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Tenofovir exposure alters associations of serum bicarbonate with chronic kidney disease risk in HIV-infected Veterans

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Abstract

Objective—Among HIV-infected persons, tenofovir disoproxil fumarate (TDF) use is associated with higher risk of developing chronic kidney disease (CKD). Because lower serum bicarbonate concentrations may precede CKD onset, this study investigated the associations between TDF use and bicarbonate concentrations, and between bicarbonate with CKD risk among TDF users and non-users.

Methods—Retrospective cohort study of 16,070 HIV-infected US veterans who initiated antiretroviral therapy between 1997–2011. The association between TDF use with longitudinal bicarbonate concentrations and associations between bicarbonate with incident CKD stratified by TDF use (never, initial, and later user) were evaluated.

Results—Compared to TDF users, never users had faster declines in bicarbonate concentrations: change in bicarbonate −0.11 mmol/L/year (95% CI −0.16, −0.05), compared with −0.04 mmol/L/year (−0.06, 0.05) in initial users and −0.02 mmol/L/year (−0.05, 0.01) in later users. Low baseline bicarbonate (<22 mmol/L) was significantly associated with CKD risk among TDF never users (1.80; 1.21, 2.68), but not among TDF users (0.98; 0.69, 1.38). Similarly, declining bicarbonate concentrations were associated with higher CKD risk among never users(HR 1.67 per mmol/L;

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M.S. and J.I. were involved in the design and research question. R.S. was responsible for statistical analyses. All authors were involved in the interpretation of the data and writing and revising the manuscript. All authors have reviewed the final manuscript.

1.34, 2.08), but not among TDF users (1.09; 0.98, 1.22). Interactions were highly significant for both analyses (p-value = 0.001).

Conclusions—Despite associations with nephrotoxicity, TDF use was associated with higher serum bicarbonate concentrations longitudinally. Additionally, TDF use obscured the strong associations of bicarbonate with CKD risk in HIV-infected persons. Therefore, the role of bicarbonate concentrations as a tool to monitor kidney health in HIV-infected persons may be limited in the setting of TDF use.

INTRODUCTION

Due to the widespread use of combination antiretroviral therapy, the overall morbidity and mortality from human immunodeficiency virus (HIV) infection has decreased. However, HIV-infected patients continue to have a high risk of chronic kidney disease (CKD) and end-stage renal disease (ESRD). Factors associated with CKD in the setting of HIV infection include inadequate control of HIV, hepatitis C co-infection, and traditional CKD risk factors such as hypertension and diabetes.(1) In addition, certain antiretroviral medications have been associated with CKD. A growing number of studies implicate tenofovir disoproxil fumarate (TDF), one of the most commonly prescribed and highly effective antiretroviral medications, with a higher risk of CKD relative to other antiretroviral medications.(2, 3) The mechanism of TDF associated renal injury is thought to be due to mitochondrial dysfunction within the proximal tubular cells.(4, 5) Some of the adverse renal effects of TDF may be reversible if TDF is withdrawn early in the course of injury; however, the optimal method to detect TDF kidney damage remains unclear.

Because TDF causes proximal tubule damage out of proportion to damage at other parts of the kidney, there may be opportunities to detect changes in tubular health above and beyond elevations in serum creatinine or changes in proteinuria. One such consequence of TDF use may be metabolic acidosis, as evidenced by low serum bicarbonate concentrations. Metabolic acidosis is a well-established, common complication of CKD(6); low serum bicarbonate concentrations are also associated with CKD progression.(7, 8) Furthermore, we have recently shown that in persons with relatively preserved kidney function, low serum bicarbonate concentrations are associated with the risk of development of CKD as well as a rapid decline in kidney function, independent of baseline estimated glomerular filtration rate (eGFR) or albuminuria.(9, 10) While these findings may indicate that mild metabolic acidosis has a deleterious effect on kidney function, they may also signify that low serum bicarbonate concentrations are a subclinical marker of underlying renal tubular disease that is not detected by creatinine-based eGFR or by glomerular injury (albuminuria). Changes in bicarbonate concentrations may function as one component as a multi-faceted strategy to predict and monitor kidney health in HIV-infect persons.

We are not aware of any large-scale studies that have investigated the association of TDF use with serum bicarbonate concentrations, and whether lower serum bicarbonate concentrations in persons using TDF are associated with more rapid loss of kidney function. We investigated these questions using a national sample of HIV-infected veterans who initiated antiretroviral therapy between 1997 and 2011 with long-term follow-up of changes in kidney

function. We hypothesized that TDF use would be associated longitudinally with lower serum bicarbonate concentrations. In addition, we hypothesized that lower bicarbonate concentrations would be associated with CKD risk in the HIV-infected population and that the association of TDF use with CKD risk would be attenuated, in part, after accounting for changes in serum bicarbonate concentrations.

METHODS

We analyzed kidney disease outcomes in a national sample of HIV-infected US veterans. Data sources used to assemble the cohort have been described elsewhere.(11) In brief, the Department of Veteran Affairs HIV Clinical Case Registry (CCR) actively monitored all HIV-infected person receiving care in the Department of Veterans Affairs nationally and automatically extracted demographic, clinical, laboratory, pharmacy, utilization, and death information from the Department of Veterans Affairs electronic medical record to a centralized database.(12)

Participants

The target population for this analysis was HIV-infected veterans who had no prior exposure to antiretroviral medications at the time they entered clinical care in the Veterans Health Administration (VHA) system, and who subsequently received antiretroviral therapy followed by regular visits and laboratory monitoring. We focused on participants who initiated therapy during or after 1997 when combination antiretroviral therapy became standard of care. The initial visit was defined as the date of starting antiretroviral therapy. Participants were followed until January 1, 2011. We excluded participants with prevalent kidney failure (receipt of chronic dialysis treatment or kidney transplant), and those who did not have at least one plasma HIV RNA value, CD4+ cell count, serum bicarbonate concentration, record of an outpatient visit, and at least two creatinine assessments after the initial visit. We required at least one serum bicarbonate measurement within one year of starting ART. A total of 16,070 HIV-infected veterans were included in the final analytic cohort.

Primary Independent Variables

The two primary independent variables evaluated in this study were TDF use and serum bicarbonate concentrations. TDF use was stratified into three categories: initial users (on TDF as part of their initial treatment regimen), later users (started TDF later in the course of their treatment), and never users. Serum bicarbonate concentrations were measured by standard clinical analyzers at each medical center without storage or freezing. Serum bicarbonate concentrations were analyzed both continuously and categorically, using the following categories in order to span the distribution with adequate resolution for each subgroup: < 22, 22–23.9, 24–26.9, 27–29.9, and ≥30 mmol/L. “Low” serum bicarbonate was defined as < 22mmol/L, as this threshold has been used in prior CKD studies.(7,13)

Longitudinal change was estimated using subject-specific slopes from linear mixed models. We then categorized the annual rate of bicarbonate changes into tertiles, defined as follows:

decrease in bicarbonate, < −0.125mmol/L; stable, −0.125 – 0.085 mmol/L; and increase, > 0.085 mmol/L per year.

Outcomes

The primary study outcomes were serum bicarbonate concentrations (mmol/L) and incident CKD. As a longitudinal outcome, bicarbonate was evaluated both continuously and as a dichotomous outcome, with low serum bicarbonate defined as < 22 mmol/L.(7, 13) We calculated estimated glomerular filtration rate (eGFR) using the Chronic-Kidney Disease Epidemiology Collaboration (CKD-EPI) formula based on age, sex, race, and serum creatinine.(14) CKD was defined by two consecutive eGFR measurements less than 60 ml/min per 1.73 m^2 that were at least 3 months apart and not obtained during inpatient admissions. For the analysis of incident CKD, we excluded persons with eGFR at baseline of less than 60 ml/min/1.73m^2.

Other Measurements

We ascertained drug utilization in CCR medication files based on pharmacy-fill information. Medication exposure was used to define antiretroviral drug predictor variables and to identify individuals with chronic diseases based on validated algorithms.(15, 16) Previous work has demonstrated that VHA pharmacy data are comprehensive and reliable for assessing medication use.(17–21) Use of antiretroviral medications was defined as in previous reports.(15, 17)

Demographic information (age, sex, and race) from CCR was supplemented with Medicare database information. We defined comorbid conditions as described previously.(15) Covariates included diabetes, glucose, systolic blood pressure, hypertension, HDL-cholesterol, LDL-cholesterol, triglycerides, cardiovascular disease (CVD), smoking, body mass index (BMI), ACE-inhibitor use, diuretic use, lung disease, and eGFR. HIV-related characteristics included CD4 T-cell count, HIV RNA load, Hepatitis C or B co-infection, and illicit drug use.(15) Analyses included the baseline values of nearly all covariates; however, CD4 count and HIV RNA load were time-updated as in our prior analyses.(2)

Statistical Analysis

Baseline demographic and clinical characteristics were summarized by categories of baseline serum bicarbonate concentrations.

We used linear mixed models to examine the associations of tenofovir use with longitudinal changes in serum bicarbonate, with random intercepts and slopes using a Toeplitz covariance structure. Interaction terms between tenofovir category and time were used to determine whether the rate of change in bicarbonate differed by category of TDF use (initial, later, or never). Multivariable adjusted models included demographics, traditional CVD risk factors, and HIV-related factors, as listed above.

We then analyzed the association of cumulative antiretroviral medication exposure with risk of a low serum bicarbonate concentration (defined as <22 mmol/L). We used generalized estimating equations (GEE) using a Poisson working model(22) to account for clustering

from repeated events to determine relative risks. Participants with serum bicarbonate < 22mmol/L at baseline were excluded from this analysis. Multivariable adjusted models included the covariates listed previously. In addition, we evaluated antiretroviral agents (ARV) simultaneously in the fully adjusted model using backward stepwise selection analysis to identify antiretroviral medications that were independently associated with low bicarbonate. In sensitivity analysis, models with and without CD4 count and HIV RNA viral load were examined to determine the extent to which HIV disease severity mediated the effects of antiretroviral medications on incident low bicarbonate.

Lastly, we used Cox proportional hazards regression models to evaluate the association of serum bicarbonate concentration with the risk of CKD in those who never used TDF compared with those who used TDF initially or later. Separate models were constructed to compare the associations of baseline and time-updated bicarbonate levels, as well as changes in bicarbonate during follow-up, with risk of incident CKD. Baseline was defined as the time of first exposure to an antiretroviral medication regimen. Bicarbonate was modeled both continuously and categorically, using cut-points listed above. Longitudinal change was estimated using subject-specific slopes from linear mixed models. Change was also categorized as stable, declining, or increasing, using tertiles to define categories. In sensitivity analyses, we evaluated the association of low bicarbonate (<22mmol/L) with risk of incident CKD events within 1 and 2 years, separately among TDF never users and users.

Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). This study was approved by the Committee on Human Research at the San Francisco Veterans Affairs Medical Center.

RESULTS

From 1997 to 2011, there were 16,070 participants, and 5.1% had serum bicarbonate concentrations < 22 mmol/L at the time of study entry. Overall, participants with the lowest serum bicarbonate concentrations were older, more often African-American, and had a higher prevalence of traditional CKD risk factors, lower CD4 counts and higher HIV RNA concentrations, lower eGFR, and a higher prevalence of proteinuria (Table 1). The unadjusted five-year event rates of CKD in TDF never users and TDF users were 7.2% (95% CI: 6.5, 8.0) and 11.4% (95% CI: 10.7, 12.2), respectively. The age-adjusted five-year events rates of CKD in TDF never users and TDF users were 6.0% (95% CI: 5.4, 6.7) and 10.3% (95% CI: 9.6, 11.1), respectively.

We compared the trajectory of bicarbonate concentrations over time among participants who started TDF initially (n=5223, 33%), those who started TDF later (n=6467, 40%), and those who never used TDF (n=4380, 27%) (Figure 1). Compared to initial or later TDF users, those who never used TDF had lower serum bicarbonate concentrations at baseline and had a more rapid decline in serum bicarbonate concentrations over time. Initial and later TDF users had similar serum bicarbonate concentrations at baseline, however initial TDF users maintained stable bicarbonate concentrations during follow-up. By contrast, those who started TDF later had declining bicarbonate concentrations during follow-up, which later stabilized (Supplemental Table 1). In unadjusted analysis, never TDF users had larger

decreases on average in bicarbonate concentrations (−0.11 mmol/L/year; 95% CI: −0.16, −0.05; p=<0.001), while the average annual changes for later TDF users and initial TDF users were −0.02 mmol/L/year (95% CI: −0.05, 0.01; p=0.18) and −0.004 mmol/L/year (95% CI: −0.06, 0.05, p=0.90), respectively.

Antiretroviral agents showed differing associations with risk of low serum bicarbonate concentrations (< 22mmol/L) during follow-up (Table 2). In unadjusted analysis, several ARVs including TDF, emtricitabine, ritonavir, and atazanavir were associated with a lower incidence of low bicarbonate concentrations, while efavirenz and stavudine were associated with a higher incidence. After multivariable adjustment for traditional and HIV-related risk factors, TDF showed the strongest independent association with a lower incidence of low bicarbonate concentrations (5% decreased risk per year of exposure). Lamivudine was also independently associated with a lower incidence of low bicarbonate concentrations, whereas efavirenz and stavudine were associated with higher incidence. When CD4 count and HIV RNA viral load were removed from the adjusted model, the observed protective association of TDF showed no attenuation (RR 0.95, 95% CI: 0.93, 0.97, p < 0.001). Similarly, efavirenz and stavudine associations remained unchanged.

The association of bicarbonate concentrations with the risk of incident CKD was much weaker in TDF users relative to non-users (test for interaction p<0.02) (Table 3). In TDF never users, lower baseline bicarbonate concentrations were associated with a significantly higher risk of incident CKD, even after controlling for traditional CKD risk factors and HIV-related factors. However, in TDF users, the association of baseline bicarbonate concentration with risk of incident CKD was much weaker, and no longer statistically significant after multivariable adjustment. In an analysis of time-updated bicarbonate concentrations, associations of low bicarbonate concentrations with incident CKD were observed in both never TDF users and TDF users, but this effect was significantly stronger in never TDF users (test for interaction p<0.04).

As a sensitivity analysis, we repeated these analyses using baseline bicarbonate concentrations, but restricted follow-up for incident CKD events to one and two years, respectively. For events occurring within one year, a bicarbonate concentration of less than 22mmol/L was associated with a higher risk of incident CKD in never TDF users (unadjusted HR 2.84, 95%CI: 0.90–8.96, p=0.08) but not among TDF users (HR 0.86, 95%CI: 0.42–1.76, p=0.67). Similarly, for incident CKD events within two years, a bicarbonate concentration of less than 22mol/L was associated with a higher risk of incident CKD in never TDF users (unadjusted HR 2.40, 95%CI: 1.18–4.86, p=0.02) but not in TDF users (HR 0.99, 95%CI: 0.60–1.63, p=0.98).

We then analyzed patterns of longitudinal changes in serum bicarbonate with risk of incident CKD (Table 4). Among those who never used TDF, decreases in bicarbonate concentrations over time were strongly associated with increased risk of incident CKD. In fully adjusted models among those who never used TDF, each 1 mmol/L decrease in bicarbonate concentration was associated with a 67% increased risk of CKD. The association was much weaker in TDF users, among whom each 1 mmol/L decrease was associated with only a 9% increased risk of CKD (test for TDF by bicarbonate interaction: p=0.001). When we

examined categories of change, we found that those with stable bicarbonate levels were least likely to develop CKD, whereas those with increasing or decreasing bicarbonate concentrations had higher CKD event rates. In fully adjusted analyses among TDF never users, those with decreasing or increasing bicarbonate had an 81% or 22% increased risk respectively, relative to those with stable levels. In TDF users, those with decreasing or increasing bicarbonate had a 25% or 21% increased risk, respectively.

DISCUSSION

Lower serum bicarbonate concentrations have emerged as a risk factor for CKD in the general population, independent of eGFR or albuminuria. Given the strong association of TDF with development of CKD and its known effects on kidney tubule health, we hypothesized that TDF use would be associated with reductions in bicarbonate concentrations over time. However, in this large, national cohort of HIV-infected persons on antiretroviral therapy, we found that participants using TDF had a *lower* incidence of reduced bicarbonate concentrations compared with those who never used TDF. Furthermore, while lower bicarbonate concentrations were strongly associated with incident CKD in those who never used TDF, we observed substantially weaker associations of bicarbonate concentrations with incident CKD in those using TDF. Although these results run counter to our *a priori* hypothesis, our findings suggest that TDF may alter the tubules' usual handling of bicarbonate in HIV-infected persons.

Metabolic acidosis, as manifested by low serum bicarbonate concentrations, is a common(6) complication of CKD and may contribute to the development of kidney disease. Such reductions in serum bicarbonate levels may trigger a compensatory increase in ammoniagenesis in the tubules, leading to inflammation by complement activation and structural damage to the kidney.(7) In small randomized trials in uninfected persons with CKD, serum bicarbonate supplementation has been shown to slow kidney disease progression.(23) Further study is needed to determine whether bicarbonate could be a modifiable risk factor for CKD onset and progression.

Given that the renal tubule is both the site of TDF toxicity and bicarbonate handling, we expected to find lower serum bicarbonate concentrations in persons using TDF and that low serum bicarbonate would be associated with CKD risk. To our surprise, neither of these hypotheses was confirmed. In contrast, we observed that TDF use was associated with higher bicarbonate concentrations and less decline in bicarbonate over time. Moreover, there was a strong association of low bicarbonate with CKD risk in TDF never users, but this association was much weaker in TDF users. The reasons for these findings are not clear and merits further investigation.

In the past, nucleoside analog reverse-transciptase inhibitors (NRTI) have been associated with type B lactic acidosis. Given this association, one may expect to observe a higher incidence of low bicarbonate concentrations in those on NRTIs as a result of lactic acidosis. However, in our analysis of antiretroviral agents, the NRTIs, except for stavudine, were in fact associated with a lower incidence of low serum bicarbonate concentrations. This finding is consistent with prior studies that have implicated stavudine most strongly with

hyperlactatemia and lactic acidosis.(24) Furthermore, in comparison with other antiretroviral agents, TDF had the lowest incidence of low bicarbonate concentrations. Although the effect size was moderate, this difference highlights the unique impact of TDF on renal physiology.

The major strengths of our study are the large number of HIV-infected participants, the national representation, and the comprehensive capture of medications, comorbid conditions and laboratory values. Our sample size gave us adequate power to detect important effect modification and to determine associations within subgroups. Like nearly all large clinical studies of kidney disease, our study is limited by the inability to directly measure GFR. In addition, our study is not a randomized control trial and our observational cohort was comprised mainly of male veterans receiving regular medical care, which may limit generalization of our findings. Furthermore, while it is established that lower serum bicarbonate concentrations are a manifestation of metabolic acidosis in CKD, low bicarbonate can also represent compensation for a primary respiratory alkalosis. In HIV patients, who are prone to pulmonary and other infections, this compensatory process may be a confounder. Low bicarbonate may also be a manifestation of a pure lactic acidosis. While we cannot distinguish between a pure lactic acidosis and an alternative metabolic acidosis, this, this uncertainty does not alter the strong association between bicarbonate concentration and CKD risk. Lastly, TDF users and nonusers may have had underlying differences not captured by our clinical data. For example, participants with worse kidney function at baseline may have not been prescribed TDF. We aimed to mitigate this possibility by separately evaluating those who were not on TDF at baseline but started TDF later as well as by adjusting for kidney function and CKD risk factors.

In conclusion, in this large cohort of HIV-infected veterans initiating antiretroviral therapy, TDF use was associated with higher serum bicarbonate concentrations longitudinally despite the known nephrotoxic effects of TDF. Furthermore, the strong associations of baseline and changes in bicarbonate with CKD risk in HIV-infected persons are obscured by the use of TDF. As a result, the role of bicarbonate concentration may be limited in optimizing a comprehensive strategy to monitor kidney health in the setting of TDF use in HIV-infected persons. Additional research should be pursued to understand the mechanism by which TDF disrupts the relationship of acidosis with CKD. Such investigation may provide further insight into how both TDF and metabolic acidosis may impair kidney function. Lastly with new antiretroviral therapies in development, including the prodrug tenofovir alafenamide fumarate(25), it will be important to continue to investigate how they affect kidney function and its component processes including acid-base balance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Mallipattu SK, Salem F, Wyatt CM. The changing epidemiology of HIV-related chronic kidney disease in the era of antiretroviral therapy. Kidney Int. 2014; 86:259–265. [PubMed: 24573317]
2. Scherzer R, Estrella M, Li Y, Choi AI, Deeks SG, Grunfeld C, Shlipak MG. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS. 2012; 26:867–875. [PubMed: 22313955]
3. Kalayjian RC, Lau B, Mechekano RN, Crane HM, Rodriguez B, Salata RA, Krishnasami Z, Willig JH, Martin JN, Moore RD, Eron JJ, Kitahata MM. Risk factors for chronic kidney disease in a large cohort of HIV-1 infected individuals initiating antiretroviral therapy in routine care. AIDS. 2012; 26:1907–1915. [PubMed: 22824630]
4. Jafari A, Khalili H, Dashti-Khavidaki S. Tenofovir-induced nephrotoxicity: incidence, mechanism, risk factors, prognosis and proposed agents for prevention. Eur J Clin Pharmacol. 2014; 70:1029–1040. [PubMed: 24958564]
5. Tourret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword? J Am Soc Nephrol. 2013; 24:1519–1527. [PubMed: 24052632]
6. Eustace JA, Astor B, Muntner PM, Ikizler TA, Coresh J. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. Kidney Int. 2004; 65:1031–1040. [PubMed: 14871424]
7. Dobre M, Yang W, Chen J, Drawz P, Hamm LL, Horwitz E, Hostetter T, Jaar B, Lora CM, Nessel L, Ojo A, Scialla J, Steigerwalt S, Teal V, Wolf M, Rahman M, Investigators C. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the Chronic Renal Insufficiency Cohort (CRIC) study. Am J Kidney Dis. 2013; 62:670–678. [PubMed: 23489677]
8. Raphael KL, Wei G, Baird BC, Greene T, Beddhu S. Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. Kidney Int. 2011; 79:356–362. [PubMed: 20962743]
9. Driver TH, Shlipak MG, Katz R, Goldenstein L, Sarnak MJ, Hoofnagle AN, Siscovick DS, Kestenbaum B, de Boer IH, Ix JH. Low serum bicarbonate and kidney function decline: the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Kidney Dis. 2014; 64:534–541. [PubMed: 24953891]
10. Goldenstein L, Driver TH, Fried LF, Rifkin DE, Patel KV, Yenchek RH, Harris TB, Kritchevsky SB, Newman AB, Sarnak MJ, Shlipak MG, Ix JH, Investigators HAS. Serum bicarbonate concentrations and kidney disease progression in community-living elders: the Health, Aging, and Body Composition (Health ABC) Study. Am J Kidney Dis. 2014; 64:542–549. [PubMed: 24953890]
11. Choi AI, Li Y, Deeks SG, Grunfeld C, Volberding PA, Shlipak MG. Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons. Circulation. 2010; 121:651–658. [PubMed: 20100969]
12. Backus LI, Gavrilov S, Loomis TP, Halloran JP, Phillips BR, Belperio PS, Mole LA. Clinical Case Registries: simultaneous local and national disease registries for population quality management. J Am Med Inform Assoc. 2009; 16:775–783. [PubMed: 19717794]
13. Shah SN, Abramowitz M, Hostetter TH, Melamed ML. Serum bicarbonate levels and the progression of kidney disease: a cohort study. Am J Kidney Dis. 2009; 54:270–277. [PubMed: 19394734]
14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, Collaboration) C-ECKDE. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604–612. [PubMed: 19414839]

15. Choi AI, Vittinghoff E, Deeks SG, Weekley CC, Li Y, Shlipak MG. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. AIDS. 2011; 25:1289–1298. [PubMed: 21516027]
16. Scherzer R, Gandhi M, Estrella MM, Tien PC, Deeks SG, Grunfeld C, Peralta CA, Shlipak MG. A chronic kidney disease risk score to determine tenofovir safety in a prospective cohort of HIV-positive male veterans. AIDS. 2014; 28:1289–1295. [PubMed: 24922479]
17. Choi AI, Rodriguez RA, Bacchetti P, Volberding PA, Havlir D, Bertenthal D, Bostrom A, O'Hare AM. Low rates of antiretroviral therapy among HIV-infected patients with chronic kidney disease. Clin Infect Dis. 2007; 45:1633–1639. [PubMed: 18190326]
18. Justice AC, Dombrowski E, Conigliaro J, Fultz SL, Gibson D, Madenwald T, Goulet J, Simberkoff M, Butt AA, Rimland D, Rodriguez-Barradas MC, Gibert CL, Oursler KA, Brown S, Leaf DA, Goetz MB, Bryant K. Veterans Aging Cohort Study (VACS): Overview and description. Med Care. 2006; 44:S13–24. [PubMed: 16849964]
19. Office USGA. Veterans healthcare: use of VA services by Medicare-eligible veterans GAO Report. Washington: DUSGAO; 1994.
20. Shen Y, Hendricks A, Zhang S, Kazis LE. VHA enrollees' health care coverage and use of care. Med Care Res Rev. 2003; 60:253–267. [PubMed: 12800686]
21. Wagner JH, Justice AC, Chesney M, Sinclair G, Weissman S, Rodriguez-Barradas M, Team VP. Patient- and provider-reported adherence: toward a clinically useful approach to measuring antiretroviral adherence. J Clin Epidemiol. 2001; 54(Suppl 1):S91–98. [PubMed: 11750214]
22. Lumley T, Kronmal R, Shuangge M. Relative Risk Regression in Medical Research: Models, Contrasts, Estimators, and Algorithms. UW Biostatistics Working Paper Series. 2006
23. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol. 2009; 20:2075–2084. [PubMed: 19608703]
24. Calza L, Manfredi R, Chiodo F. Hyperlactataemia and lactic acidosis in HIV-infected patients receiving antiretroviral therapy. Clin Nutr. 2005; 24:5–15. [PubMed: 15681097]
25. Sax PE, Zolopa A, Brar I, Elion R, Ortiz R, Post F, Wang H, Callebaut C, Martin H, Fordyce MW, McCallister S. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr. 2014; 67:52–58. [PubMed: 24872136]

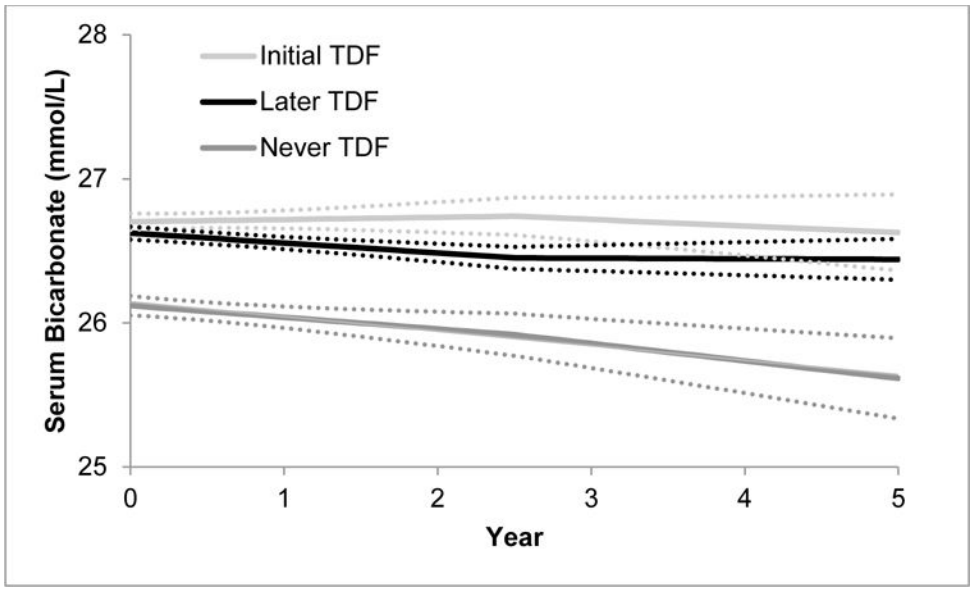

Figure 1. Association of category of tenofovir use with trajectories of serum bicarbonate concentration

Solid lines denote estimates from unadjusted linear mixed models; dotted lines denote upper and lower 95% confidence intervals. Never tenofovir (TDF) users had a steady decline in serum bicarbonate concentrations over time, whereas initial TDF users maintained stable concentrations. Later TDF users had an initial decline in serum bicarbonate concentrations, which then stabilized later during the follow up period

Table 1

Baseline clinical characteristics of HIV-infected persons, stratified by level of serum bicarbonate

	Serum Bicarbonate (mmol/L)				
	<22	**22–23.9**	**24–26.9**	**27–29.9**	**≥30**
N	**833**	**1,512**	**5,761**	**6,325**	**1,639**
Age	50 (45, 56)	49 (43, 55)	48 (42, 54)	47 (40, 53)	46 (39, 53)
Female	26 (3%)	51 (3%)	192 (3%)	131 (2%)	30 (2%)
Black	534 (64%)	860 (57%)	3062 (53%)	3439 (54%)	924 (56%)
Hypertension	248 (30%)	492 (33%)	1644 (29%)	1606 (25%)	356 (22%)
CVD	81 (10%)	104 (7%)	260 (5%)	234 (4%)	69 (4%)
Diabetes	89 (11%)	128 (9%)	398 (7%)	333 (5%)	101 (6%)
Lung Disease	89 (11%)	145 (10%)	436 (7%)	359 (6%)	95 (6%)
Smoking	163 (20%)	319 (21%)	1197 (21%)	1228 (19%)	335 (20%)
HCV	244 (29%)	429 (28%)	1452 (25%)	1479 (23%)	400 (24%)
HBV	75 (9%)	133 (9%)	423 (7%)	402 (6%)	101 (6%)
Illicit drug use	243 (29%)	401 (27%)	1589 (28%)	1559 (25%)	389 (24%)
CD4 count	188 (62, 360)	262 (121, 447)	299 (143, 484)	317 (170, 500)	330 (188, 504)
HIVRNA(/1000)	27 (0, 133)	17 (0, 110)	15 (0, 100)	13 (0, 82)	14 (0, 89)
SBP (mmHg)	124 (112, 139)	126 (115, 139)	127 (115, 139)	127 (116, 138)	126 (115, 137)
DBP (mmHg)	77 (69, 86)	78 (70, 86)	78 (70, 85)	77 (70, 85)	76 (70, 84)
BMI (kg/m^2)	24 (21, 27)	25 (22, 28)	25 (22, 28)	25 (22, 28)	24 (22, 27)
T Chol (mg/dL)	161 (128, 202)	170 (138, 200)	171 (143, 202)	171 (145, 199)	171 (146, 200)
Triglycerides (mg/dL)	162 (109, 259)	153 (107, 233)	146 (98, 229)	132 (90, 201)	125 (86, 191)
LDLc (mg/dL)	91 (68, 119)	97 (73, 123)	99 (76, 126)	101 (80, 127)	101 (80, 125)
HDLc (mg/dL)	35 (27, 45)	37 (29, 48)	38 (29, 48)	39 (31, 48)	39 (31, 49)
Proteinuria	430 (52%)	514 (34%)	1316 (23%)	1258 (20%)	307 (19%)
eGFR	81 (52, 102)	94 (76, 108)	98 (83, 110)	98 (85, 111)	98 (84, 111)
eGFR<60	234 (28%)	185 (12%)	282 (4.9%)	207 (3.3%)	75 (4.6%)
ACE-I/ARB	111 (13%)	163 (11%)	440 (8%)	401 (6%)	101 (6%)
ARB	11 (1%)	17 (1%)	28 (1%)	43 (1%)	9 (1%)
Diuretic	96 (12%)	111 (7%)	361 (6%)	403 (6%)	133 (8%)

	Serum Bicarbonate (mmol/L)				
	<22	**22–23.9**	**24–26.9**	**27–29.9**	**≥30**
N	**833**	**1,512**	**5,761**	**6,325**	**1,639**
Beta Blocker	98 (12%)	107 (7%)	325 (6%)	293 (5%)	81 (5%)

Continuous variables reported as median (interquartile range). Abbreviations: CVD cardiovascular disease, HCV hepatitis C virus, HBV hepatitis B virus, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, T Chol total cholesterol, eGFR estimated glomerular filtration rate in ml/min/1.73m^2, ACE-I angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker. Proteinuria defined by urinalysis protein 30 mg/dL or greater.

Table 2

Association of cumulative antiretroviral medication exposure (per year) with incidence of low serum bicarbonate concentration (<22 mmol/L) in HIV+ VA cohort

Antiretroviral medication	% of participants with any exposure at end of study	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Tenofovir	73%	0.95 (0.93, 0.97), p<0.001	0.95 (0.92, 0.98) p=0.003
Lamivudine	71%	0.98 (0.97, 1.00) p=0.09	0.97 (0.95, 1.00) p=0.03
Efavirenz	63%	1.02 (1.00, 1.04) p=0.04	1.05 (1.03, 1.08), p<0.001
Emtricitabine	61%	0.95 (0.92, 0.97) p<0.001	
Zidovudine	55%	0.99 (0.97, 1.01) p=0.18	
Ritonavir	53%	0.96 (0.94, 0.99) p=0.005	
Abacavir	30%	0.97 (0.94, 1.00) p=0.05	
Atazanavir	30%	0.92 (0.89, 0.96) p<0.001	
Stavudine	29%	1.04 (1.01, 1.06) p=0.005	1.05 (1.02, 1.08) p<0.001
Lopinavir/ritonavir	28%	0.98 (0.94, 1.02) p=0.32	
Didanosine	17%	1.00 (0.97, 1.03) p=0.88	
Indinavir	15%	1.02 (1.00, 1.05) p=0.10	
Nevirapine	17%	0.98 (0.95, 1.01) p=0.20	
Raltegravir	10%	0.94 (0.80, 1.09) p=0.40	
Darunavir	7.6%	0.90 (0.78, 1.03) p=0.12	
Saquinavir	7.1%	0.98 (0.93, 1.04) p=0.58	

Estimates from multivariable GEE relative risk models. Covariates in model include: age, sex, race, diabetes, glucose, systolic blood pressure, hypertension, high-density lipoprotein, low-density lipoprotein, triglycerides, cardiovascular disease, smoking, drug abuse, hepatitis B and C virus infection, body mass index, CD4 cell count, HIV viral load, diuretic use, angiotensin converting enzyme inhibitor use, lung disease, and, eGFR. CD4 and HIV viral load were time-updated.

Table 3

Association of bicarbonate with risk of chronic kidney disease in tenofovir users and non-users

	Tenofovir never users		Tenofovir users	
	Demographic-adjusted HR (95% CI)	**Adjusted for demographics, traditional, HIV-related HR (95% CI)**	**Demographic-adjusted HR (95% CI)**	**Adjusted for demographics, traditional, HIV-related HR (95% CI)**
Baseline Bicarbonate				
Continuous (per ↓mmol/L)	1.13 (1.09, 1.17), p<0.001	1.08 (1.04, 1.13), p<0.001	1.05 (1.03, 1.08), p<0.001	1.02 (1.00, 1.05), p=0.08
Categorical:				
< 22 vs. ≥30 mmol/L	3.09 (1.86, 5.13), p<0.001	1.82 (1.01, 3.28), p=0.05	1.56 (1.08, 2.24), p=0.02	1.08 (0.71, 1.65), p=0.71
22–23.9 vs. ≥30 mmol/L	1.89 (1.15, 3.10), p=0.01	1.15 (0.66, 2.02), p=0.62	1.46 (1.09, 1.96), p=0.01	1.35 (0.98, 1.87), p=0.06
24–26.9 vs. ≥30 mmol/L	1.54 (1.00, 2.36), p=0.05	1.25 (0.77, 2.03), p=0.37	1.15 (0.90, 1.47), p=0.25	1.14 (0.87, 1.50), p=0.33
27–29.9 vs. ≥30 mmol/L	1.01 (0.65, 1.58), p=0.96	0.72 (0.43, 1.19), p=0.20	0.95 (0.74, 1.22), p=0.71	1.00 (0.76, 1.32), p=0.99
Candidate cut points:				
< 20 vs. ≥20 mmol/L	2.67 (1.55, 4.61), p<0.001	1.68 (0.84, 3.38), p=0.15	1.09 (0.59, 2.04), p=0.78	0.87 (0.45, 1.69), p=0.67
< 22 vs. ≥22 mmol/L	2.35 (1.69, 3.28), p<0.001	1.80 (1.21, 2.68), p=0.004	1.44 (1.07, 1.94), p=0.02	0.98 (0.69, 1.38), p=0.90
< 23 vs. ≥23 mmol/L	2.33 (1.77, 3.07), p<0.001	1.90 (1.37, 2.63), p<0.001	1.50 (1.21, 1.87), p<0.001	1.18 (0.93, 1.51), p=0.18
Time-updated Bicarbonate:				
Continuous (per ↓mmol/L)	1.18 (1.14, 1.21), p<0.001	1.17 (1.14, 1.21), p<0.001	1.13 (1.10, 1.15), p<0.001	1.11 (1.08, 1.13), p<0.001
Categorical:				
< 22 vs. ≥30 mmol/L	6.65 (4.23, 10.47), p<0.001	6.88 (4.05, 11.7), p<0.001	3.72 (2.81, 4.92), p<0.001	3.15 (2.36, 4.20), p<0.001
22–23.9 vs. ≥30 mmol/L	2.81 (1.74, 4.53), p<0.001	2.63 (1.52, 4.55), p<0.001	1.56 (1.16, 2.10), p=0.004	1.68 (1.26, 2.25), p<0.001
24–26.9 vs. ≥30 mmol/L	1.87 (1.21, 2.87), p=0.004	2.10 (1.28, 3.44), p=0.003	1.33 (1.04, 1.68), p=0.02	1.29 (1.01, 1.64), p=0.04
27–29.9 vs. ≥30 mmol/L	1.28 (0.82, 2.00), p=0.27	1.28 (0.77, 2.13), p=0.35	1.03 (0.81, 1.32), p=0.78	1.05 (0.82, 1.34), p=0.69
Candidate cut points:				
< 20 vs. ≥20 mmol/L	4.10 (2.79, 6.02), p<0.001	3.59 (2.27, 5.66), p<0.001	3.87 (2.95, 5.09), p<0.001	3.12 (2.30, 4.25), p<0.001
< 22 vs. ≥22 mmol/L	4.12 (3.19, 5.32), p<0.001	4.05 (2.99, 5.49), p<0.001	3.27 (2.72, 3.95), p<0.001	2.63 (2.13, 3.25), p<0.001
< 23 vs. ≥23 mmol/L	3.37 (2.67, 4.25), p<0.001	3.36 (2.55, 4.41), p<0.001	2.50 (2.11, 2.95), p<0.001	2.14 (1.78, 2.58), p<0.001

Estimates from multivariable Cox regression models. Covariates in model include: age, sex, race, diabetes, glucose, systolic blood pressure, hypertension, high-density lipoprotein, low-density lipoprotein, triglycerides, cardiovascular disease, smoking, drug abuse, hepatitis B and C virus infection, body mass index, CD4 cell count, HIV viral load, diuretic use, angiotensin converting enzyme inhibitor use, lung disease, and, eGFR.

Chronic kidney disease is defined by two consecutive eGFR < 60 ml/min/1.73m^2. Baseline bicarbonate was defined at date of first tenofovir exposure.

Table 4

Association of change in bicarbonate with risk of chronic kidney disease in tenofovir users and non-users

	Unadjusted 5-year event rate % (95% CI)	HR adjusted for demographic (95% CI)	HR adjusted for demographics, traditional, HIV-related (95% CI)
Tenofovir never users			
Continuous (per ↓mmol/L)		1.53 (1.25, 1.86), p<0.001	1.67 (1.34, 2.08), p<0.001
Categorical:			
Stable bicarbonate	4.3 (3.4, 5.4)	reference	reference
Increasing bicarbonate	7.4 (6.2, 8.6)	1.42 (1.06, 1.90), p=0.02	1.22 (0.87, 1.71), p=0.24
Decreasing bicarbonate	10.0 (8.6, 11.6)	2.02 (1.53, 2.66), p<0.001	1.81 (1.32, 2.50), p<0.001
Tenofovir users			
Continuous (per ↓mmol/L)		1.08 (0.97, 1.20), p=0.18	1.09 (0.98, 1.22), p=0.13
Categorical:			
Stable bicarbonate	9.9 (8.8, 11.2)	reference	reference
Increasing bicarbonate	12.5 (11.2, 13.9)	1.26 (1.07, 1.48), p=0.005	1.21 (1.01, 1.45), p=0.04
Decreasing bicarbonate	11.9 (10.7, 13.3)	1.21 (1.03, 1.43), p=0.02	1.25 (1.05, 1.50), p=0.01

Estimates from multivariable Cox regression models. Covariates in model include: age, sex, race, diabetes, glucose, systolic blood pressure, hypertension, high-density lipoprotein, low-density lipoprotein, triglycerides, cardiovascular disease, smoking, drug abuse, hepatitis B and C virus infection, body mass index, CD4 cell count, HIV viral load, diuretic use, angiotensin converting enzyme inhibitor use, lung disease, and, eGFR.

Chronic kidney disease is defined by two consecutive eGFR < 60 ml/min/1.73m^2. Baseline bicarbonate was defined at date of first tenofovir exposure.