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ORIGINAL RESEARCH

Association of Tenofovir Use With Risk of Incident Heart Failure in HIV-Infected Patients

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***Background*—**The antiretroviral medication, tenofovir disoproxil fumarate (TDF), is used by most human immunodeficiency virus–infected persons in the United States despite higher risks of chronic kidney disease. Although chronic kidney disease is a strong risk factor for heart failure (HF), the association of TDF with incident HF is unclear.

***Methods and Results*—**We identified 21 435 human immunodeficiency virus–infected patients in the United States Veterans Health Administration actively using antiretrovirals between 2002 and 2011. We excluded patients with a prior diagnosis of HF. TDF was analyzed categorically (current, past, or never use) and continuously (per year of use). Proportional hazards regression and fully adjusted marginal structural models were used to determine the association of TDF exposure with risk of incident HF after adjustment for demographic, human immunodeficiency virus–related, and cardiovascular risk factors. During follow-up, 438 incident HF events occurred. Unadjusted 5-year event rates for current, past, and never users of TDF were 0.9 (95%CI 0.7-1.1), 1.7 (1.4-2.2), and 4.5 (3.9-5.0), respectively. In fully adjusted analyses, HF risk was markedly lower in current TDF users (HR=0.68; 95% CI 0.53-0.86) compared with never users. Among current TDF users, each additional year of TDF exposure was associated with a 21% lower risk of incident HF (95%CI: 0.68-0.92). When limited to antiretroviral-naive patients, HF risk remained lower in current TDF users (HR=0.53; 95%CI 0.36-0.78) compared to never users.

***Conclusions*—**Among a large national cohort of human immunodeficiency virus–infected patients, TDF use was strongly associated with lower risk of incident HF. These findings warrant confirmation in other populations, both with TDF and the recently approved tenofovir alafenamide fumarate. **(*J Am Heart Assoc*. 2017;6: e005387. DOI: 10.1161/JAHA.116.005387.)**

Key Words: heart failure • HIV • tenofovir

Modern antiretroviral (ARV) therapy has revolutionized medical care for patients with HIV, improving life expectancy and transitioning HIV from the realm of terminal illness to that of chronic disease.[1,2] Concomitantly, the conditions with the highest morbidity and mortality risk affecting HIV-infected patients have shifted from consequences of severe immunodeficiency to conditions more typically associated with aging. Cardiovascular disease (CVD) and heart failure (HF) have become leading causes of death among HIV-infected patients[3,4] and are projected to dramatically increase in prevalence in this population within the next 15 years.[5,6] Notably, echocardiography reveals that contemporary HIV cohorts have high rates of diastolic dysfunction,[7,8] and HF with preserved ejection fraction will likely increase in prevalence as in the non-HIV population, where it already accounts for 50% of HF cases.[9]

HIV infection has long been associated with HF via suspected etiologies related directly to viral infection, such as HIV myocarditis, increased cytokine production, and chronic inflammation.[10,11] However, a wider spectrum of HF etiologies must be considered in the modern ARV era, including both typical risk factors for HF and those specific to the HIV-infected population. There is evidence of renal and cardiac toxicity from certain ARVs used to treat HIV.[12,13] Although this is not universally found, limited past studies have shown that nucleoside reverse transcriptase inhibitors, particularly zidovudine, may be associated with systolic dysfunction, cardiomyopathies, and an increased risk of myocardial infarction, and others have proposed an increased

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risk of HF or myocardial infarction with protease inhibitors and abacavir.[14-17]

To date, little is known about the cardiac effects of 1 of the most widely used ARVs, tenofovir disoproxil fumarate (TDF), which is frequently recommended as a first-line agent and incorporated in multidrug formulations.[18] TDF has been consistently associated with higher risk of chronic kidney disease, which is 1 of the strongest independent risk factors for HF in both the general population and HIV-infected persons.[19,20] Therefore, TDF might be hypothesized to increase patients' risk for HF. In fact, a study evaluating the early period of TDF use, through 2007, among Department of Veterans Affairs (VA) patients found TDF to be associated with a nonsignificantly increased risk of HF, but findings were inconclusive due to the limited number of events and the short time of exposure.[14] To our knowledge, no other study has evaluated whether TDF use impacts the risk of HF. Accordingly, we sought to determine the association of TDF with the incidence of HF in a larger cohort of HIV-infected veterans with a greater prevalence of TDF use and longer-term exposure.

Methods

Data Source

We conducted a retrospective cohort study using the HIV Clinical Case Registry, a registry from the US VA that was developed to monitor healthcare utilization for HIV-infected US veterans. The registry included all HIV-infected veterans receiving care in the VA nationally and extracted demographic, clinical, laboratory, pharmacy, healthcare utilization, and death information from the VA electronic medical record to a centralized database. The HIV Clinical Case Registry was linked to the VA National Patient Care Database, the VA Beneficiary Identification and Records Locator Subsystem Death File, and Medicare claims to augment demographic, comorbidity, and vital status data and to capture clinical events outside of the VA system.

Study Population

We included all HIV-infected persons actively receiving clinical care from the VA who initiated or received ARV therapy between 2002 and 2011. Because FDA approval of TDF did not occur until October 2001, we defined the baseline for each patient as January 1, 2002 or the date of starting ARV therapy (whichever was later). Persons diagnosed with HF before 2002 were excluded from the analysis. In order to identify patients actively receiving treatment at the VA, we also excluded patients who did not have at least 1 of each of the following criteria: HIV viral load, CD4 cell count, outpatient visit, and assessment of kidney function. Participants were followed until January 1, 2011, yielding a maximum follow-up period of 9 years.

Outcomes

Our primary outcome was incident HF, defined as a new hospitalization discharge diagnosis or ambulatory diagnosis of HF over the study period, as determined by ICD-9 codes. Discharge diagnoses and procedural codes entered into VA and Medicare databases were based on validated algorithms defined previously.[19,21] For discharge diagnoses, we required that HF be listed as the primary, secondary, or tertiary diagnosis for the hospitalization.

Primary Predictors

Our primary predictor was exposure to TDF during the study period, analyzed both categorically and continuously (per year of use). We categorized patients primarily as: (1) current TDF users (patients whose last ARV regimen during study follow-up included TDF); (2) past TDF users (patients who discontinued TDF during follow-up); and (3) never TDF users. As an alternative categorization, we also grouped patients as being: (1) initial TDF users (included in their initial ARV regimen); (2) later TDF users (initiated TDF after at least 1 prior ARV regimen); and (3) never TDF users. When evaluating duration of TDF use, we distinguished "current duration"—length of use among current TDF users—from "total duration," which included all cumulative TDF exposure.

Covariates

For adjustment variables, we included demographic and clinical covariates, measured at each patient's baseline, as defined above: age, sex, race (black, white, other), diagnosis of diabetes mellitus, diagnosis of hypertension, lipid profile, history of CVD (coronary artery disease, stroke, transient ischemic attack, peripheral artery disease), smoking, alcoholism, illicit drug use, hepatitis C virus infection, hepatitis B virus infection, BMI, proteinuria, estimated glomerular filtration rate as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation,[22] serum albumin, CD4 count, nadir CD4 count within VA records, HIV RNA level, use of highly active antiretroviral therapy, history of AIDS, duration of HIV, and number of antihypertensive medications. We used previously validated algorithms to define the following conditions: diabetes, hypertension, hepatitis B and C virus coinfection, AIDS, illicit drug use, and smoking.[14,19,21,23,24] We adjusted for CD4 count, HIV RNA level, estimated glomerular filtration rate, and proteinuria as time-updated covariates in additional models.

Statistical Analysis

We compared baseline demographic and clinical characteristics across categories of TDF exposure (current/past/never and initial/later/never) using chi-squared tests for categorical variables and Kruskal-Wallis tests for continuous variables. We then determined the unadjusted rates of incident HF across categories of TDF exposure using the Fine-Gray method to account for the competing risk of death and plotted the cumulative incidence over time.[25] The Fine-Gray competing risk analysis is designed to account for potential bias due to informative censoring from the competing risk of death before onset of HF. We used Cox proportional hazards regression models to evaluate the associations of the TDF use with incident HF, again accounting for the competing risk of death. We modeled TDF associations using 2 separate Cox models: (1) the demographic model, which only adjusted for age, sex, and race; and (2) the multivariable Cox model, which additionally adjusted for traditional and HIV-related factors, as listed in the covariates section above, as well as time-dependent covariates (CD4, VL, estimated glomerular filtration rate, and proteinuria).

Because time-dependent covariates may both confound and mediate the effects of ARV treatment in a manner that cannot be addressed by conventional methods of analysis, we also used marginal structural models (MSM), including all baseline variables from the multivariable Cox model, to reestimate the associations of TDF exposure with risk of incident HF.[26-28] We utilized MSMs to minimize drug-channeling bias, as the decision to prescribe a specific ARV may be influenced by unmeasured confounders. We generated inverse probability of treatment weights for each patient by modeling TDF exposure as a function of demographic and clinical characteristics, selected from the candidate covariates listed above. We used separate multinomial logistic regression models[29] to calculate inverse probability of treatment weights for categories of use (current, past, or never; initial, later, or never) and linear regression models[30] to calculate weights for duration of exposure (total and current). These weights were then applied to subsequent models evaluating the associations of TDF with HF.[31]

Sensitivity Analyses

We performed multiple sensitivity analyses in order to determine whether confounding was present and whether the effects of TDF differed by subgroup. We first limited our cohort to only ARV-naive patients, defined as patients with no exposure to ARVs before the study period, to minimize the bias and confounding that may exist from previous ARV exposure in our cohort. We also performed additional sensitivity analyses to adjust for calendar year and for era of initiation, defined as early era (ARV initiation before 2003) or late era (ARV initiation in 2003 or later), to determine whether effects may differ across time.

Because numerous risk factors exist for HF that may be influenced by TDF use, we then stratified our cohort into multiple subgroups based on patient characteristics and risk factors that may represent potential confounders. We calculated the hazard ratio (HR) per year of current TDF exposure for each subgroup using the marginal structural model. We created a forest plot to help illustrate whether the overall associations from the primary analysis were driven by any particular interaction or subgroup. We stratified our cohort based on the following factors: age, race, proteinuria, chronic kidney disease, CD4 count, viral load, diabetes, hypertension, history of cardiovascular disease, cholesterol, smoking status, illicit drug use, hepatitis C infection, BMI, albumin, alcoholism, and era of initiation.

Given the history of adverse cardiac effects with abacavir use, we modeled TDF and abacavir in various combinations to determine whether abacavir use, or lack thereof, may explain any associations between TDF and HF. Finally, because myocardial infarction and ischemia are important etiologies of HF, we adjusted for interim myocardial infarction in an additional sensitivity analysis.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC). This study was approved by the Committee on Human Research at the San Francisco VA Medical Center and University of California, San Francisco, and the requirement for informed consent was waived.

Results

Patient Characteristics

We identified 21 435 HIV-infected patients who initiated ARVs in the Veterans Health Administration between 2002 and 2011. At baseline, median age was 49 years (interquartile range [IQR] 42-55), and 97% of patients were male. Median duration on TDF was 2.2 years (IQR 0.8-4.0), and mean duration was 2.6 years (SD 2.1). There were 11 881 patients whose ARV regimens at the conclusion of the study period included TDF (current TDF users), 3979 patients whose ARV regimens included TDF in the past (past TDF users), and 5575 patients who never used TDF (never TDF users). At baseline, age and sex appeared similar across these 3 groups (Table 1). Relative to past and never TDF users, current TDF users had a slightly lower proportion of diabetes mellitus, hypertension, preexisting CVD, history of alcoholism, history of illicit drug use, and hepatitis C infection at baseline. Current users also had a higher median duration on TDF and slightly higher estimated glomerular filtration rate. Former users of TDF had the lowest CD4 counts and the highest prevalence of

Table 1. Baseline Patient Characteristics Stratified by Current/Past/Never TDF Use

	Current TDF Use	Past TDF Use	Never TDF
	N=11 881	N=3979	N=5575
Age, y	48 (41, 54)	48 (42, 55)	50 (44, 56)
Female	331 (3%)	116 (3%)	121 (2%)
Black	5976 (50%)	2253 (57%)	3081 (55%)
Duration of TDF exposure, y	2.5 (1.1-4.3)	1.5 (0.5-2.7)	0
Diabetic	804 (7%)	391 (10%)	568 (10%)
Hypertension	2928 (25%)	1246 (31%)	1674 (30%)
Total cholesterol, mg/dL	174 (148, 204)	173 (144, 202)	178 (149, 210)
Low-density lipoprotein cholesterol, mg/dL	101 (79, 127)	97 (75, 123)	101 (78, 129)
High-density lipoprotein cholesterol, mg/dL	38 (30, 48)	38 (30, 48)	40 (32, 51)
Triglycerides, mg/dL	139 (93, 217)	141 (98, 223)	147 (98, 230)
Cardiovascular disease	598 (5%)	241 (6%)	420 (8%)
History of smoking	3231 (27%)	1096 (28%)	1598 (29%)
History of illicit drug use	3554 (30%)	1376 (35%)	1890 (34%)
History of alcoholism	2179 (18%)	945 (24%)	1256 (23%)
BMI, kg/m^2	25 (23, 28)	24 (22, 28)	25 (22, 28)
Serum albumin, g/dL	4.0 (3.6, 4.3)	3.9 (3.5, 4.2)	3.9 (3.5, 4.2)
Proteinuria (>30 mg/dL)	2275 (19%)	977 (25%)	1225 (22%)
eGFR by CKD-EPI	97 (84, 109)	95 (80, 108)	93 (76, 107)
Highly active antiretroviral therapy	10 399 (88%)	3202 (80%)	4378 (79%)
CD4 count, cells/mm^3 (baseline)	336 (189, 526)	291 (138, 479)	379 (206, 615)
CD4 count, cells/mm^3 (end)	455 (281, 657)	328 (144, 539)	457 (250, 687)
HIV RNA >1000, copies/mL (baseline)	6735 (58%)	2437 (62%)	2397 (45%)
HIV RNA >1000, copies/mL (end)	1696 (15%)	1401 (36%)	1516 (28%)
Chronic hepatitis C	3048 (26%)	1300 (33%)	1780 (32%)
Chronic hepatitis B	1170 (10%)	477 (12%)	567 (10%)

P<0.05 for all characteristics across all 3 groups except for smoking (*P*=0.13). The *P*-value for TDF duration is <0.0001. Continuous variables reported as median (interquartile range; IQR). Proteinuria defined by urinalysis protein 30 mg/dL or greater. Baseline defined for each patient as January 1, 2002 or the date of starting ARV therapy (whichever was later). End defined as January 1, 2011. CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; TDF, tenofovir disoproxil fumarate.

detectable HIV RNA at baseline and at end of the study (Table 1). When comparing characteristics of initial, later, and never TDF users, we found that initial TDF users had a slightly lower prevalence of comorbidities compared with later or never TDF users; however, they also had lower CD4 counts and a higher viral load at treatment initiation (Table 2).

Risk of Incident Heart Failure

Over a median of 5.4 years of follow-up, there were 438 incident HF events. The unadjusted incidence of HF was highest among never users of TDF, followed by past and current users of TDF, along with later and initial TDF users (Figure 1). Unadjusted 5-year incidences for current, past, and never users of TDF were 0.9% (110 events; 95%CI 0.7-1.1), 1.7% (79 events; 95%CI 1.4-2.2), and 4.5% (249 events; 95%CI 3.9-5.0), respectively. Unadjusted 5-year incidences of HF were similar for initial and later TDF users, although both rates were substantially lower than the incidence among never users of TDF: 1.1% (45 events; 95%CI 0.8-1.5), 1.1% (144 events; 95%CI 0.9-1.3), and 4.5% (249 events; 95%CI 3.9-5.0), respectively.

Greater cumulative TDF exposure among ever TDF users was associated with a significantly decreased adjusted HF risk in both the demographically adjusted and multivariable models (Table 3). However, additional adjustment with the MSM widened the confidence interval, and the association lost statistical significance. In contrast, current TDF exposure was more strongly and significantly associated with lower HF risk in all models; each year of current TDF use was associated with an ≈20% lower risk of HF.

In our categorical analyses comparing current, former, and never TDF users, we found that current users of TDF had

Table 2. Additional Patient Characteristics Stratified by Initial/Later/Never TDF Use

	Initial Regimen Included TDF	Later TDF (2°/3° Regimen)	Never TDF
	N=7090	N=8770	N=5575
Age, y (baseline)	49 (42, 56)	47 (41, 53)	50 (44, 56)
Female	221 (3%)	226 (3%)	121 (2%)
Black	3697 (52%)	4532 (52%)	3081 (55%)
Duration of TDF exposure, years	1.7 (0.7-3.3)	2.7 (1.1-4.5)	0
Diabetic (baseline)	470 (7%)	725 (8%)	568 (10%)
Hypertension (baseline)	1232 (17%)	2942 (34%)	1674 (30%)
Total cholesterol, mg/dL (baseline)	166 (141, 193)	180 (152, 212)	178 (149, 210)
Low-density lipoprotein cholesterol, mg/dL (baseline)	98 (77, 120)	102 (80, 130)	101 (78, 129)
High-density lipoprotein cholesterol, mg/dL (baseline)	36 (29, 46)	39 (32, 50)	40 (32, 51)
Triglycerides, mg/dL (baseline)	128 (88, 192)	151 (101, 240)	147 (98, 230)
Cardiovascular disease (baseline)	335 (5%)	504 (6%)	420 (8%)
History of smoking (baseline)	1910 (27%)	2417 (28%)	1598 (29%)
History of illicit drug use (baseline)	1969 (28%)	2961 (34%)	1890 (34%)
History of alcoholism (baseline)	1088 (15%)	2036 (23%)	1256 (23%)
BMI, kg/m^2 (baseline)	25 (22, 28)	25 (23, 28)	25 (22, 28)
Serum albumin, g/dL (baseline)	3.9 (3.5, 4.3)	4.0 (3.7, 4.3)	3.9 (3.5, 4.2)
Proteinuria (>30 mg/dL; baseline)	1952 (28%)	1300 (15%)	1225 (22%)
eGFR by CKD-EPI (baseline)	95 (81, 108)	97 (84, 110)	93 (76, 107)
eGFR by CKD-EPI (end)	91 (76, 106)	89 (72, 103)	90 (69, 106)
Highly active antiretroviral therapy (baseline)	7011 (99%)	6590 (75%)	4378 (79%)
Highly active antiretroviral therapy (ever use at end)	7074 (99.8%)	8768 (99.9%)	5422 (97%)
CD4 count, $cells/mm^3$ (baseline)	297 (157, 451)	352 (190, 564)	379 (206, 615)
CD4 count, $cells/mm^3$ (end)	432 (257, 612)	423 (234, 648)	457 (250, 687)
Nadir CD4 count, $cells/mm^3$ (baseline)	278 (141, 417)	277 (121, 463)	298 (140, 513)
Nadir CD4 count, $cells/mm^3$ (end)	240 (109, 377)	186 (59, 333)	240 (90, 408)
History of AIDS (baseline)	2857 (40%)	4219 (48%)	2503 (45%)
History of AIDS (end)	4719 (67%)	7074 (81%)	3862 (69%)
Duration of HIV (baseline)	0.4 (0.0, 3.6)	3.2 (0.6, 5.3)	2.2 (0.2, 5.0)
Duration of HIV (end)	4.2 (1.8, 7.2)	11.0 (8.0, 13.6)	8.1 (4.2, 12.0)
HIV RNA >1000, copies/mL (baseline)	4668 (68%)	4504 (52%)	2397 (45%)
HIV RNA >1000, copies/mL (end)	1266 (18%)	1831 (21%)	1516 (28%)
Chronic hepatitis C (baseline)	1666 (23%)	2682 (31%)	1780 (32%)
Chronic hepatitis B (baseline)	594 (8%)	1053 (12%)	567 (10%)

$P<0.05$ for all variables except BMI and smoking (baseline). Continuous variables are reported as median (interquartile range; IQR). Proteinuria is defined by urinalysis protein 30 mg/dL or greater. Baseline is defined for each patient as January 1, 2002 or the date of starting ARV therapy (whichever was later). End is defined as January 1, 2011. AIDS indicates acquired immune deficiency syndrome; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; TDF, tenofovir disoproxil fumarate.

≈30% to 40% lower HF risk compared to never or to past users (Table 3). There was only minimal attenuation from the demographic model to the multivariable and marginal structural models in the comparison of current to never users, and the comparison of current to past users also remained significant in the multivariable model but not in the MSM (Table 3). Initial TDF users had a more than 50% lower HF risk compared to never users of TDF, which also remained consistent across all models (Table 3). There were no statistically significant differences in adjusted HF risk between past and never TDF users or between later and never TDF users.

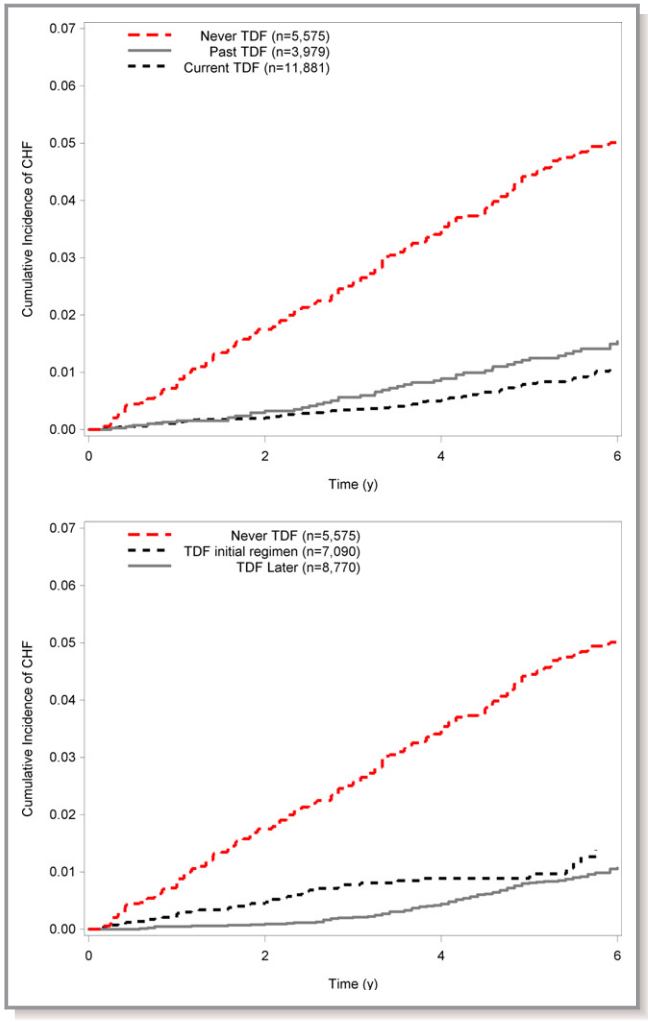

Figure 1. Cumulative incidence of heart failure by category of TDF exposure. Unadjusted incidence of heart failure was highest among never users of TDF, followed by past and current users of TDF. Similarly never TDF users also had the highest incidence of heart failure when compared with initial and later TDF users. CHF indicates heart failure, TDF, tenofovir disoproxil fumarate.

Based on HRs from the MSM, we found that current TDF use was associated with a number needed to treat of 71 over 5 years (absolute risk reduction 1.41%). This estimate decreased to a number needed to treat of 41 (absolute risk reduction 2.44%) for those who used TDF as part of their initial regimen (Table 4).

Sensitivity Analyses

In an effort to further minimize confounding, we performed several sensitivity analyses. We first repeated our analyses after restricting the patient population to those who were ARV naive at baseline (Table 5). The associations of continuous measures of total and current TDF exposure with HF risk had similar point estimates as in the overall analysis, but the wider confidence intervals led the findings to be nonsignificant by statistical criteria. However, associations of current versus never TDF users and of initial versus never TDF users were both strong and statistically significant in the ARV-naive group throughout all stages of statistical adjustment, consistent with our findings in the overall analysis (Table 5).

Additional sensitivity analyses were performed to determine whether there was a time effect, either by calendar year or by era of initiation, that may explain our results. Adjustment for calendar year of ARV initiation did not impact our results. Specifically, the association of current TDF duration (per year of exposure) with HF risk was HR 0.81 (95%CI 0.69-0.94, P=0.0049) after adjustment for calendar year. When stratified by era of ARV initiation, the protective effect of current TDF duration appears to be somewhat stronger in the early era (HR 0.76 [95%CI 0.63-0.91], P=0.0024), as compared to the late era (HR 0.89 [95%CI 0.68-1.16], P=0.39). However, there was no significant interaction between era of ARV initiation and duration (test for interaction, P=0.34).

After stratifying the cohort by subgroups based on patient characteristics and risk factors which may be potential confounders, we found that the HR for TDF had similar, protective associations with incident HF across all subgroups of patients (Figure 2). Tests for TDF-by-subgroup interaction were statistically nonsignificant (all P>0.13). This suggests that no single group was responsible for driving the overall association of TDF use with lower HF risk seen in the primary analysis. In our analysis of the effects of TDF and abacavir, we found that when modeled simultaneously, current TDF duration was associated with a lower risk of HF (HR 0.82 [95% CI 0.71-0.94], P=0.0059), whereas current abacavir duration was not significantly associated with HF risk (HR 0.97 [95% CI 0.85-1.10], P=0.64). When modeled in various combinations and compared with patients using neither, we found that the point estimates were similar for TDF use with (HR 0.76; 95% CI 0.41-1.40) or without (HR 0.75; 95% CI 0.59-0.96) abacavir, relative to users of neither agent. Use of abacavir alone was not significantly associated with incident HF (HR 1.15; 95% CI 0.87-1.52), but the point estimate was in the opposite direction from TDF. Finally, when adjusted for interim myocardial infarction, we found that the association of each year of current TDF use remained associated strongly with lower risk of HF (HR 0.83 [95% CI 0.72-0.96] P=0.014).

Discussion

We embarked on this study with the hypothesis that the use of TDF would be associated with a higher risk of incident HF due to this drug's known link to worsening kidney function and previous preliminary data.[14,19,20] However, in this large national registry of HIV-infected US veterans, we found that TDF exposure was actually associated with a significantly

Table 3. Association of TDF Exposure With Risk of Incident Heart Failure for All Patients With HIV (N=21 435), Accounting for Competing Risk of Death

Parameter	Demographic-Adjusted Cox Model* Hazard Ratio (95%CI)	Multivariable Adjusted Cox Model† Hazard Ratio (95%CI)	Marginal Structural Model‡ Hazard Ratio (95%CI)
Continuous TDF exposure (per year)			
Total TDF duration	0.88 (0.82-0.96) *P*=0.003	0.91 (0.84-0.99) *P*=0.037	0.92 (0.83-1.02) *P*=0.11
Current TDF duration	0.73 (0.62-0.85) *P*<0.001	0.78 (0.67-0.91) *P*=0.001	0.79 (0.68-0.92) *P*=0.003
Categories of TDF use			
Current vs never TDF use	0.60 (0.48-0.75) *P*<0.001	0.66 (0.52-0.84) *P*<0.001	0.68 (0.53-0.86) *P*=0.002
Past vs never TDF use	1.06 (0.82-1.37) *P*=0.67	0.98 (0.76-1.27) *P*=0.89	0.87 (0.66-1.15) *P*=0.33
Current vs past TDF use	0.57 (0.42-0.76) *P*<0.001	0.67 (0.50-0.90) *P*=0.008	0.77 (0.57-1.06) *P*=0.11
Categories of TDF use			
Initial regimen included TDF vs never TDF use	0.42 (0.30-0.58) *P*<0.001	0.47 (0.33-0.65) *P*<0.001	0.44 (0.30-0.64) *P*<0.001
Later TDF (2°/3° regimen) vs never TDF use	0.77 (0.62-0.95) *P*=0.017	0.89 (0.71-1.11) *P*=0.30	0.96 (0.76-1.21) *P*=0.73

TDF indicates tenofovir disoproxil fumarate.
*Demographic adjusted Cox model includes TDF exposure, age, sex, and race.
†Multivariable adjusted Cox model includes exposure to tenofovir plus age, sex, race/ethnicity, traditional risk factors, and HIV-related risk factors, as listed in covariates section.
‡Marginal structural model includes all baseline variables from multivariable Cox model.

lower risk of HF. Across multiple statistical models, this observed protective association of TDF persisted in both continuous and categorical measures of TDF exposure. Compared with never users of TDF, current users of TDF and patients whose initial regimen included TDF had reductions in HF risk ranging from ≈30% to 50%. To our knowledge, this is the first large national cohort study to identify a significant association between TDF use and HF risk in HIV-infected patients. These novel results suggest that TDF may offer cardioprotective benefits, but our findings require confirmation in additional settings before they can be considered to definitively represent a causal relationship.

Previously, there has been limited literature regarding the association of ARVs with CVD, including conflicting data regarding the increased risk of CVD with specific classes of ARVs, most of which focused on atherosclerosis or coronary artery disease.[16,32-36] However, despite well-known associations of HIV infection with HF and cardiomyopathies, few studies have evaluated ARVs and HF.[10,11,37] In case reports and mouse models, there was early evidence that the nucleoside reverse transcriptase inhibitor zidovudine might worsen cardiomyopathy through mitochondrial destruction.[38-40] Subsequent studies found that certain protease inhibitors may also be associated with increased HF incidence.[17,41] To our knowledge, no large study has previously concluded that any individual ARV or class of ARVs has a protective effect against the development of HF.[8,10,11]

Initially, we expected that TDF exposure would be associated with an increased risk for HF. This seemed biologically plausible due to TDF's adverse effects on kidney disease risk

Table 4. Summary of HF Events and Person-Years by TDF Exposure

Category	Events	Person-Years	Five-Year Cumulative Incidence From Fine-Gray Model	Event-Free Rate	Hazard Ratio From MSM	NNT*
Current TDF (N=11 881)	110	61 516	0.0080	0.992	0.68	71
Past TDF (N=3979)	79	22 691	0.0125	0.988	0.87	176
Never (N=5575)	249	27 918	0.0445	0.956		
Initial TDF (N=7090)	45	19 776	0.0097	0.990	0.44	41
Later TDF (N=8770)	144	64 431	0.0081	0.992	0.96	574
Never (N=5575)	249	27 918	0.0445	0.956		

$NNT(t) = \frac{1}{(S_B(t))^{HR} - S_B(t)}$, where $S_B(t)$ denotes the survival probability in the never TDF group at t=5 years, and HR indicates the hazard ratio for each TDF-use category relative to the never TDF group. HF indicates heart failure; MSM, marginal structural model; TDF, tenofovir disoproxil fumarate.
*Number needed to treat (NNT) indicates that if 71 patients were treated with TDF over 5 years, 1 case of HF would be prevented that would have otherwise occurred.

Table 5. Association of TDF Exposure With Risk of Incident Heart Failure Among ARV-Naive Only Patients With HIV (N=12 925), Accounting for Competing Risk of Death

Parameter	Demographic-Adjusted Cox Model* Hazard Ratio (95%CI)	Multivariable Adjusted Cox Model† Hazard Ratio (95%CI)	Marginal Structural Model‡ Hazard Ratio (95%CI)
Continuous TDF exposure			
Total TDF duration (per year)	0.79 (0.67-0.93) $P<0.01$	0.86 (0.73-1.00) $P=0.06$	0.81 (0.65-1.01) $P=0.06$
Current TDF duration (per year)	0.73 (0.57-0.94) $P=0.02$	0.82 (0.64-1.04) $P=0.11$	0.87 (0.68-1.12) $P=0.29$
Categories of TDF use			
Current vs never TDF use	0.47 (0.33-0.67) $P<0.01$	0.56 (0.39-0.81) $P<0.01$	0.53 (0.36-0.78) $P<0.01$
Past vs never TDF use	0.89 (0.58-1.36) $P=0.58$	0.91 (0.59-1.41) $P=0.67$	0.81 (0.51-1.29) $P=0.37$
Categories of TDF use			
Initial regimen included TDF vs never TDF use	0.44 (0.30-0.65) $P<0.01$	0.55 (0.36-0.83) $P<0.01$	0.52 (0.32-0.83) $P<0.01$
Later TDF (2°/3° regimen) vs never TDF use	0.69 (0.47-1.01) $P=0.06$	0.91 (0.61-1.35) $P=0.65$	0.94 (0.62-1.42) $P=0.77$

ARV indicates antiretroviral; TDF, tenofovir disoproxil fumarate.
*Demographic adjusted Cox model includes TDF exposure, age, sex, and race.
†Multivariable adjusted Cox model includes exposure to tenofovir plus age, sex, race/ethnicity, traditional risk factors, and HIV-related risk factors, as listed in covariates section. Also adjusted for CVD, history of AIDS, nadir CD4, duration of HIV, and number of antihypertensive medications.
‡Marginal structural model includes all baseline variables from multivariable Cox model.

and the known associations of reduced kidney function with elevated HF risk. In addition, a previous study in this population found early TDF users to have higher rates of HF in unadjusted analyses but was limited by a short mean time on TDF of 1.3 years.[14,19,20] Therefore, our finding that TDF appears to be associated with a decreased risk of HF was unexpected. Nonetheless, there are a number of candidate mechanisms for a potential protective effect. The first is potentially superior viral control of HIV with treatment combinations that include TDF, which may subsequently reduce inflammation and levels of cytokines that cause cardiac injury. Supporting this hypothesis, 1 study has found that higher HIV viral loads were associated with higher HF risk.[37]

Another intriguing possibility to explain this beneficial effect of TDF is through its known phosphaturic effects on the kidney. Although phosphate losses caused by TDF have been linked with bone disease, they also have the salient effect of lowering levels of fibroblast growth factor 23, a phosphaturic hormone that acts on the bones and kidney. Fibroblast growth factor 23 causes pathological hypertrophy of cardiomyocytes in mechanistic studies and is strongly and independently associated with left ventricular hypertrophy and HF risk in epidemiological studies.[42-47] Thus, this potentially adverse effect of TDF causing phosphorus wasting from the kidney may actually result in lower HF risk due to the favorable effects of reduced levels of fibroblast growth factor 23.

A third possible mechanism is via TDF's potential lipid-lowering effects. Multiple studies have noted a more favorable lipid profile in TDF users, and a recent trial showed significant decreases in total and low-density lipoprotein cholesterol.[48] Whereas other ARV regimens have a side effect of dyslipidemia, TDF could create a potentially beneficial reduction in atherosclerosis and subsequent coronary artery disease. Indeed, TDF use has been associated with decreased carotid intima-media thickness.[49] These favorable vascular effects could reduce the incidence of ischemic HF. However, we observed only mild changes in lipid profile across the various categories of TDF use from baseline to the end of our study period, and the protective effect of TDF remained similar after adjustment for interim myocardial infarction. Further investigation to uncover the mechanisms that may potentiate TDF's protective effect is still needed.

Several factors should be considered in interpreting our study. First, the fact that 40% of our patients had been exposed to ARVs before the start of our study period may introduce important bias and confounding, particularly if their HIV was either well controlled or difficult to control on their preexisting regimens before the introduction of TDF. However, a sensitivity analysis including only ARV-naive patients actually showed similar protective associations for TDF. Second, we were unable to distinguish between systolic and diastolic HF, and we did not have echocardiographic data to help determine the mechanisms of these putative protective effects. We were also unable to determine whether the use or avoidance of nephrotoxic medications such as nonsteroidal anti-inflammatory drugs may have influenced our findings, as we could not reliably assess the use of these over-the-counter medications. Finally, we cannot rule out unmeasured confounding as the explanation for these associations. However, our findings persisted after MSM adjustment for drug channeling bias and after numerous sensitivity and subgroup

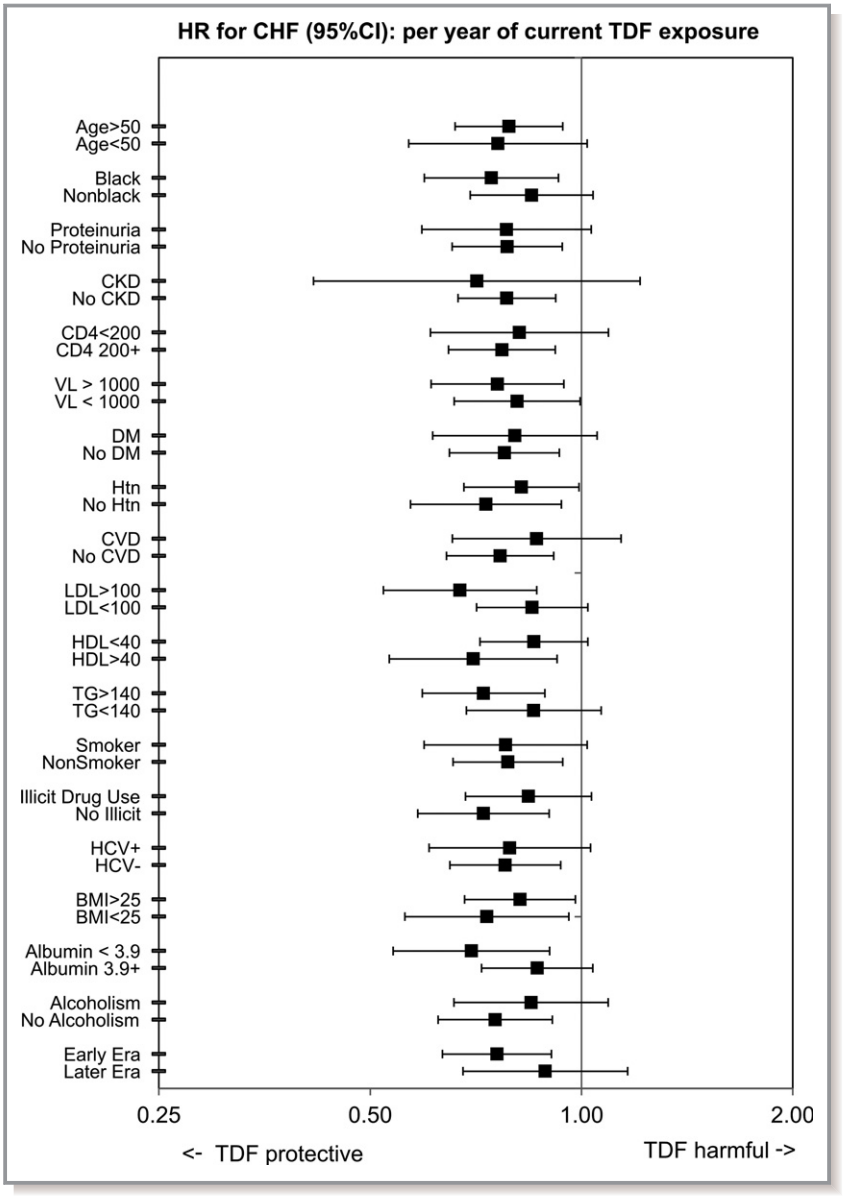

Figure 2. Association of current TDF exposure with incident HF stratified across subgroups of patient characteristics and risk factors. Point estimates of HRs for incident HF across all subgroups showed a similarly protective effect of TDF, suggesting that no single group or factor was driving the overall association of TDF use with lower risk of HF. Tests for TDF-by-subgroup interaction were statistically nonsignificant (all $P>0.13$). Patient characteristics and risk factors were obtained from covariates in marginal structural model. Early era defined as before 2003; late era defined as after 2003. CKD indicates chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HCV, hepatitis C; HDL, high-density lipoprotein; HF, heart failure; HR, hazard ratio; HTN, hypertension; LDL, low-density lipoprotein; TDF, tenofovir disoproxil fumarate; TG, triglycerides; VL, viral load.

analyses, so we believe that confounding alone is an unlikely explanation for the effect of TDF on HF risk. Our results also may not be generalizable to other populations, as our cohort consisted predominantly of male US veterans who are actively treated in a comprehensive integrated healthcare system.

In this large national sample of predominantly male patients with HIV, we observed that TDF use was strongly associated with a lower risk of incident HF. This association was most prominent for patients who were currently on TDF at the end of the study period or those who started on

TDF as part of their initial ARV regimen. The association of TDF with HF risk warrants additional study in other clinical settings and populations, including users of preexposure prophylaxis, and potential mechanisms should be evaluated. If this positive association of TDF on HF risk is confirmed across populations, then it would also need to be evaluated for the newer formulation of tenofovir, tenofovir alafenamide fumarate, which has much lower circulating concentrations than TDF.

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