.9 mL/min/1.73m^2) and severe (eGFR<30 mL/min/1.73m^2) renal dysfunction during the acute phase (Table 2). The change in eGFR slope from the pre-exposure level was non-significant (-14.0% vs -16.8%, p for difference=0.694) for patients with baseline eGFR 30-44.9 mL/min/1.73m^2, but significant (-9.3% vs -40.5%, p for difference=0.006) for those with baseline eGFR<30 mL/min/1.73m^2.

On the other hand, alternative NRTI users experienced persistent loss of kidney function during this period (Table 2). The annualized eGFR decline occurred at -23.8% and -40.8% (p

<0.001 for both), respectively for the two eGFR strata in descending order.

In general, in the two lower categories, TDF therapy initiators did not experience worse eGFR outcomes than alternative NRTI initiators during the acute phase. In addition, for individuals with eGFR <30 mL/min/1.73m^2, TDF therapy use was associated with 30.9% (p=0.026) greater gain in annualized eGFR change compared to other NRTI-containing regimens.

Incident ESRD: Incident ESRD patients in both TDF and alternative NRTI-based therapy groups experienced greater loss of kidney function during the first 6 months. The annualized eGFR decline was accelerated by 44.1% (p<0.001) and 15.5% (p=0.001) compared to pre-exposure level for TDF and alternative NRTI initiators, respectively. However, the increase in rate of eGFR decline was more significant (p<0.001) among TDF users.

Delayed eGFR change: 6 months to 1 year

Baseline eGFR≥90 mL/min/1.73m^2: Between 6 months and 1 year after therapy initiation, a delayed improvement of kidney function was observed among TDF therapy initiators in this eGFR category. The annual eGFR change was -2.7% (p<0.001), with a gain of 7.4% (p<0.001) in glomerular function relative to the acute phase (0 to 6 months). Similarly among alternative-NRTI therapy users, delayed stabilization of kidney function was observed in patients with eGFR ≥90 mL/min/1.73m^2. The eGFR decline slowed down from -6.2% during the acute phase to -2.3% per year (p for difference=0.002). The gain in annualized eGFR change was 3.5% (p=0.014) greater among TDF initiators.

Baseline eGFR 45-89.9 mL/min/1.73m^2: Similar to patients with baseline eGFR greater than 90 mL/min/1.73m^2, delayed recovery of kidney function was observed in this eGFR range among

TDF users. The annualized eGFR slopes were 1.6% (p=0.001) and 21.3% (p<0.001), respectively, for eGFR categories 60-89.9 and 45-59.9 mL/min/1.73m^2. The gain from the acute phase decline was 11.5% (p<0.001) and 48.5% (p<0.001) per year for the two corresponding eGFR groups. On the other hand, improvement of eGFR was absent for alternative-NRTI therapy initiators whose baseline eGFR were between 45 and 89.9 mL/min/1.73m^2 (Table 1).

In summary, the loss of kidney function was slowed down by a greater extent among TDF therapy initiators between 6 months and 1 year after therapy initiation. The annualized eGFR decline was 14.0% (p<0.001) and 43.4% (p<0.001) less than the acute phase, respectively, among TDF therapy users with baseline eGFR 60-89.9 and 45-59.9 mL/min/1.73m^2 compared to alternative-NRTI therapy users in the same eGFR category. However, this recovery was preceded by an acute eGFR plummeting within the first 6 months of therapy initiation as shown above.

Baseline eGFR <45 mL/min/1.73m^2: In general, a stabilized eGFR change was observed among patients whose baseline eGFR were lower than 45 mL/min/1.73m^2, regardless of the regimen types (Table 2). In addition, the difference in recovery of kidney function between the two treatment groups was not significant for subjects who fell in the 30-44.9 (p=0.308) and <30 mL/min/1.73m^2 (p=0.308) categories.

Incident ESRD: For incident ESRD patients, glomerular function was estimated to be declining at rates of -35.5% (p<0.001) and -19.1% (p=0.029) pear year for patients who initiated a TDF-based and other NRTI-based therapies, respectively, during this period. No significant difference in the rate of recovery from the acute phase was shown in the two treatment groups (TDF therapy users: 33.2% per year; alternative NRTI therapy users: 30.6% per year; p for

difference=0.264). Figure 2 shows the eGFR trajectories for ESRD cases, stratified by treatment groups.

Long-term impact on kidney function: 1 year after therapy initiation

Regardless of treatment groups, falling eGFR levels were observed in all eGFR strata one year after therapy initiation (Table 1). Patients with baseline eGFR greater than 45 mL/min/1.73m^2 had similar rates of eGFR decline (Table 1). Loss of eGFR was more rapid in patients whose eGFR were below 45 mL/min/1.73m^2 at the start of therapy (Table 1). Significance testing was conducted to compare the long-term eGFR slopes to the pre-exposure levels. Compared to the pre-initiation period, faster eGFR decline was found only in patients with normal glomerular function at baseline and the differences in annual eGFR change were -3.0% ($p<0.001$) and -3.1% ($p<0.001$), respectively, for TDF therapy and alternative-NRTI therapy initiators.

Sensitivity analyses

In the first sensitivity analysis, we excluded patients with less than one year of follow-up after therapy initiation. During the acute phase (0 to 6 months), initiation of TDF-containing therapy was associated with accelerated decline of eGFR at rates of -9.6% ($p<0.001$), -8.8% ($p<0.001$) and -15.8% ($p<0.001$) per year, respectively, in eGFR strata ≥90, 60-89.9 and 45-59.9 mL/min/1.73m^2. On the other hand, a non-significant increase in eGFR of 18.8% per year ($p=0.075$) was observed among patients whose baseline eGFR were between 30-44.9 mL/min/1.73m^2. Among those with severely reduced eGFR at baseline, kidney function improved at a rate of 46.7% per year ($p=0.025$). The rates of eGFR change between 6 months and 1 year after therapy initiation were -3.0 % ($p<0.001$), 0.7% ($p=0.465$), 9.7% ($p=0.014$), 2.7% ($p=0.793$) and 3.8% ($p=0.828$) per year for the five eGFR strata in descending order.

Compared with main analyses, no significant difference in eGFR slopes in the long term (>1 year from therapy initiation) was observed in the sensitivity analysis (results not shown).

In addition, we looked at eGFR change, specifically during the acute phase (i.e. 6 months from the baseline), among patients who exited the study within one year from therapy initiation. An accelerated decline in eGFR was observed in all eGFR strata during this period. The annualized rates of eGFR decrease were, in descending order of baseline eGFR levels, 12.0%, 18.5%, 63.7%, 58.3% and 95.6% ($p<0.001$ for all).

Risk factors associated with rapid eGFR decline

Among the 54 incident cases of ESRD who initiated a TDF-based therapy during follow-up, 40 were successfully matched to 80 non-cases selected from the same exposure group using incidence density sampling. Additional matching was conducted for baseline CKD stage. eGFR measurements were fit to two separate piece-wise log-linear mixed effects models for cases and controls. The estimated eGFR trajectories in pre- and post-exposure periods, stratified by case status, are shown in Figure 3. eGFR trajectories for the cases has been described previously. Briefly, persistent decline of eGFR was found throughout the observation window. Accelerated rate of decline occurred between 0 to 6 months (-67.1% per year, $p<0.001$). Among controls, the rate of eGFR decline was 9.9% per year ($p<0.001$) during the pre-exposure period. In contrast to the cases, accelerated loss of eGFR was not observed after the initiation of a TDF-based therapy. The long-term annualized eGFR change was -5.1% ($p=0.006$), improved from the pre-exposure level by 4.8% ($p<0.001$).

Compared with the controls, cases were more likely to be blacks (76.3% vs 38.7%, $p<0.001$), diabetes mellitus (23.7% vs 9.3%, $p=0.049$), lower CD4+ cell count ($p<0.001$) and higher HIV RNA levels ($p<0.001$). In a multivariable conditional logistic regression model that included age, race, hypertension, diabetes mellitus, hepatitis C co-infection, failure in virologic

suppression (HIV RNA >400 copies/mL) and CD4+ cell count, only black race was independently associated with higher risk of ESRD. The odds of faster progression to ESRD was 3.4 (p=0.020) times higher for blacks compared with non-black patients after adjusting for other CKD risk factors (Table 4).

Discussion

In an era of highly active antiretroviral therapy, the risk of HIV-associated nephropathy has been greatly reduced (6-10). Nonetheless, kidney disease remains as a complex and challenging issue for the clinical care of HIV-infected patients. Tenofovir has been associated with increased risk of renal toxicity in many studies. To explore differences in eGFR trajectories before and after TDF-exposure, we used data from a large collaborative cohort of HIV-seropositive patients in routine care from North America. Compared with an alternative NRTI-based therapy, initiation of TDF-based HIV therapy was associated with an acute decline and subsequent recovery of eGFR within the first year of exposure among patients with eGFR greater than 45 mL/min/1.73m^2 at the start of therapy. A reverse relationship between TDF exposure and eGFR change during this period was found in patients whose baseline eGFR were below 30 mL/min/1.73m^2. However, this subgroup analysis could be limited in its power due to the small number of individuals who fell in this category in our study population. In addition, for patients with severely decreased glomerular function, there might be a very short span of time between therapy initiation and the onset of ESRD, an endpoint for our study. The immediate improvement of kidney function might only reflect the benefits of HIV treatment for those with high tolerability to renal toxicity. In all strata of eGFRs, the rate of eGFR decline recovered to the pre-exposure levels one year after therapy initiation regardless of regimen types.

Of the 13,676 subjects who initiated TDF-based regimens during observation, 56 (0.4%) progressed to ESRD. Development of ESRD was observed in a higher proportion (106 subjects, 1.7%) of alterative NRTI-based regimen recipients. Notably, about 80% of incident ESRD patients were blacks, and the proportions were comparably in both regimen-type groups. Among ESRD cases, TDF-based therapy was associated with accelerated eGFR decline throughout the post-exposure observation window after adjusting for potential confounders. To

identify risk factors associated with progression to ESRD, we conducted a nested case-control study among TDF-based therapy treated subjects. Among all traditional and HIV-related risk factors for renal diseases with available data, only black race was independently associated with faster progression to ESRD for individuals with similar eGFR levels at therapy initiation.

Because sicker patients may have been more susceptible to tenfovir-induced nephrotoxicity and, subsequently, experienced a faster decline of eGFR after potential insults to kidney, an emigrative selection bias may result if these individuals dropped out of the analysis early due to ESRD onset or death. In the sensitivity analysis where we excluded all individuals with less than 1 year of follow-up after therapy initiation, accelerated eGFR decline and recovery, albeit with attenuated magnitudes, was still found during the first year after therapy initiation for TDF-based therapy users with baseline eGFR greater than 45 mL/min/1.73m^2, compared with alternative NRTI-based therapy users. In addition, among all patients who exited the study within a year after initiating a TDF-based therapy, we found a greater degree of eGFR decline in the first 6 months after therapy initiation. These sensitivity analyses, in combination, lend some face validity to the pattern of dropping and then recovering function. However, despite the fact that a highly susceptible subset contributed substantially to the estimates of initial decline of eGFR after TDF exposure, an acute loss of kidney function still occurred among those did not immediately go to ESRD or leave the study. This was consistent with two other studies, which reported that most of the loss in eGFR occurred within the first three months and first year of TDF exposure, respectively (36, 37). We also conducted a subgroup analysis of eGFR trajectory by excluding subjects who developed incident ESRD or died during observation (results not shown). Among TDF recipients, no significant change in eGFR slope was observed immediately after therapy initiation and throughout the post-exposure observation period. The difference in eGFR patterns between TDF-based therapy and other NRTI-based therapy users also disappeared. This affirms our hypothesis that only a

subset of HIV-infected population will experience renal toxicity associated with TDF treatment.

The biological pathways underlying TDF-induced nephrotoxicity have not been fully understood. Proximal tubular abnormality is the principal form of TDF-associated kidney damage (45). Polymorphisms in genes encoding drug transport proteins within proximal tubule cells may increase TDF uptake or reduce its elimination, which causes excessive accumulation of drug within proximal renal tubules (46-49). This results in mitochondrial toxicity leading to degenerative changes in the tubular structure (45). A primate model suggested that renal tubule lesions caused by toxic insult might be temporary and reversible (50). However, incomplete reversibility of tenofovir-associated nephrotoxicity was observed in approximately 40% - 60% of TDF-treated subjects in human observational studies (33, 36).

Practice of regular screening for renal impairment, especially in patients exposed to HIV medications with potential nephrotoxicity, facilitates early detection and management of renal abnormalities in patients infected with HIV (51, 52). The IDSA clinical practice guideline for the management of chronic kidney disease in patients infected with HIV recommended biennial testing for proteinuria, glycosuria, serum creatinine and serum phosphorus levels, especially in populations with known risk factors for kidney diseases (51, 52). In our study, over 20% of patients of black race, with baseline eGFR lower than 90 mL/min/1.73m^2, CD4+ cell count lower than 200 cells/μL or HIV RNA level greater than 4000 copies/mL, or with known HCV co-infection received less than two serum creatinine measurements each year. Some of these patients may not be engaged in regular or good-quality HIV care. Our findings of an association between acute eGFR decline after initiation of TDF-containing therapy and severe renal outcomes in a high-risk subpopulation highlight the heterogeneity in susceptibility to drug-induced nephrotoxicity. This also speaks to the importance of frequent monitoring of

kidney function in patients treated with TDF or other drugs with potential nephrotoxicity for preventing and managing drug-related kidney disorders.

Our study benefits from the extensive follow-up of a large population of HIV-positive adults enrolled in multiple clinical sites throughout North America with longitudinal information on serum creatinine levels and treatment. ESRD is a rare clinical outcome and tenofovir-related renal toxicity has not been studied in the context of ESRD (52). In this study, a substantial number of incident ESRD occurred during the ten-year observation, which powered the analysis of GFR trajectories leading to an ESRD event following TDF exposure. The results were strengthened by a thorough validation of ESRD diagnoses using standardized protocols that assured the specificity of case definition. Furthermore, by adopting a piece-wise log-linear mixed effects models, we were able to explore the nonlinear nature of eGFR change and characterize heterogeneity in loss of kidney function following TDF exposure in HIV-infected population.

There are several limitations to our analysis. Firstly, over 50% of patients were treatment-experienced during the pre-initiation period. About 41% had recent or current exposure to boosted PI-based therapy, and more importantly, a substantial number of patients were taking drugs with potential renal toxicity such as atazanavir and lopinavir. The complex history of HAART treatment and possible confounding by other nephrotoxic therapies together complicate the analysis of pre- and post-exposure eGFR patterns. We also cannot exclude the possibility of confounding by indication where individuals at a higher risk of renal disease were prescribed TDF-sparing regimens. Due to the limited scope of variables collected in the study, we were not able to consider nonadherence, HIV drug resistance, compliance with clinical practice for HIV care, clinical and socioeconomic status, smoking, recreational drug use or other factors that might have an impact on kidney function of HIV infected patients. Even though a delayed recovery of kidney function was found between 6 months to 1 year after

therapy initiation, we were not able to associate this change with therapy discontinuation or other contributing factors. A previous study has demonstrated substantial recovery of kidney function in the first three months after discontinuation of TDF-based regimens (36). Thus, a study that takes into account of the impact of therapy discontinuation and duration of therapy exposure on delayed recovery of kidney function is warranted in the future.

In summary, the data from this large prospective study suggest that TDF-based therapies are associated with an acute loss of kidney function and increased risk of ESRD, especially in a small subset of highly susceptible HIV-infected patients. Racial disparity in terms of ESRD risk associated with the use of TDF arises as an issue. Although the initial decline in kidney function following TDF exposure may not alone provide an adequate indication for therapy discontinuation, our findings speak to the importance of more frequent screening and monitoring for early signs of kidney dysfunction in TDF-exposed patients with other ESRD risks. Recognizing the great heterogeneity in ESRD risk has key implications on improving the care and outcomes of kidney diseases in HIV-infected populations.

Table 1. Demographic and clinical characteristics of patients in the North-American AIDS Collaboration Cohort on Research and Design Study who initiated a TDF or an alterantive NRTI-based therapy during observation. Data were presented for all patients and incident ESRD cases.

Characteristics	Overall (n=19,653)	TDF initiators (n=13,676)	NRTI initiators (n=5,977)	Incident ESRD cases	
				TDF initiators (n=56)	NRTI initiators (n=107)
Age, years, median (P_{25}, P_{75})	42.6 (36.5-48.8)	42.9 (36.8-48.9)	42.0 (35.9-48.5)	44.5 (38.8-51.5)	43.5 (38.5-50.8)
Black race, N (%)	6808 (34.6)	4479 (32.8)	2329 (39.0)	44 (78.6)	88 (82.2)
Male, N (%)	15339 (78.0)	10871 (79.5)	4468 (74.8)	43 (76.8)	72 (67.3)
eGFR, mL/min/1.73m^2, median (P_{25}, P_{75})	102.3 (87.8-114.2)	101.8 (88.0-113.2)	103.9 (87.4-116.1)	52.5 (27.9-92.8)	36.6 (19.3-65.3)
eGFR category, mL/min/1.73m^2, N (%)					
≥90	13452 (68.4)	9509 (69.5)	3943 (66.0)	15 (26.8)	13 (12.1)
60-89.9	4588 (23.3)	3336 (24.4)	1252 (20.9)	9 (16.1)	18 (16.8)
45-59.9	440 (2.2)	272 (2.0)	168 (2.8)	10 (17.9)	14 (13.1)
30-44.9	145 (0.7)	72 (0.5)	73 (1.2)	5 (8.9)	10 (9.3)
<30	132 (0.7)	30 (0.2)	102 (1.7)	16 (28.6)	48 (44.9)
CD4+ count, cells/μL, median (P_{25}, P_{75})	294.5 (157.0-460.5)	302.0 (168.0-468.0)	272.0 (128.2-443.0)	163.0 (65.5-279.2)	229.0 (116.0-339.5)
HIV RNA, $\log_{10}$ copies/mL, median (P_{25}, P_{75})	3.1 (1.9-4.6)	3.0 (1.9-4.5)	3.5 (2.0-4.7)	4.3 (2.8-4.9)	4.1 (3.1-4.7)
HIV RNA <400 copies/mL, N (%)	7160 (38.0)	5327 (40.2)	1833 (32.9)	10 (17.9)	14 (13.3)
History of ARV use					
On HAART prior to therapy initiation, N (%)	10656 (54.2)	7977 (58.3)	2679 (44.8)	43 (76.8)	54 (50.5)
Dates of HAART initiation, median (P_{25}, P_{75})	2002.6 (1999.5-2006.0)	2003.4 (1999.5-2006.5)	2001.5 (1999.5-2004.5)	2000.1 (1998.0-2002.8)	2000.6 (1998.2-2003.3)

Time since HAART initiation, years, median (P_{25}, P_{75})	4.3 (2.3-6.5)	4.7 (2.5-6.8)	3.4 (1.9-5.3)	4.5 (3.6-6.0)	3.4 (2.0-5.0)
Current or recent boosted-PI use, N (%)	7655 (39.0)	5867 (42.9)	1788 (29.9)	26 (46.4)	30 (28.0)
Current or recent indinavir use, N (%)	889 (4.5)	497 (3.6)	392 (6.6)	7 (12.5)	5 (4.7)
Current or recent atazanavir use, N (%)	5969 (30.4)	4978 (36.4)	991 (16.6)	28 (50.0)	26 (24.3)
Current or recent lopinavir use, N (%)	4523 (23.0)	3255 (23.8)	1268 (21.2)	27 (48.2)	27 (25.2)
Discontinued therapy during observation, N (%)	8986 (45.7)	5524 (40.4)	3462 (57.9)	22 (39.3)	18 (16.8)
Time to last use of therapy during observation, years, median (P_{25}, P_{75})	2.2 (1.0-4.1)	2.3 (1.1-4.0)	1.9 (0.8-4.2)	1.9 (0.9-4.4)	2.8 (1.6-5.3)
Time to therapy discontinuation, years, median (P_{25}, P_{75})	1.3 (0.6-2.9)	1.4 (0.7-2.9)	1.2 (0.6-2.9)	1.0 (0.2-2.0)	0.5 (0.4-1.8)
Time to ESRD, years, median (P_{25}, P_{75})	1.7 (0.7-3.1)	1.9 (0.7-3.3)	1.7 (0.6-2.7)	1.9 (0.7-3.3)	1.7 (0.6-2.7)
Diabetes, N (%)	1090 (5.5)	724 (5.3)	366 (6.1)	15 (26.8)	17 (15.9)
Hypertension, N (%)	3219 (16.4)	2335 (17.1)	884 (14.8)	27 (48.2)	57 (53.3)
Hepatitis B infection, N (%)	1050 (5.3)	861 (6.3)	189 (3.2)	8 (14.3)	3 (2.8)
Hepatitis C infection, N (%)	3033 (15.4)	2064 (15.1)	969 (16.2)	10 (17.9)	33 (30.8)

Data are available for individuals who initiated a TDF- or alternative NRTI-containing therapy and had at least one serum creatinine measurement during observation.

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; TDF, tenofovir disoproxil fumarate; NRTI, nucleoside reverse transcriptase inhibitor; ARV, antiretroviral drug; PI, protease inhibitor; HAART, highly-active antiretroviral therapy.

Table 2. Expected percent eGFR change per year before initiation of, 0 to 6 months, 6 months to 1 year and 1 year after the initiation of a TDF or an alternative NRTI-based therapy. eGFR changes were presented for each of the five eGFR strata and ESRD cases.

	Time since TDF/NRTI-base therapy initiation							
	Pre-initiation		0 to 6 months		6 months to 1 year		≥1 year after initiation	
Characteristics	**%GFR change**	**P-value**	**%GFR change**	**P-value**	**%GFR change**	**P-value**	**%GFR change**	**P-value**
eGFR≥90								
TDF	0.1	0.566	-10.1	<0.001	-2.7	<0.001	-2.8	<0.001
NRTI	0.3	0.151	-6.2	<0.001	-2.3	0.001	-2.5	<0.001
60≤eGFR<90								
TDF	-3.0	<0.001	-9.9	<0.001	1.6	0.082	-1.9	<0.001
NRTI	-4.3	<0.001	1.6	0.289	-0.9	0.552	-3.4	<0.001
45≤eGFR<60								
TDF	-8.0	<0.001	-27.2	<0.001	21.3	<0.001	-3.4	0.006
NRTI	-17.1	<0.001	11.5	0.015	16.6	0.001	-13.6	<0.001
30≤eGFR<45								
TDF	-16.8	<0.001	-14.0	0.068	24.3	0.021	-12.5	<0.001
NRTI	-11.4	0.001	-23.8	0.001	-11.6	0.178	-18.3	<0.001
eGFR≤30								
TDF	-40.5	<0.001	-9.3	0.617	9.8	0.638	-24.0	0.041
NRTI	-41.1	<0.001	-40.8	<0.001	-19.0	0.138	-46.8	<0.001
ESRD cases								
TDF	-24.4	<0.001	-68.5	<0.001	-35.5	<0.001	-52.5	<0.001
NRTI	-34.2	<0.001	-49.7	<0.001	-19.1	0.029	-60.8	<0.001

Data are estimated from piecewise log-linear mixed effects models.
Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; TDF, tenofovir disoproxil fumarate; NRTI, nucleoside reverse transcriptase inhibitor

Table 3. Expected percentage eGFR change per year during observation for ESRD cases and matched controls

	Time since TDF initiation							
	Pre-initiation		0 to 6 months		6 months to 1 year		≥1 year after initiation	
Case status	**%GFR change**	**P-value**	**%GFR change**	**P-value**	**%GFR change**	**P-value**	**%GFR change**	**P-value**
Case	-25.3	0.003	-67.1	<0.001	-55.9	<0.001	-60.7	<0.001
Change[a]	--	--	-41.8	<0.001	11.2	0.138	-4.8	0.364
Control	-9.9	<0.001	-11.4	0.079	13.5	0.061	-5.1	0.006
Change[a]	--	--	-1.5	0.818	24.9	0.047	-18.6	0.010

[a]Showing the difference in %GFR change per year comparing each period to the previous one. Data are estimated from piecewise log-linear mixed effects models.
Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; TDF, tenofovir disoproxil fumarate.

Table 4. Factors Associated With Faster Progression to ESRD among TDF-exposed patients who were infected with HIV

Variables	**OR (95% CI)**	**P-value**
Age/10 years	0.6 (0.4-1.0)	0.056
Black Race	3.4 (1.2-9.6)	0.020
Diabetes Mellitus	2.0 (0.6-6.8)	0.285
Hypertension	1.8 (0.7-4.9)	0.243
Hepatitis C co-infection	0.8 (0.3-2.6)	0.736
Baseline CD4+ Cell Count <200 cells/μL	1.6 (0.6-4.5)	0.348
Baseline HIV RNA >400 copies/mL	1.2 (0.4-3.3)	0.785

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; TDF, tenofovir disoproxil fumarate; NRTI, nucleoside reverse transcriptase inhibitor; CI, confidence interval.

Figure 1. Flow of patient selection for this analysis.

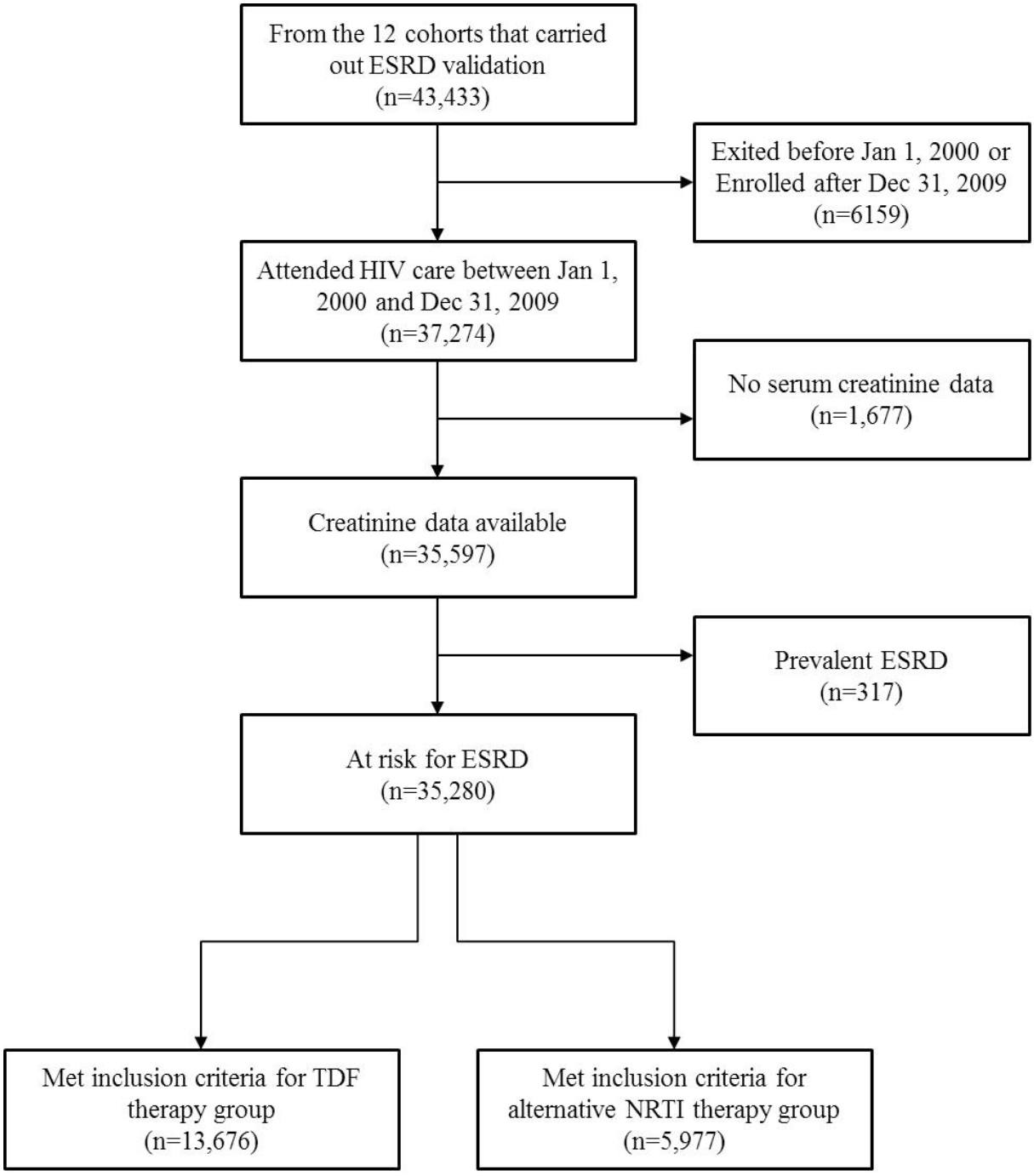


Figure 2. Log(eGFR) change over time estimated from a piecewise log-linear mixed effects model. Orange line represents the group who initiated a TDF-containing therapy at time zero, blue line represents the group who initiated an alternative NRTI-containing therapy at time zero. Shaded areas represent the 95% confidence intervals estimated for each time point.

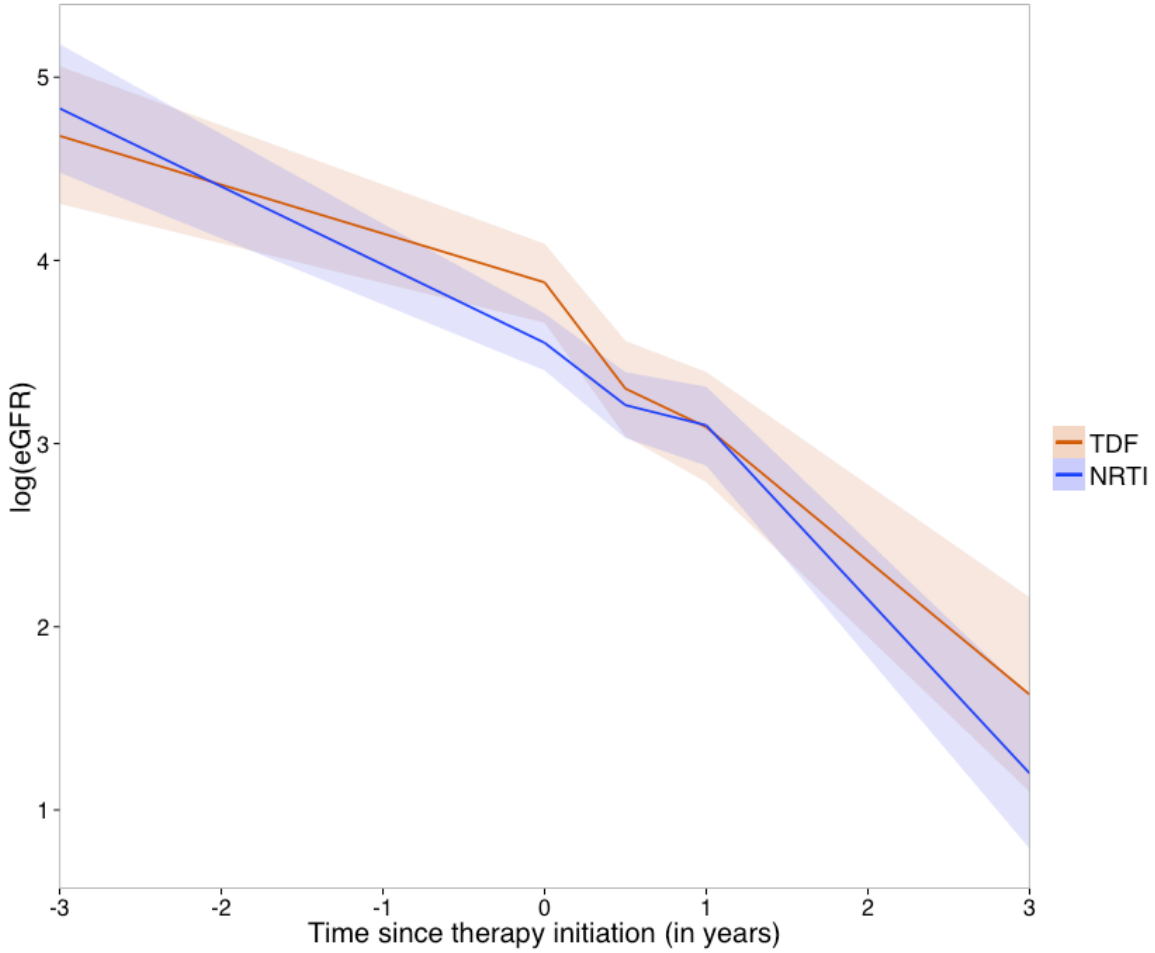
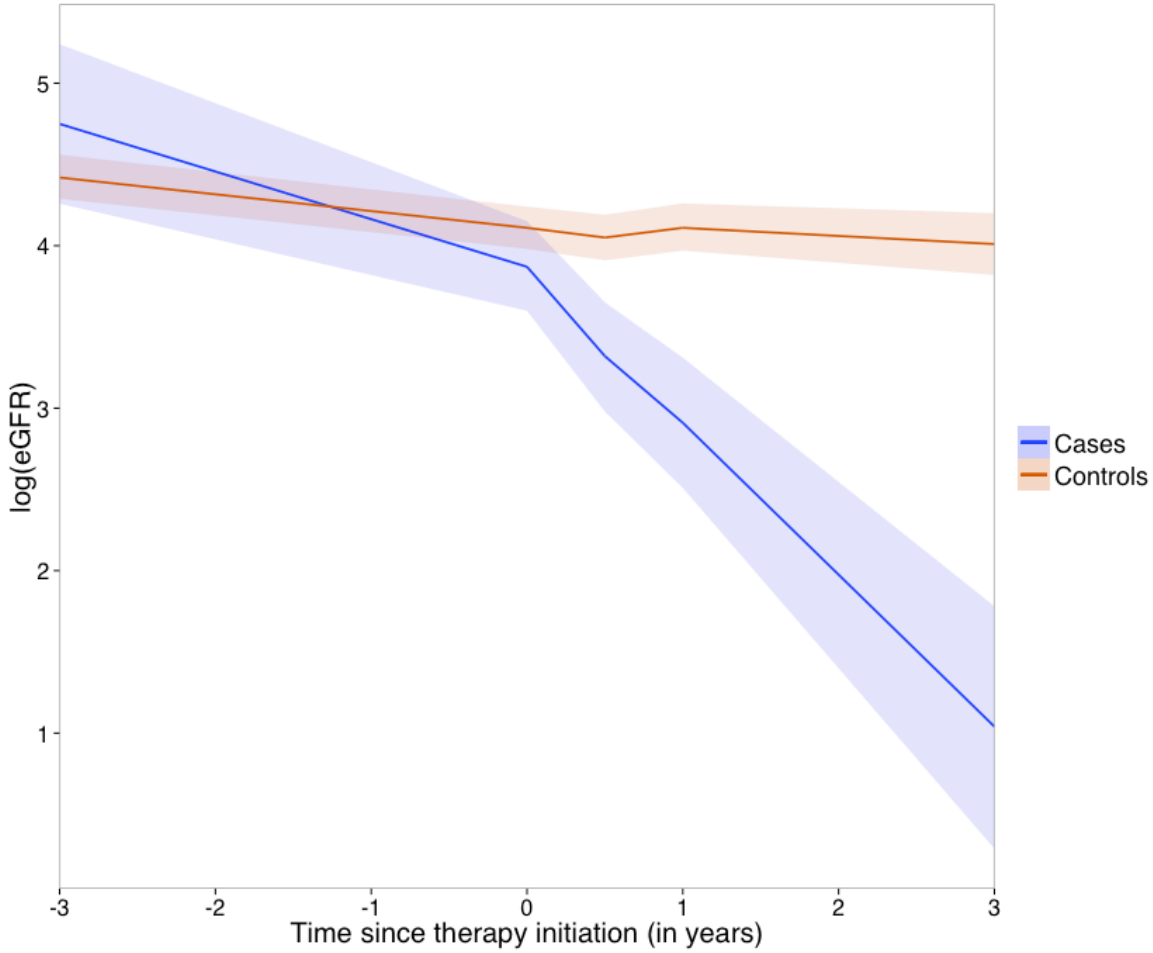


Figure 3. Log(eGFR) change over time for individuals who initiated a TDF-containing therapy at time zero, estimated from a piecewise log-linear mixed effects model. Blue line represents the group who progressed to ESRD after time zero, i.e. cases. Orange line represents the group who did not develop ESRD by the time they were chosen as controls. Shaded areas represent the 95% confidence intervals estimated for each time point.



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PROFILE

Master of Health Science student studying infectious disease epidemiology with a strong focus towards statistical modeling for longitudinal cohort data. Public health professional with strong analytic and programming skills. Additional training in vaccine science and policy. Fluent in English and Chinese.

EDUCATION

Master of Health Science (MHS), GPA: 4.0/4.0 Expected May 2015

Johns Hopkins Bloomberg School of Public Health (JHSPH), Baltimore, MD

Concentration (Track): Infectious disease epidemiology

Relevant Coursework (to be completed by March 2015):

- *Epidemiology core courses:* Epidemiologic Method 1, 2 and 3, Methodologic Challenges in Epidemiologic Research
- *Statistical analysis courses:* Statistical Methods in Public Health I, II, III and IV, Advanced Methods for Design and Analysis of Cohort Studies, Survival Analysis I and II, Causal Inference in Medicine and Public Health I, Analysis of Longitudinal Data
- *Infectious disease courses:* Epidemiologic and Public Health Impact of HIV and AIDS, Advanced Topics On Control and Prevention of HIV/AIDS
- *Programming courses:* STATA programming, Statistical computing
- *Others:* Vaccine science and policy-related courses

Bachelor of Science, Honors (B. Sc. Hons), GPA: 4.62/5.0 May 2013

National University of Singapore

Honors: Dean's List awarded to accolade outstanding academic achievements (2011)

WORK EXPERIENCE

Biostatistician/Programmer Apr. 2015 - present

Center for the Analysis and Management of MACS data (CAMACS), Johns Hopkins Bloomberg School of Public Health

- **Main duties** include processing incoming research data, creation of data files and codebooks according to established protocol, compiling limited data requests, processing repository requests, and performing data analyses.

Research Assistant Mar. 2014 - present

Department of Medicine, The Johns Hopkins University School of Medicine

- **Impact of the Verigene® Gram-Positive Blood Culture Nucleic Acid Test (BC-GP) on patients with Gram-positive bacteremia with and without antimicrobial stewardship team interventions.** Advisor: Sara Cosgrove, M.D., Edina Avdic, Pharm.D.
- Performed data collection (reviewed >1000 medical records in the Johns Hopkins Hospital system), database construction and management, and data analysis.

Teaching Assistant Oct. - Dec. 2014

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

- **Course: Epidemiologic Methods 2.** Course Faculty: Stephan Ehrhardt, M.D., Gypsyamber D'Souza, Ph.D.
- Main duty: conducted ten lab sessions by facilitating in-group discussions and leading class discussions
- Other duties included grading assignments and exams, holding office hours, answering student questions after lectures, assisting in preparation of course materials and piloting exams.

Teaching Assistant Oct. 2013 - Jan. 2014

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

- **Course: Advanced Topics on Control and Prevention of HIV/AIDS.** Course Faculty: Homayoon Farzadegan, Ph.D.
- Main duty: guided student discussions in preparation of in-class presentations
- Other duties included grading student presentations, assisting in preparation of course materials, communicating with guest lecturers and holding office hours.

RESEARCH EXPERIENCE

Graduate-level Thesis Research 2014 - present

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

- **The impact of a tenofovir (TDF)-containing regimen on estimated GFR comparing to an efavirenz (EFV)-containing regimen in HIV-infected population using the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) data**. Advisor: Alison G. Abraham, Ph.D.
- Skills learnt:
    - Data cleaning and management for large datasets
    - Conducting longitudinal data analysis for cohort data

Research project under the Antimicrobial Stewardship Program Mar. - Jul. 2014

Department of Medicine, The Johns Hopkins University School of Medicine

- **Impact of cefepime therapy on survival outcomes for patients with cefepime-susceptible extended-spectrum beta-lactamase (ESBL)-producing enterobacteriaceae bacterial infections.** Advisor: Pranita Tamma, M.D.
- Skills learnt:
    - Data cleaning and management for clinical data
    - Conducting survival analysis
    - Using advanced statistical methods (propensity score and inverse probability weighting) to adjust for confounding

Course project Sep. - Oct. 2014

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

Course: Advanced Methods for Design and Analysis of Cohort Studies

- **Impact of age at HAART initiation on Time to Death and Time to AIDS diagnosis in the Multicenter AIDS Cohort Study (MACS).** Course Faculty: Alvaro Muñoz, Ph.D., Christopher Cox, Ph.D.
- Skills learnt:
    - Conducting survival analysis using semi-parametric and parametric regression models (Gamma, Weibull and Log-normal models)

Undergraduate-level Research Experience Jul. 2012 - Apr. 2013

Department of Biochemistry, National University of Singapore

- **Role of a STAT-regulated novel protein in somatic cell reprogramming.** Advisor: Xin-Yuan Fu, Ph.D

PROFESSIONAL DEVELOPMENT

Language Skills: English (fluent); Chinese (fluent); Japanese (conversational)

Computer Skills: STATA; R; SAS; Microsoft Office Suite.