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The Cost-effectiveness and Budget Impact of 2-Drug Dolutegravir-Lamivudine Regimens for the Treatment of HIV Infection in the United States

Michael P. Girouard,[1,2] Paul E. Sax,[3,4] Robert A. Parker,[1,4,5] Babafemi Taiwo,[6] Kenneth A. Freedberg,[1,2,4,7,8,9] Roy M. Gulick,[10] Milton C. Weinstein,[9,11] A. David Paltiel,[12] and Rochelle P. Walensky[1,2,3,4,7]

[1]Medical Practice Evaluation Center, and [2]Division of General Internal Medicine, Massachusetts General Hospital, [3]Division of Infectious Diseases, Brigham and Women's Hospital, [4]Harvard Medical School, and [5]Biostatistics Center, Massachusetts General Hospital, Boston, Massachusetts; [6]Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, Chicago, Illinois; [7]Division of Infectious Diseases, Massachusetts General Hospital, [8]Department of Epidemiology, Boston University School of Public Health, and [9]Department of Health Policy and Management, Harvard T. H. Chan School of Public Health, Boston, Massachusetts; [10]Division of Infectious Diseases, Weill Medical College of Cornell University, New York, New York; [11]Department of Biostatistics, Harvard T. H. Chan School of Public Health, Boston, Massachusetts; and [12]Yale School of Public Health, New Haven, Connecticut

(See the Editorial Commentary by Koenig and Pape on pages 792–4.)

Background. Recommended human immunodeficiency virus (HIV) treatment regimens in the United States contain 3 antiretroviral agents, costing >$30 000/person/year. Pilot studies are evaluating the efficacy of dual therapy with dolutegravir (DTG) and lamivudine (3TC). We examined the potential cost-effectiveness and budget impact of DTG + 3TC regimens in the United States.

Methods. Using a mathematical model, we projected the clinical and economic outcomes of antiretroviral therapy (ART)–naive patients under 4 strategies: (1) no ART (for modeling comparison); (2) 2-drug: initial regimen of DTG + 3TC; (3) induction-maintenance: 48-week induction regimen of 3 drugs (DTG/abacavir [ABC]/3TC), followed by DTG + 3TC maintenance if virologically suppressed; and (4) standard of care: 3-drug regimen of DTG/ABC/3TC. Strategy-dependent model inputs, varied widely in sensitivity analyses, included 48-week virologic suppression (88%–93%), subsequent virologic failure (0.1%–0.6%/month), and Medicaid-discounted ART costs ($15 200–$39 600/year). A strategy was considered cost-effective if its incremental cost-effectiveness ratio (ICER) was <$100 000/quality-adjusted life-year (QALY).

Results. The 3 ART strategies had the same 5-year survival rates (90%). The ICER was $22 500/QALY for induction-maintenance and >$500 000/QALY for standard of care. Two-drug was the preferred strategy only when DTG + 3TC 48-week virologic suppression rate exceeded 90%. With 50% uptake of either induction-maintenance or 2-drug for ART-naive patients, cost savings totaled $550 million and $800 million, respectively, within 5 years; savings reached >$3 billion if 25% of currently suppressed patients were switched to DTG + 3TC maintenance.

Conclusions. Should DTG + 3TC demonstrate high rates of virologic suppression, this regimen will be cost-effective and would save >$500 million in ART costs in the United States over 5 years.

Keywords. HIV; ART; cost-effectiveness; dolutegravir; lamivudine.

Combination antiretroviral therapy (ART) containing 3 active drugs from at least 2 different classes has been the standard of care for human immunodeficiency virus (HIV) treatment in the United States since the mid-1990s [1]. To reduce toxicity, complexity, and costs, strategies that decrease the number of active drugs have been evaluated, both as initial therapy and as "maintenance" therapy for patients who achieve virologic suppression. Although most efforts have yielded unacceptably high rates of treatment failure [2–5], 2-drug regimens with a boosted protease inhibitor (PI) plus lamivudine (3TC) have demonstrated favorable results [6–8].

Dolutegravir (DTG) is an integrase strand transfer inhibitor approved by the US Food and Drug Administration in 2013. As part of a 3-drug initial regimen, DTG has proven superior or noninferior to other first-line options [9–11]. In these studies, no patients experiencing virologic failure on DTG-based therapy developed resistance to DTG or nucleoside analogues, suggesting a high resistance barrier. Based on these findings, pilot studies are evaluating 2-drug DTG + 3TC as both initial and maintenance therapy, with results expected in early 2016 [12, 13].

Dolutegravir is available both individually (Tivicay, ViiV Healthcare) and as part of a single-tablet, 3-drug regimen combined with abacavir (ABC) and 3TC (Triumeq, ViiV Healthcare). DTG/ABC/3TC is 1 of 5 regimens currently recommended for initial HIV therapy by the 2015 Department of Health and Human Services (DHHS) guidelines [1]. As the average wholesale price (AWP) of branded DTG/ABC/3TC is $31 800/person/year, a maintenance or 2-drug strategy including branded DTG and

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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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generic 3TC (AWP $22 900/person/year) could produce substantial economic savings [14].

While pilot studies are ongoing, our objective was to use simulation modeling to examine the potential cost-effectiveness and budget impact of DTG + 3TC first-line ART strategies in the United States.

METHODS

Analytic Overview

We used the Cost-Effectiveness of Preventing AIDS Complication (CEPAC)–US model, a previously published microsimulation of HIV disease and treatment [15–17], to project the clinical and economic outcomes of HIV-infected, ART-naive patients in the United States under 4 strategies: (1) no ART, for modeling comparison; (2) 2-drug, an initial 2-drug regimen of DTG + 3TC; (3) induction-maintenance, an initial 3-drug regimen of DTG/ABC/3TC, followed by DTG + 3TC maintenance for patients with virologic suppression at 48 weeks; and (4) standard of care (SOC), an initial 3-drug regimen of DTG/ABC/3TC. In the absence of comparative clinical trial data, the SOC 3-drug regimen was conservatively assumed to have both higher rates of 48-week virologic suppression and lower rates of later virologic failure than the 2-drug DTG + 3TC regimen. All simulated patients initiated ART upon entering care according to national guidelines and were eligible to receive subsequent ART regimens upon virologic failure [1].

Clinical and economic outcomes were assessed at 1-year, 5-year, 10-year, and lifetime horizons and included quality-adjusted life expectancy (QALE), the proportion of patients remaining on first-line ART, total medical costs, and ART costs. Lifetime projections of clinical and cost outcomes, discounted at 3% per year [18], were used to compute incremental cost-effectiveness ratios (ICERs) for each strategy compared to the next less expensive strategy. We classified a strategy as "cost-effective" if its ICER fell below a frequently cited willingness-to-pay threshold in the United States of <$100 000/QALY, from a modified societal perspective [19]. We also conducted a budget impact analysis (BIA) to estimate the potential cost savings of these strategies in the first 1, 3, and 5 years [20].

The CEPAC-US Model

The CEPAC-US Model is a patient-level microsimulation of HIV disease, treatment, and medical care costs in the United States [15–17]. Individual patients enter the model with characteristics drawn randomly from user-defined distributions of age, sex, CD4 cell count at presentation, and HIV RNA level. The model simulates a unique trajectory for each patient using specified transition probabilities, which determine monthly transitions between health states.

All modeled patients are eligible to initiate ART, regardless of CD4 cell count, in accordance with DHHS guidelines [1]. Efficacy of ART in the model depends on a patient's level of adherence, drawn from a logit distribution (0%–100%), with more highly adherent patients experiencing greater rates of virologic suppression (HIV RNA < 50 copies/mL) at 48 weeks. Patients on suppressive ART experience increases in CD4 cell count and are subject to a monthly, regimen-specific probability of virologic failure (HIV RNA ≥ 200 copies/mL) after 48 weeks, also stratified by adherence. Patients whose virologic failure is detected and confirmed by standard viral load monitoring are eligible to receive PI-based ART; probabilities of virologic suppression and subsequent failure similarly depend on adherence. Clinical events and costs are recorded over the patient's lifetime; cohorts of 1 million patients are simulated to achieve stable per-person estimates.

Input Parameters

Cohort Characteristics

Cohort characteristics reflected previously untreated HIV-infected patients initiating ART in the United States. Parameters were derived from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), where mean age was 43 years (standard deviation [SD], 12 years), 84% were male, and mean CD4 count at ART initiation was 360 cells/μL (SD, 280 cells/μL) (Table 1) [21].

ART Efficacy and Adherence

The distribution of adherence levels in the cohort was derived from 2 studies of medication possession ratios (MPRs) of commercially and publicly (Medicaid) insured HIV-infected patients in the United States [22, 23]. We derived MPR levels (mean, 89% [interquartile range, 86%–98%]) using a logit-normal distribution. We assumed adherence was comparable between once-daily 1-pill and 2-pill regimens, as was shown in a recent meta-analysis of the effect of pill burden on HIV treatment adherence [29].

Patients in the 2-drug strategy were assumed to have virologic suppression of 88% at 48 weeks, based on findings for analogous 2-drug regimens [6, 24]. Patients in the induction-maintenance and SOC strategies—whose early suppression rates would, by definition, be the same—had overall suppression of 93% at 48 weeks (Table 1) [9, 11]. After suppression at 48 weeks, patients experienced virologic failure at rates derived from 96-week clinical trial data. Patients in 2-drug and induction-maintenance strategies were assumed to experience virologic failure at a rate of 0.6%/month [7, 24], and those in SOC experienced virologic failure at 0.1%/month [25]. These parameters were derived from clinical trial results and exclude loss to follow-up, protocol deviation, and death (Supplementary Appendix).

ART Costs

ART costs were from Red Book AWP; branded DTG/ABC/3TC was $31 800/person/year and DTG + 3TC was $22 900/person/year [14]. After applying a 23% and 70% Medicaid discount on branded and generic drugs, respectively, annual cost for model input was $24 500 for branded DTG/ABC/3TC and $15 200 for DTG + 3TC (Table 1) [28]. Subsequent PI-based and multidrug

Table 1. Base Case Input Parameters for an Analysis of Alternative Dolutegravir-Containing First-line Antiretroviral Therapy Strategies in the United States

Parameter	Value	Reference
Cohort characteristics		
Age, y, mean (SD)	43 (12)	[21]
Male/female, %	84/16	[21]
CD4 count at presentation, cells/μL, mean (SD)	360 (280)	[21]
ART efficacy		
Adherence distribution, %, mean (IQR)	89 (86–98)	Calculated from [22, 23]
First-line suppression <50 copies/mL at 48 wk, %[a]		
2-drug (DTG + 3TC)	88	[6, 24]
Induction-maintenance (DTG/ABC/3TC)	93	[9, 11]
Standard of care (DTG/ABC/3TC)	93	[9, 11]
Virologic failure for suppressed patients, %/mo[a]		
2-drug (DTG + 3TC)	0.6	[7, 24]
Induction-maintenance (DTG + 3TC)	0.6	[7, 24]
Standard of care (DTG/ABC/3TC)	0.1	[25]
Retention in care (/100 PY)		
Loss to follow-up		[26]
Adherence >95%	0.1	
Adherence <50%	84.5	
Return to care	18.1	[27]
Annual costs[b] (2014 USD)		[14, 28]
First-line ART		
2-drug	15 200	
Induction-maintenance[c]	24 500/15 200	
Standard of care	24 500	
Subsequent-line ART[d]	30 000–39 600	

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; DTG, dolutegravir; IQR, interquartile range; PY, person-years; SD, standard deviation; USD, US dollars.

[a] The boxes around these parameters indicate that they are, by definition, equal (as the regimens are the same) and are varied in lockstep in sensitivity analysis. Initial virologic suppression of induction-maintenance was always equal to that of the standard of care (DTG/ABC/3TC), and later failure of 2-drug was always equal to that of induction-maintenance (DTG + 3TC).

[b] ART costs were calculated as the average manufacturing price, based on Medicaid reductions of 23% of the average wholesale price (AWP) for brand-name drugs and 70% of AWP for generic drugs.

[c] Induction regimen cost is equal to that of standard of care (DTG/ABC/3TC) for the first 48 weeks; after 48 weeks, maintenance regimen cost is equal to that of 2-drug (DTG + 3TC).

[d] Those who switched to second-line ART upon virologic failure also experienced a quality-of-life decrement of 25% in the first month (0.25 quality-adjusted life-months) to account for side effects related to ritonavir-boosted protease inhibitors.

regimens ranged from $30 000 to $39 600 annually after Medicaid discount. Costs of routine medical care were stratified by CD4 cell count [17]. Costs were reported in 2014 US dollars.

Details of other model parameters can be found in the Supplementary Appendix and/or have been previously reported [16, 17].

Sensitivity Analyses

Univariate Sensitivity Analysis

In univariate analyses, we varied 48-week suppression of DTG/ABC/3TC for SOC and induction-maintenance (88%–93%); 48-week suppression of DTG + 3TC for 2-drug (83%–93%); rate of post–48-week virologic failure for DTG + 3TC for induction-maintenance and 2-drug (0.1%–1.2%/month); annual costs for DTG/ABC/3TC ($19 850–$29 150) and DTG + 3TC ($10 550–$19 850); and annual costs for PI-based regimens ($22 600–$37 400).

Multivariate and Probabilistic Sensitivity Analysis

We subjected influential parameters to additional, multivariate sensitivity analysis. We also conducted a probabilistic sensitivity analysis, specifying distributions for these key model parameters to determine the probability that each strategy was the most cost-effective at a willingness-to-pay threshold of <$100 000/QALY [30]. Probability distributions for ART efficacy inputs were derived from clinical trial data of DTG/ABC/3TC for the standard of care and of PI-based 2-drug regimens for 2-drug and induction-maintenance (Supplementary Appendix).

Budget Impact Analysis

Finally, we conducted a BIA of implementing these alternative DTG + 3TC regimens in the United States, examining potential cost savings over 1-, 3-, and 5-year time horizons. We accounted for the difference in costs between the regimen alternatives, the additional costs for those requiring second-line therapy, and deaths during the horizon. Anticipated "incident" annual HIV diagnoses were based on Centers for Disease Control and Prevention (CDC) data from 2013 (approximately 47 350 new diagnoses) [31]. Of those newly diagnosed, we assumed that an estimated 37% receive ART [32] and that only 50% were initiated on an induction-maintenance or 2-drug regimen, as some providers and/or patients might opt out of these strategies. In additional analyses, we evaluated the impact of switching various proportions of currently suppressed patients in the United States who have never experienced virologic failure (approximately 20% of the CDC-estimated 1.2 million HIV-infected individuals in the United States) to a DTG + 3TC maintenance strategy [32]. We varied assumptions about strategy uptake and ART regimen costs in sensitivity analyses. By convention, BIA results were undiscounted [20].

RESULTS

Base Case

Clinical Outcomes

Five-year survival was 90% in 2-drug, induction-maintenance, and SOC (Table 2). The proportion of patients remaining on first-line ART at 5 years varied, ranging from 89% in 2-drug to 97% with SOC. Among the ART strategies, undiscounted QALE was 22.56, 22.67, and 22.75 QALYs in 2-drug, induction-maintenance, and SOC, respectively.

Cost and Cost-effectiveness Outcomes

Per-person discounted 5-year cumulative medical costs were lowest for 2-drug ($91 100), intermediate for induction-maintenance ($96 500), and highest for SOC ($121 900) (Table 2, Figure 1). First-line ART costs comprised 59%, 67%, and 76%

Table 2. Base Case Clinical and Economic Model Outcomes of Alternative Dolutegravir-Containing Antiretroviral Therapy Regimens

	Undiscounted Results					Discounted Results			
Strategy	Proportion of Patients Alive at 5 y (%)	Proportion of Patients Alive at 10 y (%)	Proportion of Patients on First-line ART at 5 y[a] (%)	Proportion of Patients on First-line ART at 10 y[a] (%)	QALYs	5-y Per-Person Cost (2014 USD)	Lifetime Per-Person Cost (2014 USD)	QALY	ICER[b] ($/QALY)
No ART	53	21	. . .	. . .	5.90	68 700	118 600	4.98	–
2-drug	90	79	89	88	22.56	91 100	324 900	14.11	Weakly dominated[c]
Induction-maintenance	90	79	94	93	22.67	96 500	325 000	14.17	22 500
Standard of care	90	80	97	96	22.75	121 900	431 800	14.20	>500 000[d]

Abbreviations: ART, antiretroviral therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; USD, US dollars.

[a] Proportion of patients on first-line ART is out of all patients alive and on ART. Second-line therapy is assumed to be human immunodeficiency virus protease inhibitor based.

[b] ICERs are evaluated using a willingness-to-pay threshold of <$100 000 in 2014 USD.

[c] By convention, a strategy is labeled "weakly dominated" if it costs more and is less effective than some combination of other strategies [39].

[d] ICER for standard of care vs no ART is $34 000/QALY (Supplementary Appendix).

of total costs for 2-drug, induction-maintenance, and SOC, respectively.

Discounted lifetime costs were $118 600 for no ART and $431 800 for SOC; excluding the dual-therapy strategies, the ICER for SOC was $34 000/QALY compared with no ART and was cost-effective (Table 2). The costs for 2-drug ($324 900) and induction-maintenance ($325 000) were nearly identical. With no ART as comparator and including both dual-therapy strategies, the ICER for induction-maintenance was $22 500/QALY; compared to induction-maintenance, the ICER for SOC was >$500 000/QALY and was not cost-effective. While in the base case, 2-drug was weakly dominated by the combination of no ART and induction-maintenance, its clinical and economic outcomes were nearly identical to those in induction-maintenance (2-drug ICER compared with no ART, $22 600/QALY).

Sensitivity Analyses

Univariate Sensitivity Analyses

The most influential parameters in univariate sensitivity analyses were 48-week virologic suppression for DTG/ABC/3TC and DTG + 3TC; post–48-week virologic failure for DTG + 3TC;

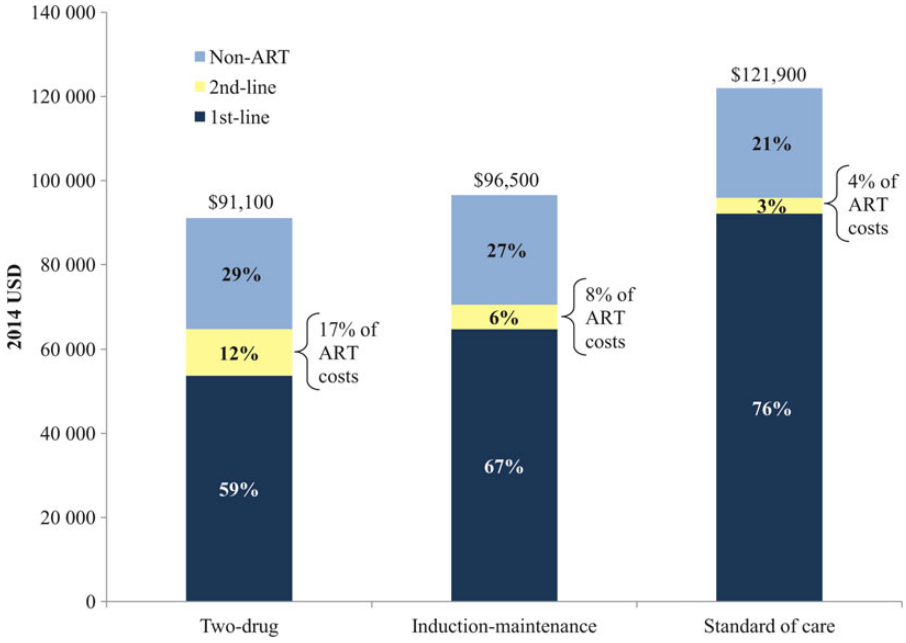

Figure 1. Cumulative discounted 5-year per-person costs (in 2014 US dollars [USD]) for the 2-drug, induction-maintenance, and standard-of-care strategies. Discounted costs stratified into first-line antiretroviral therapy (ART) costs (dark blue), second-line ART costs (yellow), and non-ART costs (light blue); the proportion of each cost category of total medical costs is labeled in each bar. Additionally, the proportion of 5-year ART costs comprised of second-line ART costs is shown.

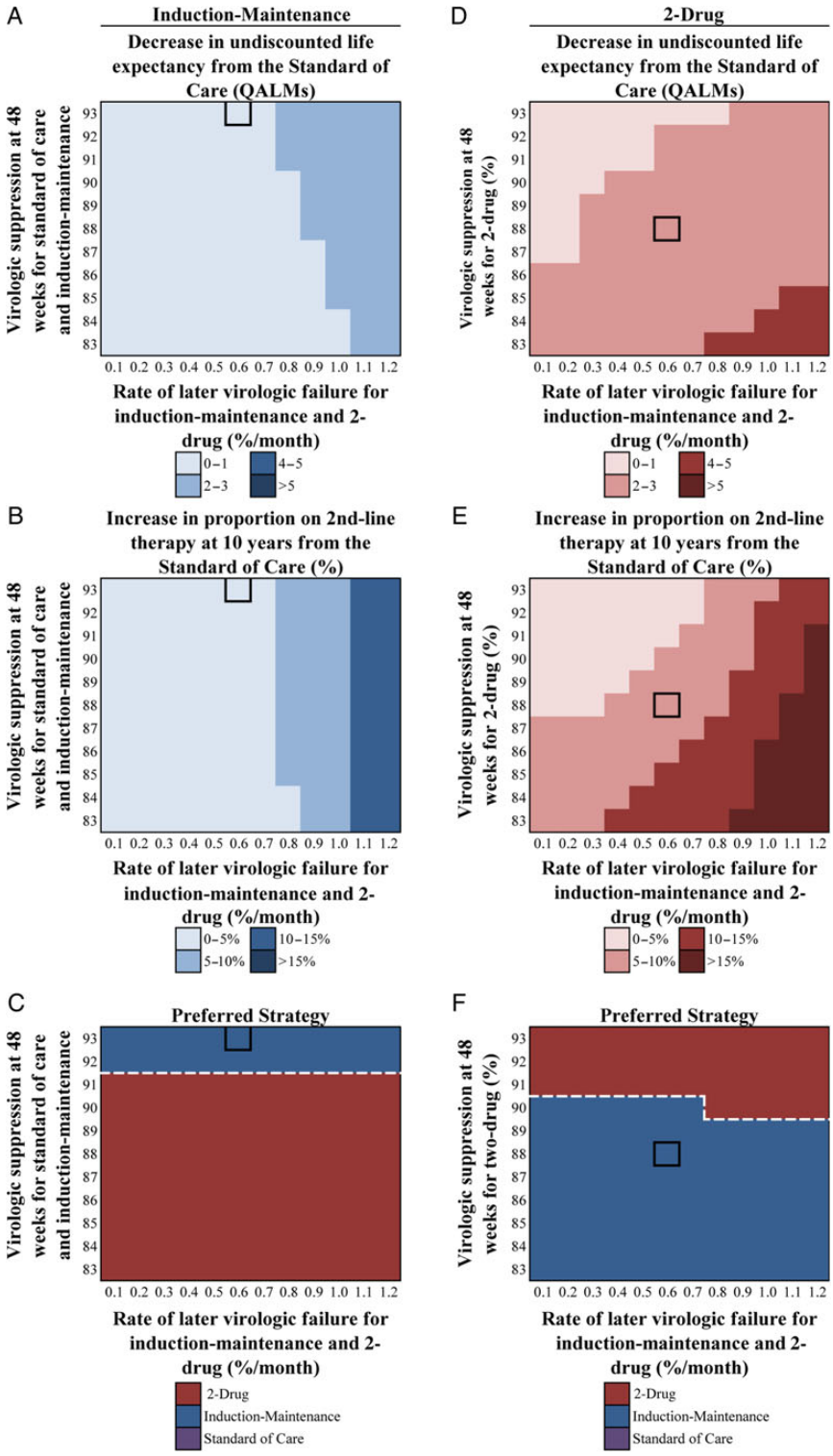

Figure 2. Multivariate sensitivity analyses varying 48-week virologic suppression and post–48-week later virologic failure for the induction-maintenance and 2-drug strategies. Analyses of induction-maintenance parameters. *A–C*, The y-axes vary the 48-week virologic suppression of the standard of care (SOC) and induction-maintenance strategy (dolutegravir [DTG]/abacavir [ABC]/lamivudine [3TC]); the x-axes vary the rate of post–48-week virologic failure for the induction-maintenance and 2-drug (DTG + 3TC) regimens. The open black boxes represent base case values. The decrease in undiscounted quality-adjusted life-months (QALMs) (*A*) and increase in proportion on second-line antiretroviral therapy (ART) at 10 years (*B*) of induction-maintenance compared to SOC are shown. *C*, The most cost-effective strategy with a threshold of <$100 000/quality-adjusted life-year (QALY) as the parameters on the axes are varied, keeping all others constant. Analyses of 2-drug parameters: *D–F*, The y-axes vary the 48-week virologic suppression of the 2-drug regimen (DTG + 3TC); the x-axes vary the rate of post–48-week virologic failure for the induction-maintenance and 2-drug (DTG + 3TC) regimens. The decrease in undiscounted QALMs (*D*) and increase in proportion on second-line ART at 10 years (*E*) of 2-drug compared to SOC are shown. *F*, The most cost-effective strategy with a threshold of <$100 000/QALY as the parameters on the axes are varied, keeping all others constant.

cost of DTG + 3TC; and cost of subsequent PI-based regimens (Supplementary Appendix).

Multivariate Sensitivity Analyses

Induction-Maintenance Parameters. In multivariate sensitivity analyses, we varied (1) 48-week virologic suppression for induction-maintenance and SOC (simultaneously, since they should be identical) and (2) later virologic failure for induction-maintenance and 2-drug (simultaneously, since they too should be identical) (Figure 2*A*–*C*). Only when later virologic failure for induction-maintenance was >0.7%/month did induction-maintenance result in a QALE decrease of >1 month (Figure 2*A*) or an increase in those on second-line ART at 10 years of >5% (Figure 2*B*) when compared to SOC. Induction-maintenance remained the most cost-effective strategy unless its 48-week virologic suppression rate was <92%, at which point 2-drug became the most cost-effective (Figure 2*C*); SOC was never the preferred strategy.

Two-Drug Parameters. We also varied ranges in 48-week virologic suppression for the 2-drug strategy with ranges of later virologic failure for induction-maintenance and 2-drug (Figure 2*D*–*F*). In general, these variations resulted in greater clinical changes compared to SOC. For example, 2-drug decreased QALE between 4 and 5 months when its initial virologic suppression was <86% and later virologic failure was ≥1.1%/month (Figure 2*D*). Under certain parameter variations, 2-drug resulted in >15% more patients receiving second-line ART at 10 years compared to SOC (Figure 2*E*). Two-drug became the most cost-effective strategy when its 48-week virologic suppression was >90% or when suppression was equal to 90% and later virologic failure for DTG + 3TC was >0.7%/month (Figure 2*F*); SOC was never the preferred strategy.

Probabilistic Sensitivity Analyses

In probabilistic sensitivity analysis, at a willingness-to-pay threshold of <$100 000/QALY, induction-maintenance was the most cost-effective strategy in 59.4% of simulations, 2-drug was the most cost-effective strategy in 40.4% of simulations, and SOC was the most cost-effective strategy in 0.2% of simulations.

Budget Impact Analysis

If half of newly diagnosed patients initiating ART in the United States were started on induction-maintenance annually, anticipated cost savings in the first 5 years would reach $550 million; cost savings would reach $800 million with a 2-drug strategy (Table 3). If, in addition, 25% of the estimated 240 000 eligible currently suppressed patients were switched to DTG + 3TC maintenance, 5-year savings could reach $3.150–$3.400 billion. Sensitivity analyses varying uptake of these strategies (50%–75% incident and 0%–50% prevalent cases) resulted in 5-year savings ranging from $3.150 to $6.410 billion. Anticipated cost savings are slightly more for 2-drug than for induction-maintenance, attributable to the cost savings for incident diagnosed patients in the first year of treatment (Table 3).

DISCUSSION

Dolutegravir-based therapy offers a potent, well-tolerated, and convenient HIV treatment option with a high barrier to resistance. Two small pilot studies are actively examining dual therapy with DTG + 3TC in HIV-infected patient populations: one as initial therapy among treatment-naive patients and another as a maintenance strategy for patients on suppressive ART [12, 13]. Using a mathematical simulation of HIV disease and treatment, we demonstrate that an induction-maintenance strategy of 3-drug initial therapy with DTG/ABC/3TC followed by DTG + 3TC maintenance would be cost-effective in the United States under plausible virologic efficacy assumptions; DTG + 3TC as initial therapy could be even more cost effective. The difference between these 2 DTG + 3TC strategies depends on whether DTG + 3TC can achieve sufficiently high levels of initial virologic suppression. Furthermore, we find that the induction-maintenance and 2-drug strategies, if adopted, could save more than $500 million or $800 million, respectively, in HIV therapy costs in the first 5 years compared to the current SOC.

Table 3. Budget Impact Analysis Showing the Potential Cost Savings of 2 Alternative Dolutegravir-Containing Regimens in the United States

	Induction-Maintenance[a]			2-Drug[b]		
Start/Switch Condition	Year 1	Year 3	Year 5	Year 1	Year 3	Year 5
Start 50% incident	. . .	170	550	60	340	800
Start 50% incident/switch 25% prevalent	550	1760	3150	610	1930	3400
Start 50% incident/switch 50% prevalent	1090	3350	5740	1150	3530	6010
Start 75% incident/switch 25% prevalent	550	1840	3420	640	2100	3810
DTG + 3TC 25% price reduction	. . .	240	780	90	480	1150
DTG + 3TC 25% price increase	. . .	100	310	40	190	460
Best case (start 75% incident/switch 50% prevalent)	1090	3430	6020	1180	3700	6410

Data are shown as 2014 US dollars (in millions).

Abbreviations: 3TC, lamivudine; DTG, dolutegravir.

[a] Patients initiated with 3-drug regimen and switched to DTG + 3TC at 48 weeks if virologically suppressed.

[b] Patients initiated on a DTG + 3TC regimen.

In the absence of induction-maintenance or 2-drug efficacy data, we deliberately used estimates for 48-week virologic suppression and risk of subsequent virologic failure that were inferior to the SOC. Our results demonstrate that if the 48-week suppression rate of a DTG + 3TC initial regimen were >90% (compared to the base case), 2-drug initial therapy would become more cost-effective than induction-maintenance. In this situation, the budget impact would be even more favorable than that with induction-maintenance, since it would obviate the need for the more costly 3-drug induction strategy. Over wide variation in DTG + 3TC early efficacy and later failure estimates, we also find that, with these alternative strategies efficacious and available, the current SOC with DTG/ABC/3TC (or other comparably priced initial 3-drug regimens) provides little to no additional clinical benefit and is likely not cost-effective.

The potential cost-savings of any dual-therapy strategy must be balanced with its potential for clinical harm. Prior dual-therapy strategies have been associated with virologic failure and drug resistance [2–5], although we find that the potential for poorer clinical outcomes—on projected 5- and 10-year survival and on life expectancy—is very small, as second-line ART options are now so effective. However, the ethics of recommending an even marginally clinically inferior regimen on the grounds of cost savings would need to be considered in light of results of future clinical studies. In our model, the biggest disadvantage of either of the dual-therapy strategies was the increased proportion of patients who receive a more expensive, more complicated, and perhaps more toxic second-line PI-based regimen.

Based on US HIV treatment guideline development, neither pilot studies of DTG + 3TC nor our analysis will change guidelines without evidence from a fully powered clinical trial [1]. Indeed, all 5 recommended initial ART regimens in the 2015 DHHS HIV treatment guidelines have the highest-level recommendation and strongest evidence base (A1: strong recommendation, data from randomized controlled clinical trials). However, our results demonstrate, in advance of clinical data, that a trial of this nature has the potential for tremendous cost savings and is, thus, policy relevant. Currently, no fully powered study of DTG + 3TC is planned, although 2 additional single-arm studies of DTG + 3TC as initial therapy (AIDS Clinical Trials Group A5353) and maintenance therapy (French National Agency for AIDS Research LAMIDOL study) will be conducted (personal communication, Yazdan Yazdanpanah, MD, PhD, Hôpital Bichat, Paris, France).

If the DTG + 3TC pilot study efficacy data fall within the ranges associated with favorable cost-effectiveness in our analysis, this would provide strong justification for a large-scale, fully powered noninferiority trial of dual therapy for use as first-line or induction-maintenance HIV treatment in the United States. Several larger studies are investigating DTG as dual therapy with the nonnucleoside reverse transcriptase inhibitor rilpivirine [33–35]; because rilpivirine is a patented drug, the potential for cost savings is lower than with DTG and generic 3TC. While a noninferiority trial of DTG + 3TC would cost an estimated $20–$30 million [36], these costs would be recouped within 1–2 years by the cost savings of this dual therapy, if it is proven to be noninferior.

Results of this study should be interpreted in light of several limitations. The most important is that the efficacy of DTG + 3TC dual therapy is currently unknown, and, as a result, virologic suppression and failure rates were derived from regimens that did not contain DTG. Nonetheless, our results were robust to large variation in these estimates, and our recommendations would hold if pilot study data are consistent with these. Our analysis did not include the cost of HLA-B*5701 genotype testing or hypersensitivity reactions for patients initiating ABC; however, inclusion of this cost (approximately $150) does not change our policy conclusions [37]. We also assumed that the cost difference between a 3-drug and 2-drug regimen would remain constant over time, assuming that DTG will remain under patent in the United States at least 7 years from its US Food and Drug Administration approval in 2013; we vary the cost difference estimates in the BIA to anticipate possible changes in DTG + 3TC cost over the analysis horizon but recognize that drug costs may vary over time as some drugs become generic and other therapeutic options arise [38]. Finally, model inputs for 48-week virologic suppression exclude loss to follow-up, withdrawal of consent, and switching for other reasons and do not reflect reported intention-to-treat values; as such, our reported estimates of virologic suppression thresholds for DTG + 3TC are likely higher than those that would be observed in a clinical trial and could be as low as 85% (reported 90%).

In conclusion, we find that a 48-week induction strategy for ART-naive patients with DTG/ABC/3TC—or likely any triple-therapy regimen—followed by a 2-drug maintenance regimen of DTG + 3TC for those virologically suppressed would likely be cost-effective in the United States. Similarly, DTG + 3TC as initial treatment would be even more cost-effective if early virologic suppression rates are close to those achieved by triple therapy. If half of the potentially eligible treatment-naive patients in the United States adopted a DTG + 3TC strategy, >$500 million in ART savings would accrue over 5 years. Savings would be considerably greater if eligible patients currently on 3-drug regimens were switched to DTG + 3TC maintenance. Given this substantial potential economic benefit alongside excellent clinical outcomes, if upcoming pilot data are promising, a fully powered clinical trial to evaluate the noninferiority of these strategies should be conducted.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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