ORIGINAL RESEARCH

Modeling the Impacts of Restrictive Formularies on Patients With HIV

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ABSTRACT

OBJECTIVES: To model the impacts of restrictive formulary designs on outcomes for patients with HIV and to demonstrate the costs of restricting access to novel HIV regimens with better safety and efficacy profiles.

STUDY DESIGN: We modified an epidemiological model of HIV incidence, progression, and treatment to simulate the effects of 5 formulary scenarios on patient outcomes in the United States.

METHODS: Using a cohort of HIV-susceptible individuals, we followed patients through HIV infection, disease progression, and death. Patients transitioned in and out of treatment states once infected. Treatment discontinuation, efficacy, and the rate of adverse events (AEs; renal failure and bone fracture) in each formulary scenario depended on the treatment path and regimens included. Outcomes of interest included all-cause cumulative deaths, annual rates of AEs, and costs associated with treating those AEs.

RESULTS: All outcomes of interest were more favorable in less restrictive formulary scenarios that provided fewer barriers to appropriate treatments. By 2025, more restrictive formularies would have resulted in 171,500 more cumulative bone and renal events among treated patients with HIV compared with an open formulary. This corresponds to AE treatment costs of $3.65 billion in more restrictive formularies compared with $1.43 billion in an open formulary. Finally, compared with an open formulary, there would be an additional 16,200 cumulative deaths in more restrictive formularies.

CONCLUSIONS: Less restrictive formulary designs, which allow patients with HIV to initiate potentially safer and more efficacious regimens based on their proclivity to AEs, yield better outcomes and reduce costs.

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The past 20 years have seen a rapid development of innovative antiretroviral therapies allowing patients with HIV to live longer and healthier lives and reducing the risk of transmission.[1] Molecules approved since the early 2000s are more effective and associated with fewer and less serious adverse events (AEs) than earlier HIV therapies.[2] The combination of these therapies into single-tablet regimens (STRs) has also simplified treatment administration, enhancing adherence and viral suppression.[3-6] Despite the availability of these improved treatment options, fewer than half of the 1.1 million Americans living with HIV in 2015 were engaged in care and achieved viral suppression.[7,8]

Many factors impact engagement in care and viral suppression. Formulary and utilization management policies, such as tiering and step therapy, that require patients to initiate therapy on cheaper regimens before moving to potentially more effective alternatives can reduce access to drugs that receive less desirable formulary placement.[9-11] For patients with HIV, formulary restrictions may have a number of repercussions, such as reduced adherence and viral suppression.[12-14] Further, requiring patients to initiate one regimen before accessing others, without consideration of patient heterogeneity, may adversely impact those with comorbid conditions.[1] Healthcare costs and utilization may also increase because of reduced viral suppression or increased AEs.

New therapies, such as those based on tenofovir alafenamide (TAF), continue to reduce the likelihood and severity of AEs, decreasing the possibility of a patient switching or discontinuing treatment.[15-23] Although common AEs like nausea and headaches still occur across all HIV regimens, more serious events like renal failure or bone fractures are mitigated with the newest options.[18,19,23] Still, despite demonstrated improvements in reducing AEs, new regimens are not always immediately available for patients because of formulary and utilization management policies.

Study Objectives

We aimed to model the impacts of restrictive formulary designs on outcomes for patients with HIV and to demonstrate the costs

of restricting access to novel HIV regimens that have better efficacy and safety profiles.

TAKEAWAY POINTS

This study evaluated the impact of formulary designs on HIV patient outcomes, specifically the frequency and costs of certain adverse events and excess mortality. Findings are relevant for policy makers developing formulary management approaches for HIV treatments.

- Compared with an open formulary, more restrictive formularies would have 171,500 more cumulative bone and renal events among treated patients by 2025.
- Cumulative costs from these events in the more restrictive formularies would total $3.65 billion by 2025 compared with $1.43 billion in an open formulary.
- In more restrictive formulary scenarios, there would be 16,200 more cumulative deaths by 2025 compared with an open formulary.

METHODS

Model Overview

We modified a previously developed epidemiological model of HIV incidence, progression, and treatment to simulate the effects of 5 HIV formulary scenarios on patient outcomes in the United States (**eAppendix A** [eAppendices available at **ajmc.com**]).[24,25] Our model incorporated incoming cohorts of HIV-susceptible individuals, natural progression of HIV for treated and untreated individuals, and death. Individuals transitioned to different disease stages at rates based on the HIV-infected population size and infectivity in treated and untreated populations. The HIV natural history progression was defined according to the CDC's clinical classifications of HIV disease stages[26]: Patients in stage 1 had CD4+ cell counts greater than 500 cells/mcL; stage 2, 350 to 499 cells/mcL; stage 3, 200 to 349 cells/mcL; and stage 4, fewer than 200 cells/mcL. We used data from the CDC to estimate the distribution of recently infected individuals by stage.[26] We also included transitions between treated and untreated states according to treatment initiation and discontinuation rates and the possibility of switching HIV regimens (described later).[24,25]

Our model started with 1.2 million people infected with HIV in 2016.[26] We used published estimates from the CDC's Medical Monitoring Report and HIV Surveillance reports to obtain the distribution of the initial population by disease stage and treatment status (eAppendix Table 2).[26,27] We modeled HIV incidence through 2 categories of HIV transmission: (1) between untreated HIV-infected patients and susceptible individuals and (2) between treated HIV-infected patients and susceptible individuals. A lower rate of transmission was used for the latter category, reflecting the lower transmission rates observed for treated versus untreated infected patients.[28,29] eAppendix A presents the details of the model and parameters.

Treatment Regimens and Formulary Scenarios

Our model included 4 STRs: emtricitabine/rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF), and abacavir/dolutegravir/lamivudine (ABC/DTG/3TC). A fifth regimen, darunavir/ritonavir (protease inhibitor [PI]) plus 2 or more nucleoside reverse transcriptase inhibitors (PI/2NRTIs), was included as a second-line therapy in the event of virologic failure in certain formularies.

To encapsulate a range of formulary treatment policies, we developed 5 formulary scenarios that differed in access to HIV treatment regimens (**eAppendix B**). Within each formulary, patients faced AEs (specifically, renal toxicity or bone fracture) associated with certain HIV medications. Patients who experienced AEs or virologic failure switched to a different treatment regimen, determined by the rules of the particular formulary. Different efficacy and AE rates were used depending on pre-existing clinical conditions for patients. Treatment discontinuation rates were defined as the number of patients randomized to treatment who discontinued because of death, pregnancy, or study withdrawal, but did not include patients who discontinued treatment due to an AE. All parameter estimates were derived from the published literature or clinical trials. Detailed schematics for each formulary scenario can be found in eAppendix B.

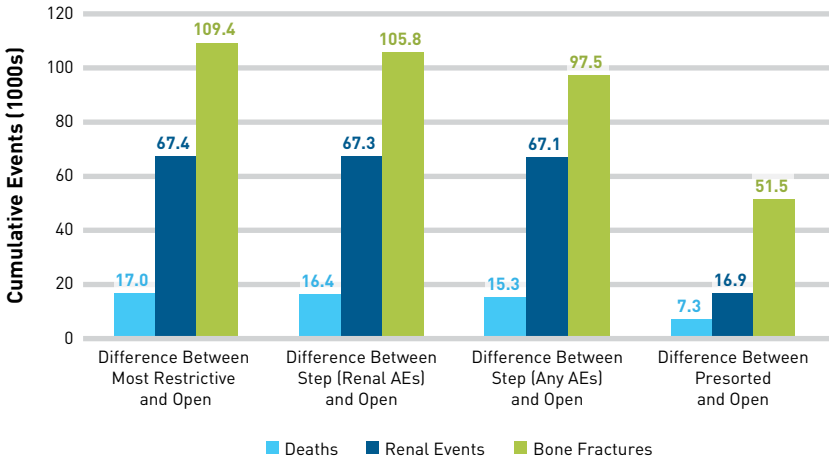
The first formulary scenario, "most restrictive," distributed patients equally across the TDF-based regimens and only allowed access to the initial treatment, regardless of AEs. In the event of a virologic failure, however, patients were transitioned to a PI/2NRTIs regimen.

Under the second and third formulary scenarios, "step (renal)" and "step (any AEs)," respectively, patients were distributed equally across the TDF-based regimens and were transitioned to an alternative regimen (either ABC/DTG/3TC or EVG/COBI/FTC/TAF) after the occurrence of an AE. The step (renal) scenario only allowed patients to transition to EVG/COBI/FTC/TAF if they experienced a renal AE. Patients with a bone fracture event were moved to ABC/DTG/3TC. In contrast, the step (any AEs) scenario allowed for transitions to EVG/COBI/FTC/TAF if a patient experienced either of the AEs. Under both step scenarios, patients with virologic failure on their first-line regimen were moved to a second-line treatment of PI/2NRTIs.

The fourth scenario, "presorted" formulary, allowed pre-existing clinical conditions to determine the initial treatment regimen. Under this scenario, patients with an existing bone disease, osteopenia, started on ABC/DTG/3TC or EVG/COBI/FTC/TAF; patients with a disposition to a renal event started on EVG/COBI/FTC/TAF; and all other patients started on a TDF-based regimen. Switching regimens occurred in the case of an AE or treatment failure, as in the step formularies.

The last scenario, "open" formulary, was the least restrictive and reflected current market trends among a population facing minimal or no co-pays. Patients with osteopenia (35.1%) were started on

FIGURE 1. Difference Between Other Formulary Scenarios and Open Formulary in the Number of Cumulative All-Cause Deaths, Renal Events, and Bone Fractures (2016-2025)



AE indicates adverse event.

ABC/DTG/3TC or EVG/COBI/FTC/TAF, whereas patients with a disposition to a renal AE (6.2%) were started on EVG/COBI/FTC/TAF. Additional patients were started on the TAF-based regimen such that this overall percentage matched the market distribution of treatment-naïve patients in the Ryan White program, a government program that provides cost-sharing assistance (and other services) to low-income people with HIV, as of the second quarter of 2016 (46%).[30] All other patients were started on a TDF-based regimen. Patients switched to an alternative regimen after treatment failure or AE.

An estimated 3% to 8% of individuals have allele HLA-B*5701, which is associated with hypersensitivity reactions from the abacavir component in ABC/DTG/3TC.[31-33] Based on those estimates, we assumed that 5.5% of the population had the allele. In the relevant formularies, we respected the hypersensitivity of those patients by using EVG/COBI/FTC/TAF, where ABC/DTG/3TC would have otherwise been chosen.

AE Costs

The costs of bone and renal AEs were calculated using data from the 2014 Medical Expenditure Panel Survey (**eAppendix C**).[34] Costs included inpatient, outpatient, emergency department, prescription, and office-based costs for each medical condition.

Model Outcomes

Our model projected the annual number of renal AEs and bone fractures for the treated population, the cumulative value of treatment costs associated with these events over the next 10 years, and cumulative all-cause deaths. Costs are represented in 2016 US$ and discounted at an annual rate of 3%.[35]

Model Calibration

We calibrated the model by comparing the percentage of patients with HIV treated by 2020, cumulative deaths from 2016 to 2025, and number of prevalent HIV cases in 2025 with published estimates from Shah et al[36] by adjusting HIV infectivity and the rate of disease progression across treated and untreated stages.

RESULTS

All outcomes of interest were most favorable for patients in the open formulary, followed by the presorted formulary. By 2025, the number of renal and bone AEs, costs associated with those events, and cumulative all-cause deaths were considerably lower in the open formulary than in the other scenarios (**Figure 1**).

Calibration

Our calibrated parameters produced estimates of HIV cases by 2025 and the percentage of individuals on treatment in 2020 that aligned with those reported in Shah et al (**eAppendix D**).[36] Our model showed an increase in the HIV-infected population from 1.2 million in 2016 to approximately 1.53 million in 2025 under the 3 most restrictive formulary scenarios and 1.52 million in the open scenario. Those results fell within Shah et al's CI of 1.24 million to 1.57 million. Across the formulary scenarios, our model produced a range of 515,000 to 532,000 cumulative deaths from 2016 to 2025, all of which fall within Shah et al's CI of 364,000 to 578,000.

Bone and Renal Events

The open scenario led to 171,500 and 68,500 fewer cumulative bone and renal events among treated patients with HIV by 2025 compared with the average of the 3 more restrictive scenarios and the presorted formulary scenario, respectively (Figure 1 and **Figure 2**). Although the number of AEs was the greatest under the most restrictive formulary scenario, both step therapy formulary scenarios resulted in more AEs than the presorted and open formularies.

Costs

From 2016 to 2025, cumulative costs associated with both bone fractures and renal disease were $2.23 billion higher in the step (renal) formulary, $2.19 billion higher in the step (any AEs) formulary, and $648.7 million higher in the presorted formulary, relative to the open formulary (**Figure 3**). Although there were fewer renal AEs across all scenarios, treatment costs for renal events were much higher than for bone fractures, leading to greater overall total costs.

Inpatient costs incurred by a renal event or bone fracture were the largest component of the cumulative costs in 2016-2025,

representing 52% and 48%, respectively (**Table**). Office-based provider costs were the second largest component, comprising 35% of renal AE costs and 19% of bone fracture AE costs. These 2 components alone represented $1.2 billion in cumulative costs in the open formulary, $1.7 billion in the presorted formulary, and slightly more than $3.0 billion in the step (any AEs) and step (renal) scenarios over 10 years (Table).

Second-Line Therapy

In more restrictive scenarios, considerably more people switched to a second-line treatment of PI/2NRTIs compared with the less restrictive formularies. In 2025, about 58,000 patients in the 3 most restrictive formularies were on a second-line regimen because of virologic failure. In contrast, an estimated 41,000 patients in the presorted formulary and 27,000 patients in the open formulary, were on the second-line regimen due to virologic failure.

Deaths

Compared with the open formulary, restricting access to HIV treatments led to 16,200 more deaths, on average, in the more restrictive formularies by 2025 (Figure 1). The presorted formulary resulted in about 7300 more cumulative deaths by 2025 than the open formulary.

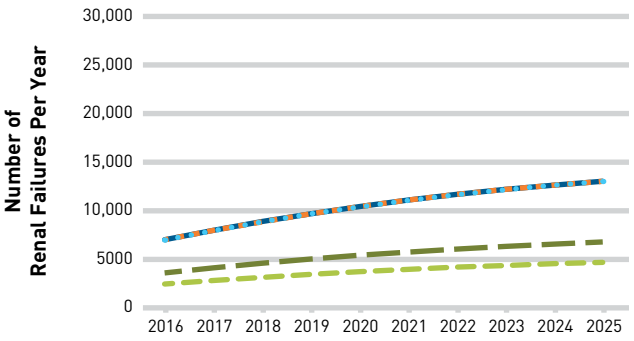
DISCUSSION

Our findings illustrate that a scenario that matches the distribution of treatments observed in a treatment-naïve HIV population that obtains a high degree of access to available treatments—Ryan White patients—significantly reduces AE treatment costs and mortality rates relative to more restrictive formulary designs. These results are driven by a greater initial utilization of therapies with better efficacy and AE profiles in our open design, along with sorting patients who are predisposed to certain AEs to more tolerable regimens. The open design outperforms the presorted design because even more patients are started on the newer TAF-based therapy, which has demonstrated lower rates of serious AEs and improved efficacy.[37] Compared with the open formulary, we estimated that the average restrictive formulary design, which initiates fewer people on therapies with better efficacy and safety profiles and allows switching to those therapies only under particular circumstances, would result in $2.28 billion in additional healthcare costs over 10 years and 3.5% more deaths of patients with HIV.

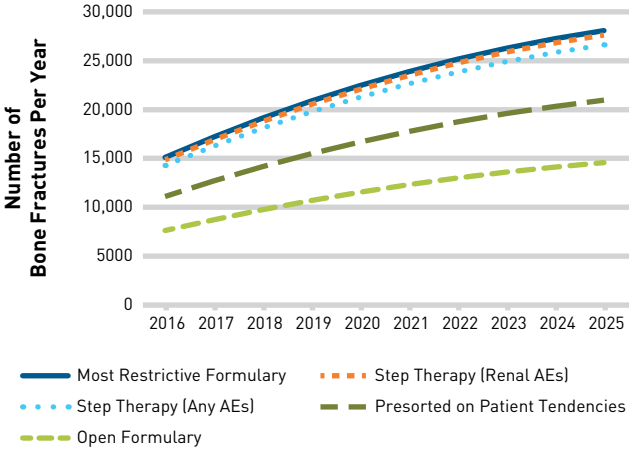
Although step therapy approaches aim to reduce the costs of treatment by prioritizing less-costly regimens, in practice, the number of people receiving non-STR therapies may contribute to future increases in healthcare costs.[38] Our analysis, which incorporates a second-line multitablet regimen (MTR) therapy in the event of virologic failure on a first-line treatment, complements other research findings that STRs are associated with lower per patient healthcare and hospitalization costs compared with MTRs.[39]

FIGURE 2. Annual Number of Renal Events and Bone Fractures (2016-2025)

A. Number of renal failures per year, 2016-2025, across formularies



B. Number of bone fractures per year, 2016-2025, across formularies



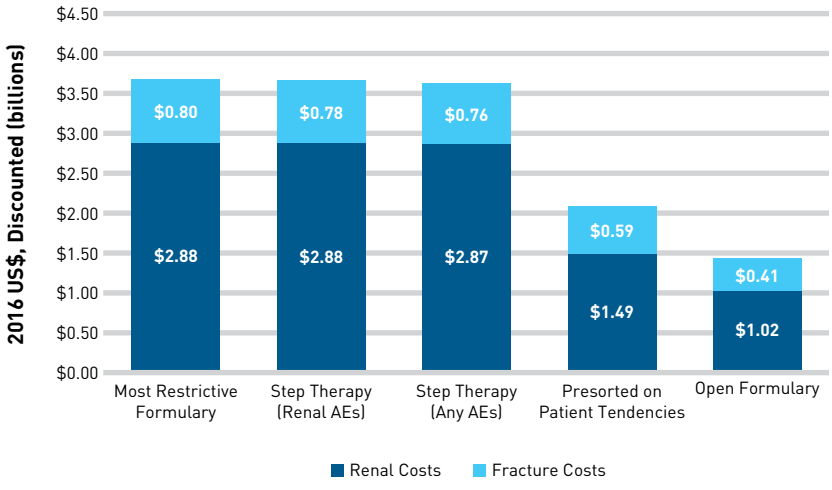
AE indicates adverse event.

Fewer cumulative all-cause deaths in the less restrictive formulary scenarios are attributable to several factors. First, more patients are receiving more efficacious regimens. Second, lower AE rates for those on the TAF-based therapy result in fewer patients switching regimens. Using values for a statistical life reported in the literature, the discounted value of the additional lives saved over 10 years in the open formulary versus the more restrictive formularies ranges from $58 billion to $188 billion, depending on the value of a statistical life used ($4.3 million, $9.2 million, or $13.8 million in 2016 US$).[40] This implies that additional spending in that range is justified by a standard social value criterion of the benefits exceeding the costs (based only on lives saved, and excluding savings from reduced AEs).

Policy Implications

Our findings demonstrate that policies that reduce patient access to HIV regimens with better outcomes in terms of efficacy, AE

FIGURE 3. Cumulative Treatment Costs of Renal Events and Bone Fractures (2016-2025)



AE indicates adverse event.

TABLE. Cumulative Treatment Costs of Bone and Renal AEs by Component (2016-2025)

	Formulary				
Category of Care	Most Restrictive	Step (renal AEs)	Step (any AEs)	Presorted	Open
Renal AEs (2016 US$, discounted millions)					
Inpatient hospital	1483.4	1482.3	1479.2	768.3	528.0
Outpatient hospital	224.4	224.2	223.7	116.2	79.9
Emergency department	6.9	6.9	6.9	3.6	2.5
Office-based provider	1017.6	1016.9	1014.7	527.1	362.2
Prescriptions	147.0	146.9	146.6	76.2	52.3
TOTAL	2879.4	2877.1	2871.2	1491.4	1024.9
Fracture AEs (2016 US$, discounted millions)					
Inpatient hospital	385.0	378.8	364.7	286.0	198.1
Outpatient hospital	91.8	90.3	86.9	68.2	47.2
Emergency department	73.2	72.0	69.3	54.4	37.7
Office-based provider	154.8	152.2	146.6	115.0	79.6
Prescriptions	92.5	91.0	87.6	68.7	47.6
TOTAL	797.2	784.3	755.2	592.3	410.1

AE indicates adverse event.

profiles, or adherence can have significant health and economic consequences. Some Medicaid plans have used preferred drug lists (PDLs), requiring a prescriber to receive prior authorization (PA) from the plan, and some health insurance Marketplace insurers have used restrictive formulary designs for HIV therapies.[41-44] Our analysis suggests that the implications of such restrictions should be carefully considered. Effects on outcomes depend on the specific drugs chosen and the nature of the restrictions. With respect to Medicare, our analysis illustrates the possible benefits from the protected class status that CMS has always maintained for antiretroviral drugs, ruling out closed formularies, limiting utilization management strategies, and expediting formulary review.

Limitations

Our study has several limitations. First, our model included some simplifying assumptions. For example, we assumed a uniform progression rate between stages 1 and 4 for treated patients that is intended to capture net progression, thereby embedding immunological recovery due to treatment. We did, however, calibrate our model so that key outputs were consistent with projections from a more complex published model. This approach may have resulted in an under- or overestimation of the projected burden of HIV. Second, although we varied transmission rates for untreated versus treated patients, we did not vary transmission rates by infection stage and instead used average rates based on the literature. This simplification might understate the outcome differences across the scenarios because transmission by treated patients would be relatively lower for formulary designs that generate better efficacy.

Third, the treatment efficacy parameters were based primarily on clinical trial data, which may not match real-world outcomes. Fourth, we focused only on fractures and renal AEs in our analysis. Thus, the cost differences across formularies would be greater if the frequencies of other events are, on balance, correlated with those included here. Certain cardiovascular events have been associated with ABC/DTG/3TC because of the abacavir component,[45] but they were not included in our analysis because their occurrence was not explicitly analyzed in the clinical trials used in our model.

Fifth, the model did not incorporate effects of an aging population due to the limited follow-up of patients involved in the clinical trials used in this study. Also, the median age of patients in the trial data ranged from 33 to 38 years, while the median age of patients with HIV is above 45 years.[19,27,46] Because the risk of osteopenia and osteoporosis in patients with HIV increases with age, as does the

risk of fractures, it is reasonable to think that the differences among the formularies in terms of AE costs and rates will be greater than our modeling indicates and may increase as the population ages and patients spend more time on HIV regimens.[47-49] Additionally, there may be varying quality-of-life effects experienced by an aging population that we did not capture.

Sixth, we acknowledge that, in practice, the definition of step therapy could vary across health plans. Our chosen formulary designs reflect a range of access restrictions. For example, a tiered co-payment design bears similarities to step designs: A preferred drug with a low co-pay is likely to be prescribed first, with movement to a higher-tier drug in the case of treatment failure or serious AE. There is also similarity between the use of PDLs or PA requirements and step therapy designs.

Finally, our characterization of an "open" formulary may be overly optimistic. Although the scenario matched the real-world utilization rates for therapies that have been observed in a treatment-naïve population facing low or no co-pays, we assumed that all patients with low kidney function or osteopenia were among those started on either TAF- or ABC-based regimens. Although this characterization captures the view that providers will sort patients to the most appropriate regimens, to the extent that they fail in this regard, outcomes will not be as favorable.

CONCLUSIONS

The findings from this study suggest that less restrictive formulary designs, which allow providers to start patients with HIV/AIDS on different regimens based on their proclivity to AEs (and result in more people using a TAF-based regimen, which is more effective and has a better AE profile), yield better outcomes and reduce AE treatment costs compared with more restrictive step therapy formularies. Although tiered co-pay designs and other utilization management strategies were not directly studied here, a similar impact on the sequencing of therapies for patients suggests that these practices would likely also result in suboptimal patient outcomes. ■

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Authorship Information: Concept and design (JB, CH, MK, LY, JR); acquisition of data (CH, LY); analysis and interpretation of data (JB, CH, MK, LY, JR); drafting of the manuscript (JB, CH, MK, LY, JC); critical revision of the manuscript for important intellectual content (JB, CH, JC, JR); statistical analysis (JB, MK); administrative, technical, or logistic support (CH, MK, LY, JC); and supervision (JB).

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eAppendix: Modeling the Impacts of Restrictive Formularies on HIV Patient Outcomes

eAppendix A. Description of Epidemiological Model

Conceptual Model

We adapted an epidemiological model of human immunodeficiency virus (HIV) transmission and progression first described by Granich, et al (2009) to evaluate the health and economic impacts of formulary restrictions to HIV treatments.[1,2] The model was adapted to the United States setting by Goldman et al (2014) to assess the effects of early access to antiretroviral therapy (ART) for HIV patients.[1] eAppendix Figure 1 and eAppendix Table 1 show the model schematics. The population of uninfected individuals, who were susceptible to HIV through sexual transmission, was represented by *S* in the figure. Births, determined by the population size (*N*) and birth rate (β), repopulated the susceptible population. We used the Centers for Disease Control and Prevention's (CDC's) four disease classifications as the disease stages through which patients progressed[3], identified by index i = {1,2,3,4}. Disease stages were defined based on cluster of differentiation 4 (CD4) count: ≥500 cells/mm^3 (Stage 1), 350–499 cells/mm^3 (Stage 2), 200–349 cells/mm^3 (Stage 3), and 0–199 cells/mm^3 (Stage 4). Once infected with HIV, individuals progressed untreated to the first disease stage, as indicated by the box I_1. Infected individuals would further progress untreated to the more advanced stages of disease, which was determined by ρ_i, the untreated rate of progression by disease stage. Alternatively, individuals in each disease stage could be treated according to a treatment initiation rate and transition to a treated state indicated by box A_i. We assumed similar rates of treatment initiation in each disease stage ($\tau = 0.15$) regardless of formulary scenario (see eAppendix Table 2 for parameter values). Once in a treated state, infected individuals might discontinue treatment and progress into the infected untreated disease stage at a rate indicated by φ. Treatment discontinuation rate was adjusted according to each HIV treatment formulary scenario, but was assumed the same for each disease stage within each formulary (eAppendix Table 3). Conversely, patients might continue on treatment but progress between the disease stages 1–4 at a calibrated rate of 0.046 indicated by σ. Patients could only flow out of the model because of death. Causes of death could be from acquired immune deficiency syndrome (AIDS), as indicated by D, due to progression from stage 4 (AIDS) to death at a rate of 0.1187 indicated by

σ_D, or by another cause, as indicated by μ, which was equivalent to the average United States mortality rate for the age 25–44 population of 0.00138.

We developed five hypothetical formulary scenarios described in the following sections. We ran the model separately for each scenario to generate the outcomes of interest. Under all scenarios, patients in the treatment states (A_i) could switch regimens due to renal failure or fracture adverse events, or virologic failure, or discontinue treatment and transition to the corresponding non-treated state.

We initiated our model in 2016. Each model cycle lasted 1 year (52 weeks), and we used a ten-year horizon for our analyses.

Incidence, Prevalence and Infectivity

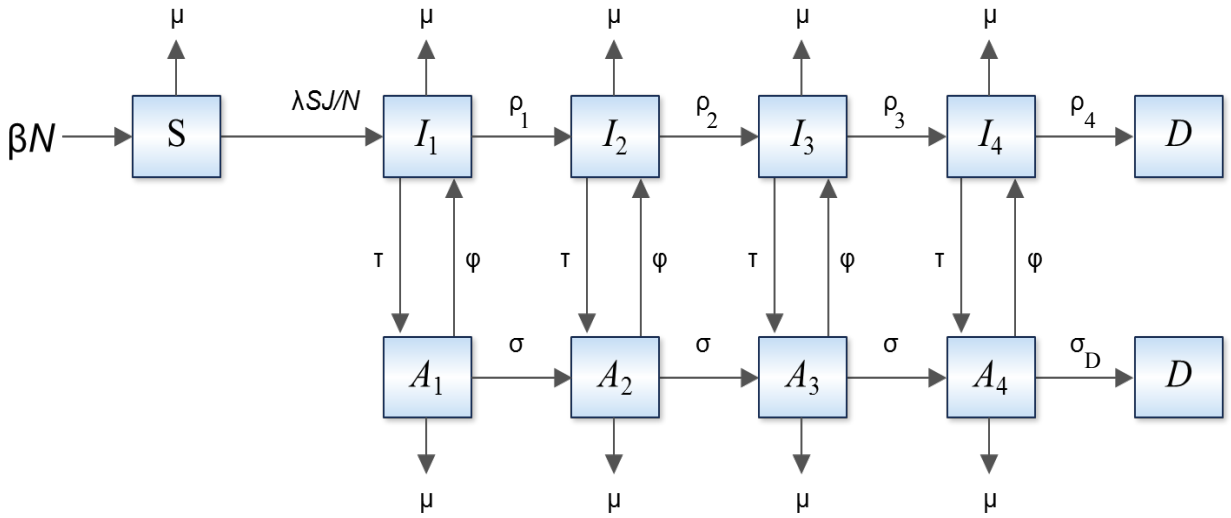
The incidence of new HIV cases depended on the infectivity of currently infected individuals. Treated HIV patients with a low viral load were much less likely to infect susceptible individuals than are HIV patients with a high viral load. HIV transmission was accounted for by considering an incidence rate rather than simulating the interactions between HIV-infected and susceptible individuals. We used an infectivity parameter of 0.05 according to the literature, indicating that a treated person was only 5% as likely to transmit the disease as an untreated person.[4-6] Patients who remained on highly effective treatment subsequently had lower viral loads and infectivity. Conversely, patients who did not respond to treatment or discontinued treatment because of an adverse event or other reason would likely have higher viral loads and greater infectivity.
As HIV is transferred through sexual activity in this model, we used the number of men who have sex with men (MSM) in the United States, 4.3 million, as a proxy for the susceptible population at the start of our model, in 2016.[7] While this estimate did not incorporate heterosexual men and women (14% and 17% of new HIV diagnoses, respectively), MSM represented an increasing majority of new HIV infections.[8]

According to estimates from the CDC, 1.1 million individuals were infected with HIV in the United States in 2015.[9,10]. To derive the population that receives treatment in the model, we multiplied the size of the HIV population by the estimated percentage of HIV patients who were on continuous treatment (48%) to generate our initial treated population..

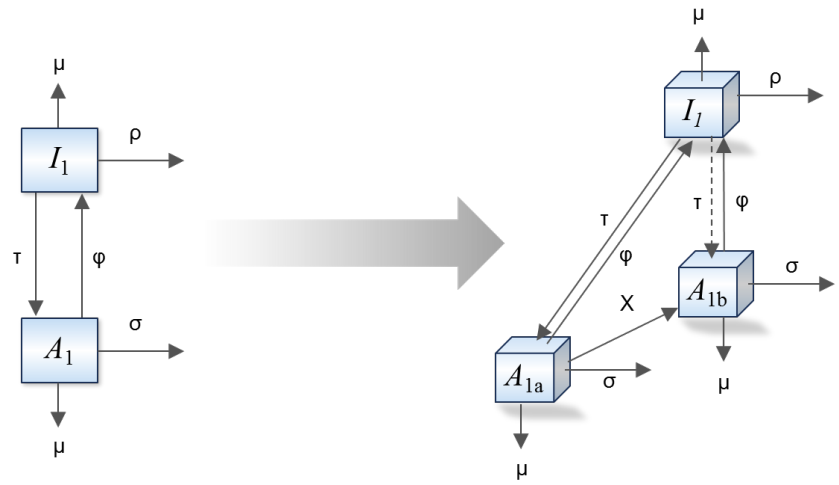
We stratified all HIV-infected individuals into four disease stages according to the CDC's 2015 Medical Monitoring Report. The report estimated that 49.2%, 22.9%, 15.8%, and 12.1% of

all HIV patients were in HIV stages 1–4, respectively.[11] We used these estimates to assign the initial disease stages to the HIV-infected population in 2016.

eAppendix Figure 1. Conceptual Framework of HIV transmission Model*



Conceptual Model of Regimen Switching



* Our epidemiological model was based on two previously published epidemiological models by Granich et al[2] and Goldman et al.[1]

eAppendix Table 1. Parameters for HIV Epidemiological Model

Parameter	Description[2]
i	HIV stage based on CD4 count: ≥500 cells/mm^3: Stage 1: ≥500 cells/mm^3 Stage 2: 350-499 cells/mm^3 Stage 3: 200-349 cells/mm^3 Stage 4: 0-199 cells/mm^3
β	Rate of inflow into susceptible compartment
N	Population
S	Susceptible compartment
$\lambda SJ/N$	Rate at which infection occurs
$\lambda = \lambda_0 e^{-\propto(N-S/N)n}$	Transmission parameter, calibrated $\propto$and n: parameters that account for heterogeneity in sexual behavior
$J = \Sigma i(Ii+\varepsilon Ai)$	Total number of people in infected compartments. ε allows for a reduction in the infectiousness of the people receiving ART, i = 1, …, 4
I_i	Compartment corresponding to non-treated population in HIV stage i, i = 1, …, 4
A_i	Compartment corresponding to treated population in HIV stage i, i = 1, …, 4
D	Death compartment
σ	HIV progression rate for treated population between stages 1–4
σ_D	HIV progression rate for treated population between stage 4 (AIDS) to death
τ	Rate of treatment initiation
φ	Combined rate of treatment discontinuation
ρi	HIV progression rate for non-treated population, i = 1, …, 4
μ	Background (all-cause) mortality rate

eAppendix Table 2. Model Parameters

Parameter	Value	Source
Population and Model Inputs		
Starting susceptible population in 2016	4,300,000	[7]
Starting infected population in 2016	1,120,000	[11]
Disease stage distribution among treated: proportion of total infected population		
Stage 1[a]	0.177	[11]
Stage 2	0.082	
Stage 3	0.057	
Stage 4	0.044	
Disease stage distribution among untreated: proportion of total infected population		
Stage 1[a]	0.315	[1,12-13]
Stage 2	0.147	
Stage 3	0.101	
Stage 4	0.077	
Mortality rate	0.00138	[14]
Birth rate	0.018	[15]
Infectivity rate	0.05	[5,7]
Age threshold for sexual transmission, years	13	[10]
Average age at infection, years	35.5	[11]
Disease progression rate among untreated (ρ) calibrated		
Stage 1 to stage 2[a]	0.249	
Stage 2 to stage 3	0.305	
Stage 3 to stage 4	0.490	
Stage 4 to death	0.540	
Disease progression rate between stages 1-4 among treated (σ)[b]		[1]
Base value	0.0460	
Most restrictive	0.0460	
Step therapy any AEs	0.0460	
Step therapy renal	0.0459	
Presorted	0.0446	
Open	0.0439	
Disease progression rate from stage 4 to death among treated (σ_D)[b]		[13, 16]
Base value	0.1187	
Most restrictive	0.1187	
Step therapy any AEs	0.1187	
Step therapy renal	0.1185	
Presorted	0.1151	

Open	0.1133	
Baseline prevalence of comorbidities		
Osteopenia	0.351	[17]
Renal impairment	0.062	[18]
Baseline prevalence of HLA-B*5701 allele (%)	5.5	[19-21]
Event Rates		
Treatment efficacy		
First-line therapy, no pre-existing condition[c]		
EVG/COBI/FTC/TDF	0.890	[22-24]
FTC/RPV/TDF	0.840	[25,26]
ABC/DTG/3TC	0.880	[27]
TAF-based regimen	0.920	[24]
First- or second-line therapy, renally impaired[c] population		
EVG/COBI/FTC/TDF	0.790	[28]
TAF-based regimen	0.920	[29]
First- or second-line therapy, low BMD[d] population		
TAF-based regimen	0.970	[30]
ABC/DTG/3TC	0.850	[31]
Second-line therapy, virologic failure		
PI+ 2 NRTIs	0.710	[32]
Treatment failure		
First-line therapy, no pre-existing condition		
EVG/COBI/FTC/TDF	0.050	[33]
FTC/RPV/TDF	0.080	[34]
TAF-based regimen	0.036	[24]
ABC/DTG/3TC	0.040	[27]
First-line therapy, renally impaired population		
TDF-based regimen	0.030	[35]
TAF-based regimen	0.010	[35]
First- or second-line therapy, low BMD population		
TDF-based regimen	0.030	[29]
TAF-based regimen	0.010	[30]
ABC/DTG/3TC	0	-
Second-line therapy, virologic failure		
PI+ 2 NRTIs	0.065	[32]
Treatment discontinuation		
No pre-existing condition		
EVG/COBI/FTC/TDF (first-line therapy)	0.060	[23]
FTC/RPV/TDF (first-line therapy)	0.051	[25]
TDF-based regimen (second-line therapy)	0.075	[29]
TAF-based regimen	0.040	[24]
ABC/DTG/3TC (first-line therapy)	0.065	[27]

ABC/DTG/3TC (second-line therapy)	0.010	Assumption
PI+ 2 NRTIs (second-line therapy)	0.210	[32]
Treatment discontinuation due to AE		
No pre-existing condition		
EVG/COBI/FTC/TDF	0.028	[22-24]
FTC/RPV/TDF	0.034	[25]
TAF-based regimen	0.010	[24]
ABC/DTG/3TC	0.024	[27]
Renally impaired population		
TDF-based regimen[e]	0.120	[28]
TAF-based regimen	0.110	[35]
Low BMD population		
TAF-based regimen	0.010	[31]
ABC/DTG/3TC	0.040	[31]
Adverse event		
Bone fracture, no pre-existing condition		
TDF-based regimen	0.0325	[23, 36, 37]
TAF-based regimen	0.0012	[24]
ABC/DTG/3TC	0.0150	[27]
Bone fracture, second-line therapy, no pre-existing condition		
PI+ 2 NRTIs	0.0150	[38]
Bone fracture, renally impaired population		
TDF-based regimen	0.0325	[29]
TAF-based regimen	0.0250	[35]
Bone fracture, low BMD population		
TAF-based regimen	0	[30]
ABC/DTG/3TC	0.0186	[39]
Renal AE, no pre-existing condition		
EVG/COBI/FTC/TDF	0.0100	[24]
FTC/RPV/TDF	0.0100	Assumption
ABC/DTG/3TC	0	[27]
PI+ 2 NRTIs	0.0150	[38]
Renal AE, second-line therapy healthy population		
TDF-based regimen	0.0030	[29]
Renal AE, renally impaired population		
TDF-based regimen	0.0900	[28]
TAF-based regimen	0.0800	[35]
Renal AE, low BMD population		
TAF-based regimen	0.0020	[30]
ABC/DTG/3TC	0.0036	[39]

ABC/DTG/3TC indicates abacavir/dolutegravir/lamivudine; AE, adverse event; BMD, bone mineral density; EVG/COBI/FTC/TAF, elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide; EVG/COBI/FTC/TDF, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; FTC/RPV/TDF, emtricitabine/rilpivirine/tenofovir disoproxil fumarate.

[a]Stage 1, CD4+ ≥500 cells/mcL; stage 2, CD4+ 350-499 cells/mcL; stage 3, CD4+ 200-349 cells/mcL; stage 4, CD4+ 0-199 cells/mcL.

[b]σ were used for all disease progression transitions between stages 1 and 4 within each formulary scenario. The base values of σ and σ_D were based on the reference, and then adjusted by the authors based on the relative efficacies and discontinuation rates between formularies**.**

[c]Pre-existing conditions: renal impairment or osteopenia. Renal impairment defined as estimated glomerular filtration rate Cockroft-Gault (eGFRCG) 30-69 mL/min.

[d]Osteopenia defined as a T-score of –1 to –2.5; osteoporosis defined as a T-score of –2.5 or below.

[e]Estimate for EVG/COBI/FTC/TDF only.

eAppendix B. Formulary Scenarios

To simulate the economic and health-related effects of limiting access to HIV treatments, we developed five formulary scenarios that ranged in their restrictiveness (eAppendix Figure 2). We selected four single-tablet regimens, based on their current market share or innovativeness as a treatment option: emtricitabine/rilpivirine/ tenofovir disoproxil fumarate (FTC/RPV/TDF; brand name: Complera), elvitegravir/cobicistat/ emtricitabine/ tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF; Stribild), elvitegravir/cobicistat/ emtricitabine/ tenofovir alafenamide (EVG/COBI/FTC/TAF; Genvoya), and abacavir/dolutegravir/ lamivudine (ABC/DTG/3TC; Triumeq). In all scenarios, patients who experience virologic failure were allowed to switch to a second-line regimen, darunavir/ritonavir plus 2 or more nucleoside reverse transcriptase inhibitors (NRTIs).

The first scenario, "Open" formulary was designed to be the least restrictive in design. Patients with osteopenia were started on ABC/DTG/3TC or EVG/COBI/FTC/TAF. We used the published literature to estimate that 35.1 percent of patients with HIV had osteopenia not attributable to treatments.[17] Patients with a disposition to a renal event were started on EVG/COBI/FTC/TAF. We estimated that approximately 6.2 percent of HIV patients had renal impairment (eGFR of 30–69 ml/min), based on the published literature.[40] All other patients were started on a TDF-based or TAF-based regimen in proportions such that the overall distribution reflects the current market distribution of patients in the Ryan White program on TAF-based products, 46 percent, as of the second quarter of 2016.[41] Patients moved to an alternative regimen with treatment failure or occurrence of an adverse event. This scenario reflected current market trends among a population facing minimal co-pays and provided the fewest restrictions on access to treatment.

The second scenario, "Pre-Sorted" formulary, was designed to represent a situation in which patients with certain pre-existing tendencies began on therapies better suited to their pre-existing conditions. In this scenario, we stratified patients according to the presence of pre-existing reduced kidney function or low bone mineral density. Patients with no baseline conditions initiated treatment on a TDF-based regimen. In the event of a virologic failure, patients were switched to darunavir/ritonavir plus 2 or more NRTIs. Patients who experienced an adverse event, except renal adverse events, transitioned to ABC/DTG/3TC. In the event of a renal adverse event, patients transitioned to EVG/COBI/FTC/TAF. Patients with renal

impairment initiated on EVG/COBI/FTC/TAF. Patients with reduced kidney function who experienced virologic failure transitioned to darunavir/ritonavir plus 2 or more NRTIs, but patients who experienced an adverse event stayed on EVG/COBI/FTC/TAF. Finally, patients with pre-existing osteopenia initiated treatment on EVG/COBI/FTC/TAF or ABC/DTG/3TC. If these patients experienced virologic failure, they were placed on darunavir/ritonavir plus 2 or more NRTIs. If these patients experienced a renal or fracture adverse event, they transitioned to either ABC/DTG/3TC or EVG/COBI/FTC/TAF—whichever they did not begin on (except that patients experiencing a renal event either remain on or switch to EVG/COBI/FTC/TAF).

Three additional scenarios represented more restrictive formulary designs. In those designs, patients first began on a TDF-based regimen with changes to another therapy allowed if particular events occurred. In the third scenario, "Step Therapy Any AEs", all patients began on a TDF-based regimen and were transitioned to darunavir/ritonavir plus 2 or more NRTIs in the event of a virologic failure. Patients who discontinued treatment because of the occurrence of any adverse event, however, were transitioned to EVG/COBI/FTC/TAF.

The fourth scenario, "Step Therapy Renal," was similar to Step Therapy Any AEs in that all patients began on a TDF-based regimen (EVG/COBI/FTC/TDF or FTC/RPV/TDF). Patients who experienced a virologic failure transitioned to darunavir/ritonavir plus 2 or more NRTIs. Similarly, patients who discontinued treatment because of a fracture adverse event transitioned to ABC/DTG/3TC. Patients who experienced a renal adverse event, however, transitioned to EVG/COBI/FTC/TAF.

The final scenario, "Most Restrictive" formulary, was designed to understand the impacts of a restrictive formulary design. In this scenario, all patients were placed on one of two TDF-based regimens (EVG/COBI/FTC/TDF or FTC/RPV/TDF). Patients were allowed to switch to darunavir/ritonavir plus 2 or more NRTIs only in the event of a virologic failure.

We used estimates from clinical trials with differing patient selection criteria to simulate the effects of the different formulary designs. In the Step and Most Restrictive formulary scenarios, the FTC/RPV/TDF and EVG/COBI/FTC/TDF efficacy and failure rates reflected the experience of the general population with HIV. In contrast, in the Pre-Sorted and Open formulary scenarios, patients without osteopenia or renal impairment were given efficacy, failure, and adverse event rates from trials that were restricted to patients without those conditions. Further, in these formularies, efficacy and failure rate estimates for patients with

bone or renal conditions were derived from clinical trials with patient populations that were renally impaired or had low bone mineral density.

Treatment Efficacy, Failure and Discontinuation

The treatment efficacy, failure and discontinuation rates were derived from Phase III clinical trials lasting 48 weeks. We used the 48-week period as a proxy for our 52-week model cycle. The efficacy rate was determined by a plasma HIV-1 RNA count of less than 50 copies per ml. The virologic failure rate was determined by the number of patients who had 2 visits of plasma HIV-1 RNA greater than or equal to 50 copies per ml and less than 1 $\log_{10}$ reduction from baseline at week 8. Finally, we calculated the rate of treatment discontinuation as the number of patients randomized to treatment who discontinued because of death, pregnancy, withdrawal or similar reasons.

As a way to draw distinctions in efficacy and adverse event rates across different formulary scenarios, the model made use of results from clinical trials that differed in terms of inclusion criteria. For example, in the Open and Pre-Sort by Existing Conditions formularies, people with reduced kidney function are placed on EVG/COBI/FTC/TAF at the beginning of treatment, while people without any predisposing conditions for bone or renal problems may be placed on a TDF-based regimen. Hence, at that stage of these formularies, the clinical trial parameters for patients on EVG/COBI/FTC/TAF who have reduced kidney function were taken from a study that was restricted to patients having low kidney function, while the clinical trial parameters for the TDF or TAF patients were based on studies that excluded people with osteopenia or low kidney function.[29,30,35] Alternatively, in the step therapy designs that start all patients on TDF-based regimens, we used parameters from TDF clinical trials that reflected a broader range of patients.[29] Given the above details, we calculated the combined rates of treatment discontinuation and efficacy for each formulary scenario (eAppendix Table 3).

Adverse Event Calculations

We selected the occurrence of two adverse events, renal adverse events and bone fractures, as outcomes of interest. We selected these events, as they are often serious in nature and are associated with certain HIV treatment regimens.[42,43] Our outcomes of interest were the number of renal adverse events and bone fractures in each of the formulary scenarios through 2025. To

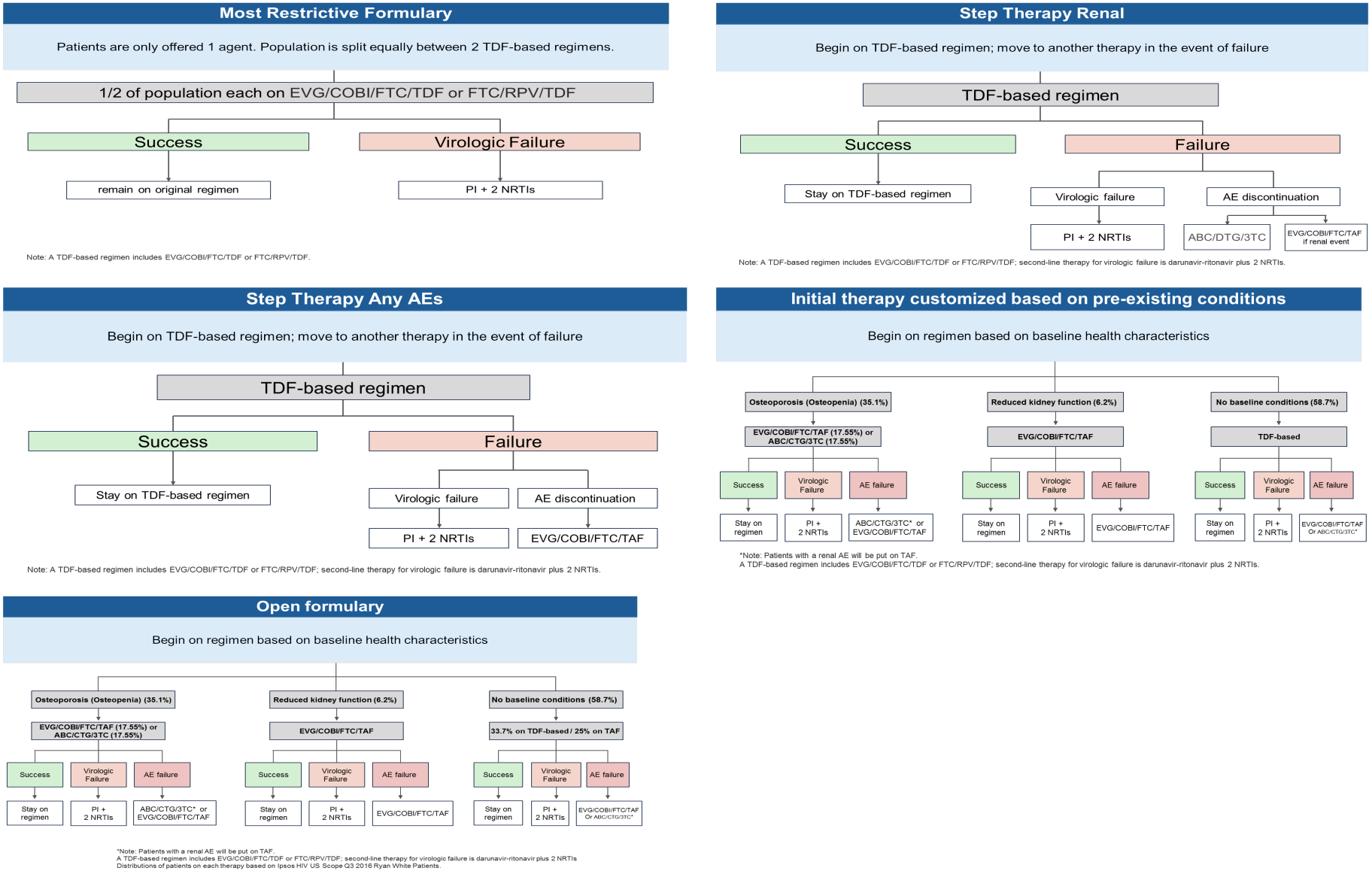
calculate the number of renal adverse events, we used estimates from Phase III clinical trials on the frequency of renal events over 48 weeks (the trial period). For every model cycle, we applied these rates to the populations treated by each regimen, according to our scenario designs.

We used a similar methodology to calculate the number of bone fractures. Again, we used estimates from Phase III clinical trials on the frequency of bone fractures over 48 weeks (trial period). We then applied these rates every cycle to the populations treated by each regimen, according to the scenario design. The combined rates of adverse events for each formulary scenario are presented in eAppendix Table 3.

eAppendix Table 3. Combined Rates of Treatment Efficacy, Discontinuation, and Adverse Events for each Formulary Scenario

Formulary Scenario	Efficacy	Discontinuation	Renal Failure	Bone Fracture
Closed Formulary	85.11%	6.60%	1.46%	3.14%
Step Formulary Renal	85.11%	6.56%	1.46%	3.09%
Step Formulary Any Adverse Event	85.24%	6.47%	1.45%	2.97%
Pre-Sorted Formulary	87.77%	6.00%	0.74%	2.30%
Open Formulary	89.18%	5.51%	0.50%	1.57%

eAppendix Figure 2. Formulary Scenario Schematics



eAppendix C. Adverse Event Costs

We also selected the medical costs associated with the renal adverse events and bone fractures as other outcomes of interest. To calculate the medical costs of each event, we selected ICD-9 diagnosis codes associated with HIV treatment-related renal adverse event or bone fracture per the published literature (renal adverse event codes: 270, 584, 585; bone fracture codes: 733, 800–829). Using data from the 2014 Medical Expenditure Panel Survey (MEPS), we calculated the mean condition-specific costs associated with the ICD-9 diagnosis codes to derive an estimate for the costs of a renal adverse event and bone fracture (eAppendix Table 4).[44] Finally, we multiplied the cost by the number of each of the events (renal adverse event or bone fracture) over each model cycle. We report cumulative costs from the first ten cycles of the model. All costs were updated to 2016 USD and discounted annually at a rate of 3.0%.

eAppendix Table 4. Cost Values Associated with Adverse Events

Component	**2016 US dollar value**
Bone Fracture	
Inpatient hospital	$1974
Outpatient hospital	$470
Emergency room	$375
Office-based provider	$794
Prescriptions	$474
Condition-specific costs	$4,088
Renal Adverse Event	
Inpatient hospital	$16,391
Outpatient hospital	$2479
Emergency room	$76
Office-based provider	$11,244
Prescriptions	$1625
Condition-specific costs	$31,814

eAppendix D. Comparisons of Model Outcomes

eAppendix Table 5. Model Comparisons of Patients Treated, Cumulative Deaths and HIV Prevalence

Parameter	Shah et al.[7]	Our model formularies			
		Step Therapy Renal	*Step Therapy Any AEs*	*Pre-Sorted*	*Open*
Percent of HIV patients treated in 2020	50	51.57	50.69	51.36	52.05
Cumulative deaths in 2016–2025	375,000 (364,000–578,000)	532,000	530,000	520,000	515,000
Projected number of prevalent HIV cases in 2025 (million)	1.47 (1.24–1.57)	1.5295	1.5289	1.5273	1.5245

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