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The Epi-TAF for Tenofovir Disoproxil Fumarate?

Rochelle P. Walensky,[1,2,3,4] Tim H. Horn,[5] and A. David Paltiel[6]

[1]Medical Practice Evaluation Center, [2]Division of Infectious Disease, and [3]Division of General Internal Medicine, Massachusetts General Hospital, and [4]Harvard University Center for AIDS Research, Harvard Medical School, Boston, Massachusetts; [5]Treatment Action Group, New York, New York; and [6]Yale School of Public Health, New Haven, Connecticut

Approximately 84% of human immunodeficiency virus (HIV)–infected US residents on antiretroviral therapy currently receive some form of tenofovir disoproxil fumarate (TDF) as part of their HIV treatment regimen. The TDF analogue tenofovir alafenamide (TAF) has demonstrated equal efficacy but with decreased renal injury and bone mineral density loss compared with TDF. We examine how much more society ought to be willing to pay for TAF over TDF, in exchange for its improved toxicity profile. Using cost-effectiveness methods, we find that current conditions warrant an annual premium of up to $1000 over the average wholesale price (AWP) of TDF. Once generic coformulations of tenofovir/lamivudine become accessible, however, the appropriate premium for TAF will likely merit a downward adjustment, using generic TDF-based costs as the benchmark.

Keywords. tenofovir disoproxil fumarate; tenofovir alafenamide; costs; cost-effectiveness; generics.

For more than a decade, tenofovir disoproxil fumarate (TDF) has been a mainstay in the human immunodeficiency virus (HIV) armamentarium and is listed as a World Health Organization (WHO) "essential medicine" [1]. Recently, Gilead Sciences, Inc. (Foster City, California) has stepped up development of tenofovir alafenamide (TAF), a TDF analogue. Compared with TDF, TAF has been known since 2001 to achieve higher intracellular concentrations of the active moiety tenofovir diphosphate and lower plasma levels of tenofovir while requiring one-tenth of the active drug, thereby resulting in a more favorable toxicity profile [2]. Now, phase 3 trials confirm that TAF-based combinations are as effective and produce fewer side effects than TDF-inclusive regimens [3].

On 5 November 2015, the US Food and Drug Administration (FDA) approved TAF as a new component in the coformulated elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/FTC/TAF; Genvoya). Gilead has priced the new combination competitively at an average wholesale price (AWP) of $37 118. This AWP is identical to the current AWP of the coformulated combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/FTC/TDF; Stribild), which was used as the comparator in the phase 3 studies [3–5]. In an economic climate that continues to demand cost containment, particularly for healthcare expenditures, we sought to estimate what a cost-effectiveness analysis might say about the premium that society should be willing to pay over this base price in exchange for a drug that promises to be just as effective but less toxic.

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Correspondence: R. P. Walensky, Medical Practice Evaluation Center, Massachusetts General Hospital, 50 Staniford St, 9th Flr, Boston, MA 02114 (rwalensky@partners.org).

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TENOFOVIR DISOPROXIL FUMARATE

TDF has long been a cornerstone of antiretroviral therapy regimens worldwide. First approved for HIV treatment by the FDA in 2001, it has subsequently been approved both for treatment of chronic hepatitis B (2008) and, as part of TDF/FTC (Truvada), for prevention of HIV infection (2012). Since early 2003, TDF/FTC has been a recommended first-line treatment in the United States for HIV infection, first in combination with efavirenz and subsequently with other first-line agents, including darunavir/ritonavir, elvitegravir/cobicistat, raltegravir, rilpivirine, and, most recently, dolutegravir (DTG) [4]. An estimated 84% of HIV-infected US residents on antiretroviral therapy currently receive some form of TDF/FTC [6]. In a testament to its safety and efficacy, tenofovir is listed as an "essential medicine," both alone and in fixed-dose combinations, by the WHO [1]. Annual sales of branded products containing TDF worldwide exceeded $10 billion in 2014 [7].

TDF is remarkably effective and tolerable. Suppression rates using TDF as a nucleoside reverse transcriptase inhibitor (NRTI) backbone exceed 90% [3]. The list of frequent side effects is short: nausea, diarrhea, and headache [3]. However, TDF has been associated with nephrotoxic effects and decreases in glomerular filtration rates (GFRs). This has limited its use in patients with a GFR <70 mL/min [4]. TDF has also been associated with a greater loss of bone mineral density (BMD) than other NRTIs. While these 2 side effects constitute the basis for further drug development, the overall impact of these metabolic toxicities is thought to be clinically meaningful but generally low, compared to its benefits. One editorial on the topic carries the subtitle "Does statistically significant mean clinically significant?" [8]. Tenofovir's exceptional tolerability perhaps explains its viability for use among HIV-uninfected individuals as part of preexposure prophylaxis (PrEP).

TENOFOVIR ALAFENAMIDE

Gilead Sciences, Inc. has recently received FDA approval of TAF for use as a lower-toxicity alternative to TDF. The phase 3 double-blind study of E/C/FTC/TAF compared with E/C/FTC/TDF confirmed comparable rates of virologic suppression between the 2 arms [3]. As anticipated, subjects in the E/C/FTC/TDF arm had worse toxicity outcomes related to rises in serum creatinine, increased proteinuria, and more loss of BMD in the spine and hip compared with those in the E/C/FTC/TAF arm. For the treatment of HIV, TAF will likely be marketed in coformulations at 2 different doses: 10 mg will be for use when dosed in combination with cobicistat (as in the above phase 3 trial and as recently FDA approved) or with boosted protease inhibitors; 25 mg will be used for all other dosing combinations and has yet to receive approval.

COST-EFFECTIVENESS OF TAF REGIMENS

FDA approval of these TAF-inclusive coformulations has hinged—and will continue to hinge—on evidence of TAF's superior toxicity profile when compared to TDF. Unaddressed in the FDA's evaluation will be the question of pricing and whether the substitution of TDF with TAF makes a justifiable incremental claim on scarce HIV treatment resources. With the clinical improvements of TAF over TDF, there should be no reason to continue Stribild prescribing; it has less overall efficacy at identical costs as Genvoya. This is only true, however, if there is parity across US payer systems such that the equivalent AWP also translates to matching rebates for certain public insurers and equal out-of-pocket costs and access among those patients in need.

From the payer perspective, it seems a fitting time to ask how much more society might be willing to pay for TAF-inclusive coformulations vs what it currently pays for TDF-based regimens. To address that question, we conduct the following "what-if" assessment: Assuming that all US patients currently receiving TDF-based therapies could immediately be switched to comparable TAF-based regimens, what is the maximum price that might justify the adoption of TAF as a cost-effective alternative to TDF? We use a simple spreadsheet model to compare anticipated TAF/FTC regimens with alternative TDF/FTC-based regimens at current TDF/FTC-based regimen costs, over a 1-year time horizon. In conformity with widely accepted practice, we calculate incremental cost-effectiveness ratios (ICERs), determining the price at which each TAF-based strategy would confer adequate value.

Because our goal is to identify the highest justifiable price for TAF, we deliberately tilt the scales in favor of TAF, setting our base case input parameter values to the extreme ends of their plausible ranges. We do so by portraying the efficacy and toxicity profile of TAF in a plausible but optimistic light while simultaneously depicting TDF-based regimens in a highly unfavorable light. For example, we assume that downstream outcomes of TDF-related toxicities (eg, hemodialysis from nephrotoxicity and fracture from bone loss) occur immediately and that costly treatment for some of those events (eg, hemodialysis) is incurred from the moment the events are first observed. Finally, we define "adequate value" using a $100 000 per quality-adjusted life-year (QALY) threshold, a value that lies at the high end of the range typically cited in the literature on the societal willingness to pay for life-saving treatment [9–11]. In the sensitivity analysis described below, we relax these extreme assumptions to consider the impact that generic availability of TDF might have on our findings.

INPUT PARAMETER ASSUMPTIONS

Parameters Related to TDF-Associated Renal Disease

On rare occasions, TDF demonstrates nephrotoxic effects including proteinuria, phosphate wasting, and metabolic acidosis. These are most commonly seen among those with prior renal disease and/or those concomitantly receiving boosted protease inhibitors. In one systematic review, including >400 000 person-years of TDF exposure, <0.2% of subjects experienced renal impairment; the increased risk difference of acute renal injury in cases compared with controls was 0.7% [12]. A smaller study (n = 24) noted that after an average of 13 months of follow-up in those who had TDF-induced renal insufficiency with drug discontinuation, renal function largely improved, but return to pre-TDF renal function ("normalization") was variable and incomplete [13].

Because our approach in this analysis is to portray the incremental impact of TAF vs TDF in the starkest light possible, we assume that 0.5% of patients receiving TDF have treatment-limiting nephrotoxicity (4/867 discontinued TDF due to renal adverse events) [3]. Although none of these patients progressed to requiring renal replacement therapy—and while TDF-induced nephrotoxicity requiring dialysis is exceedingly rare, even with cumulative doses in the long term—we conservatively assume that one-quarter of these patients require hemodialysis in the current year, costing $87 600 [12, 14]. The quality-of-life multiplier (on a scale where 0 is equivalent to death and 1 is equivalent to perfect health) associated with dialysis is 0.65 [15]; the quality-of-life multiplier with renal disease but without dialysis is assumed to be half the difference between that of dialysis and perfect health, 0.83. By contrast, we assume no nephrotoxic effects—and, consequently, no associated quality-of-life decrement—for patients receiving TAF.

Parameters Related to TDF-Associated Bone Disease

TDF has been associated with a greater loss of BMD than other NRTIs, although the impact of this metabolic toxicity is generally low. Only 2 of the 17 included studies (n = 1111) in the TDF systematic review reported any incidence of bone fracture; the relative risk of fracture while receiving a TDF-containing regimen compared with controls was not significant [12]. However, one Veterans Administration Case Registry review (>46 000 person-years of follow-up) demonstrated that TDF exposure was associated with a yearly hazard for osteoporotic fracture

of 1.06 in multivariable analyses (P = not significant) compared with other HIV-infected patients [16].

For this analysis, we assume, using data from the phase 3 trial, that 33% of patients have excess bone density loss at the hip (384/767 in the TDF arm and 131/780 in the TAF arm), and 19% of patients have bone density loss at the vertebrae (354/773 in the TDF arm and 208/784 in the TAF arm). Although bone loss leading to fracture is rare and generally requires years of cumulative exposure, we assume that 5% of patients with any TDF-associated bone density loss experience a fracture at that site in the current year [12]. The quality-of-life multiplier associated with a hip fracture is 0.70; that of a vertebral fracture is 0.59 [17]. Once again, we portray TAF in a comparatively favorable light by assuming no bone-metabolic effects and no associated loss of quality of life for patients receiving TAF.

Parameters Related to Regimen Costs

Antiretroviral net costs to employer and private plans (including Qualified Health Plans), Medicare, 340B providers, Medicaid/Medicaid managed care programs, and AIDS Drug Assistance Programs are highly variable. For this analysis, we employ the AWP, a recognized benchmark of drug-related resource use to different payers. The current annual AWP of coformulated E/C/FTC/TDF is $37 120 [4]; the current annual AWP of DTG + TDF/FTC is $38 730 [4]. Of this total regimen AWP, the TDF/FTC component accounts for $19 750 (varied in the analysis) and the DTG component accounts for $18 980 (unchanged).

MAXIMAL PERMISSIBLE PRICING FOR TAF

Table 1 reports the AWP at which the ICER of TAF-based regimens (compared to their TDF-based analogues) will just equal $100 000 per QALY. At any AWP below these values, the TAF-based regimens satisfy our stated criterion to be labeled "cost-effective" and, therefore, worth paying for. At any AWP above these ceilings, the incremental benefits of reduced toxicity using TAF cannot be justified on cost-effectiveness grounds. Although we have deliberately chosen input parameter values that portray TAF-based regimens under the most favorable light possible, we find that the permissible price increase over the AWP of current TDF-based regimens can be no greater than approximately $1 000 per year. Improving the profile of TDF in any way—for example, decreasing the annual hemodialysis or fracture frequency or assuming they occur in the more distant future—would reduce the permissible price increase related to TAF.

Table 1. Annual Average Wholesale Price of Tenofovir Alafenamide Regimen That Will Yield Incremental Cost-effectiveness Ratio >$100 000 per Quality-Adjusted Life-year

Regimen Comparator	Maximum Permissible AWP	Maximum Permissible Premium Over TDF AWP
E/C/FTC/TAF (vs E/C/FTC/TDF)	$38 110	$990
DTG + TAF/FTC (vs DTG + TDF/FTC)	$39 730	$990

Abbreviations: AWP, average wholesale price; C, cobicistat; DTG, dolutegravir; E, elvitegravir; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

SENSITIVITY ANALYSIS: IMPACT OF GENERICALLY AVAILABLE TENOFOVIR

The baseline analysis above ignores the potential for cost containment as TDF becomes generically available, anticipated in late 2017 [18]. As a generic drug, TDF will be easily coformulated with lamivudine (3TC), also generic, and will likely be available at a fraction of the cost of brand-name TDF/FTC. If we assume that generic AWPs will be a conservative 25% lower than brand-name TDF/FTC and that the efficacy of 3TC vs FTC is comparable [19], the anticipated annual AWP of a DTG + generic TDF/3TC regimen will be $33 800. Under such circumstances, and conducting similar calculations as above, a competing TAF-based regimen would have to cost <$34 790 to be economically attractive (ICER <$100 000/QALY). The AWP of this regimen is already lower than that of the DTG + branded TDF/FTC ($38 730).

This finding should be interpreted with caution: From a cost-effectiveness perspective, it suggests that society ought to be willing to pay up to $34 790 for TAF-inclusive coformulations, roughly $990 more than the anticipated AWP of generic TDF-based regimens. But it also suggests that, in the presence of generically available TDF, there does not exist a TAF premium over the current $38 730 AWP for branded TDF-based regimens that society ought to be willing to pay.

TAF FOR USE AS PrEP

Because current FDA approval efforts focus on TAF as HIV treatment, we did not consider TAF use for PrEP to be germane to our analysis. Pending the results of animal data, TAF coformulated with FTC will likely enter human pharmacokinetics, pharmacodynamics, safety, and efficacy trials as PrEP. The pricing of TAF as PrEP will then warrant further study and will need to be considered in the context of comparative safety data and whether generic TDF/3TC is already available.

IMPLICATIONS AND CONCLUSIONS

The recent FDA approval of Genvoya and the anticipated approval of other TAF formulations forces us, once again, to confront the painful balance that must be struck between doing what is absolutely best for our patients and exercising reasonable restraint in the face of competing claims on scarce resources. While we should be prepared to pay more for safety, efficacy, and dosing improvements, we must also insist, whenever possible, on judicious cost containment.

The clinical case for TAF over TDF appears solid. With fewer milligrams of the active pharmaceutical ingredient, TAF is almost certainly as effective and less toxic. In terms of clinical effectiveness, it is superior to TDF. Viewed through the (admittedly narrow) lens of doing what is clinically best for patients,

TAF will likely emerge as the better choice—one which can demand a higher price.

But "better" does not necessarily imply "worth it." Society cannot and should not be willing to pay any price for TAF's clinical superiority. The toxicities associated with TDF—the drug that TAF will replace—are both infrequent and most often managed by substituting another antiretroviral agent without the general interruption of HIV therapy. Viewed through the (admittedly equally narrow) lens of a cost-effectiveness analysis, we find that an annual premium of up to $990 over the current AWP of TDF-based coformulations can be justified. Depending on what we believe about the quality-of-life loss related to TDF toxicity, price increases beyond $990 annually are unlikely to confer sufficient value. Under alternative assumptions where TDF toxicity leads to fewer events or better quality of life than denoted above, the defensible price differential related to TAF may be even smaller. Moreover, when generic TDF/3TC becomes easily available, the price of the generic combination will impose an even more restrictive ceiling on what society will be willing to pay.

Notes

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