Cost–effectiveness of CYP2B6 genotyping to optimize efavirenz dosing in HIV clinical practice

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Accessibility
Cost–effectiveness of CYP2B6 genotyping to optimize efavirenz dosing in HIV clinical practice

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Abstract

Aims—To assess the cost–effectiveness of CYP2B6 genotyping to guide efavirenz dosing for initial HIV therapy in the USA.

Methods—We used the Cost–Effectiveness of Preventing AIDS Complications (CEPAC) microsimulation model to project quality-adjusted life expectancy and lifetime costs (2014 US dollars) for efavirenz-based HIV therapy with or without CYP2B6 genotyping. We assumed that with genotyping 60% of patients would be eligible to receive lower doses.

Results—Current care without CYP2B6 genotyping has an incremental cost–effectiveness ratio >$100,000/QALY compared with genotype-guided dosing, even if lower dosing reduces efficacy.

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Supplementary data
To view the supplementary data that accompany this paper, please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/pgs.15.142

Disclosure
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The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.
When we assumed generic efavirenz availability, conclusions were similar unless lower dosing reduces efficacy by 6% or more.

**Conclusion—** *CYP2B6* genotyping can inform efavirenz dosing and decrease HIV therapy cost.

**Keywords**

antiretroviral therapy; cost–effectiveness; dose optimization; genotyping; HIV

Efavirenz is included among alternative first-line antiretroviral therapy (ART) regimens for human immunodeficiency virus type-1 (HIV) infection in the USA, although it is no longer included in recommended first-line regimens [1–3]. In adults, efavirenz is prescribed at a dose of 600 mg once daily, often co-formulated with tenofovir disoproxil fumarate (TDF) and emtricitabine. Efavirenz is metabolized by cytochrome P450 (CYP) 2B6. Three *CYP2B6* polymorphisms, 516G→T (rs3745274) [4–7], 983T→C (rs28399499) [7–9] and 15582C→T (rs4803419) [7] predict increased plasma efavirenz exposure. The various combinations of these loss-of-function alleles, which are common in all race/ethnicity groups, define 10 plasma efavirenz concentration strata spanning an approximately tenfold range. Pharmacogenetic data indicate that once-daily efavirenz doses of 400 mg (for intermediate metabolizers) and 200 mg (for slow metabolizers) would maintain median minimum concentration (Cmin) values comparable to fast metabolizers [7], and therefore should not compromise efficacy. This is supported by pilot data on efavirenz dose reduction based on *CYP2B6* genotype [10]. In a genetic association study involving over 1000 AIDS Clinical Trials Group (ACTG) participants, most could receive less than 600 mg doses of efavirenz [7].

In the ENCORE1 trial, which tested the efficacy of lower dose efavirenz (without *CYP2B6* genotyping or stratification), virologic response in those randomized to initiate 400 mg efavirenz was noninferior to the response for 600 mg, all prescribed in multipill regimens [11,12]. Moreover, no consistent association between *CYP2B6* polymorphisms and virologic failure with efavirenz-containing regimens has been observed [6,9,13]. Conversely, higher plasma efavirenz exposure has been associated with increased central nervous system symptoms in some reports [5,9,14–17], but not in others [18,19]. This suggests that central nervous system symptoms might decrease with lower doses. In one observational study in which doses were reduced in patients already receiving efavirenz, guided by *CYP2B6* genotype and therapeutic drug monitoring, there were decreased central nervous system symptoms, continued virologic control and cost savings [20]. Economic considerations may increasingly affect ART prescribing, particularly with multiple options for initial ART with varying costs [1]. Using *CYP2B6* genetic association data, we assessed the potential cost–effectiveness of *CYP2B6* genotyping to guide efavirenz dosing in ART-naïve individuals in the USA.

**Methods**

**Analytic overview**

We used the Cost–Effectiveness of Preventing AIDS Complications (CEPAC) microsimulation model, a widely published state transition simulation model of HIV disease...
[21] to identify key determinants of cost–effectiveness of CYP2B6 genotyping to guide efavirenz dosing in first-line ART. In a simulated cohort of patients for whom efavirenz-based ART would be the initial regimen, we compared a genotyping strategy to current standard care (i.e., without genotyping) (Figure 1). With the genotyping strategy, all simulated patients were genotyped for CYP2B6 516G→T, 983T→C and 15582C→T, and were assigned an efavirenz metabolizer status based on genotype results prior to ART initiation. They then initiated once-daily ART with efavirenz at either 600 mg, 400 mg, or 200 mg based on genotype results; patients for whom genotyping was inconclusive were assigned 600 mg. With the standard care strategy (i.e., without genotyping), all simulated patients initiated once-daily ART with efavirenz 600 mg.

In the USA, although efavirenz is typically prescribed in fixed-dose tablets co-formulated with TDF (300 mg) and emtricitabine (200 mg), it is also available without co-formulation in 600 mg and 200 mg tablets. We considered a 600 mg efavirenz-based regimen to comprise one tablet (co-formulated with TDF/emtricitabine); a 400 mg efavirenz-based regimen to comprise three tablets (two efavirenz 200 mg tablets plus one co-formulated TDF/emtricitabine tablet); and a 200 mg efavirenz-based regimen to comprise two tablets (one efavirenz 200 mg tablet plus one co-formulated TDF/emtricitabine tablet). All regimens are once daily. The 400 mg and 200 mg efavirenz-based regimens would be prescribed ‘off-label’ (i.e., using efavirenz dosages that are not approved by the US FDA).

For all strategies, simulated patients who prematurely discontinue efavirenz due to side effects were assumed to require two extra outpatient visits and were switched to a different recommended or alternative first-line ART regimen [1]. This was considered a medically supervised drug substitution within the first-line ART regimen and was assumed to occur within the first month of ART initiation. Analyses were conducted based on current average wholesale prices (AWPs) for all drugs, adjusted to reflect discounts to institutional purchasers, and were repeated with an assumed much lower cost (25% of AWP) for generic versions of efavirenz 600 mg and 200 mg tablets when these become available [22,23]. We evaluated scenarios that varied assumptions regarding effects of lower efavirenz doses on regimen efficacy. We also separately considered a universal (i.e., without genotyping) lower dose strategy, in which all simulated patients initiate once-daily ART with efavirenz 400 mg based on the strategy evaluated in the ENCORE1 trial [11,12]. Although the ENCORE1 strategy is unlikely to be widely adopted in the USA, it could conceivably be applied in situations with severely constrained budgets.

Results are reported as quality-adjusted life years (QALYs) and lifetime medical costs from the health system perspective in 2014 US dollars, discounted to present value at 3% annually [24]. A cost–effectiveness ratio >$100,000/QALY is frequently considered not cost–effective by US standards [25,26].

**HIV disease model**

We project quality-adjusted life expectancies and lifetime costs accrued by simulated cohorts of HIV-infected patients using the CEPAC state transition model. In the CEPAC model, simulated patients’ health states are characterized by CD4 count, plasma HIV RNA level and presence or absence of opportunistic infections [27–29]. Without treatment,
patients’ CD4 counts decline at a rate dependent on their HIV RNA level [30]. As CD4 counts decline, patients are more likely to develop opportunistic infections and are subject to increased HIV-related mortality. The probability of HIV-related death is also dependent on prior history of opportunistic infections [27,30,31]. Opportunistic infection prophylaxis and ART are initiated according to current US guidelines [1,32]. Patients also face a risk of non-HIV-related mortality that depends on age and sex [33].

Each simulated patient is assigned a predisposition to adhere to ART medications (0–100%) [34], based on contemporary data from US population-based studies [35]. The level of adherence is correlated with probability of HIV RNA suppression, with highly adherent patients (>95%) more likely to achieve HIV RNA suppression. Once suppression is achieved, CD4 count increases, with the greatest gain during the first two months on therapy [36]. With increasing CD4 counts, simulated patients are less likely to develop opportunistic infections or die of HIV-related causes. Patients who experience virologic rebound are switched to the next available ART regimen, up to a maximum of five additional regimens. The probability of virologic rebound is inversely correlated with adherence level. During treatment, patients are also subject to a monthly probability of loss to follow-up. As with virologic rebound, this probability is inversely correlated with adherence. Simulated patients discontinue ART while lost to follow-up. Lost patients have a monthly probability of returning to care; those who experience a severe opportunistic disease return to care immediately.

Data for the model

Characteristics of the simulated cohort initiating ART, including CD4 count, age, sex and HIV RNA distribution, were from published sources (Table 1). We derived an overall HIV RNA suppression rate of 91% for the 600 mg efavirenz-based regimen from recent data [37] and assumed the same efficacy when simulated patients are switched to a substitute regimen. We varied suppression rates for the 400 mg and 200 mg efavirenz-based regimens from 91% (no difference from 600 mg) down to 75% to reflect potential decreased efficacy due to lesser adherence with multitablet regimens or due to lower dose. Efficacies of regimens containing 400 mg or 200 mg of generic efavirenz were varied over the same range. The cost of a generic version of efavirenz was assumed to be 25% of the AWP [22]. The weighted average cost of alternative regimens was 18% higher than the cost of the 600 mg efavirenz-based regimen [38]. Nonantiretroviral medical costs were from a recent evaluation of the lifetime cost of HIV care [29].

Model inputs for genotype prevalence and efavirenz concentration associations were derived from a published genetic association study [7]. These include a 39.7% probability of CYP2B6 genotyping showing eligibility for the standard 600 mg dose, a 47.1% probability of being eligible for 400 mg and a 13.2% probability of being eligible for 200 mg. We assumed that genotyping is 99.7% conclusive [46]. We assumed a genotype assay cost of $349, based on our previous estimate of the cost of UGT1A1 genotyping to inform atazanavir prescribing [43].

Inputs for early discontinuation are from clinical trials data, with a 5% average baseline probability of discontinuing the 600 mg efavirenz-based regimen due to treatment-limiting
toxicity [3,47]. Consistent with this 5% average discontinuation level regardless of \textit{CYP2B6} genotype, we assigned a 3% base case probability of discontinuing efavirenz to those with genotypes showing eligibility for the 600 mg dose, 6% to those eligible for 400 mg but who receive 600 mg, and 9% to those eligible for 200 mg but who receive 600 mg. In scenarios where lower doses were prescribed, we decreased these discontinuation probabilities accordingly and varied these assumptions in sensitivity analyses (Table 2). During the month of treatment-limiting toxicity prior to switch to a substitute regimen, we assumed that patients experience a decrease in quality of life and incur the cost of additional clinic visits with laboratory testing (Table 1).

\textbf{Analysis}

Using the CEPAC model, we first projected quality-adjusted life expectancy and lifetime costs for simulated cohorts initiating first-line ART regimens with efavirenz 600 mg, 400 mg, or 200 mg or cohorts switching to a substitute regimen prior to achieving viral suppression, varying first-line efficacy as described above. We then weighted the results to determine average quality-adjusted life expectancy and lifetime costs for each strategy, taking into account genotype test costs, treatment-limiting toxicity event costs and quality of life. We first compared genotyping to standard care. In a separate analysis we compared three strategies (standard care, genotyping and universal lower dose), considering the possibility that the universal lower dose strategy may be considered in some situations with severely constrained budgets (Figure 1).

All cost–effectiveness ratios are calculated on an incremental basis by ranking strategies from least to most expensive, then comparing each strategy with the next least expensive strategy. Strategies are considered ‘dominated’ (i.e., an inefficient use of resources) and excluded from incremental cost–effectiveness calculations if they result in higher costs but fewer QALYs gained [24].

\textbf{Sensitivity analyses}

For each analysis, we varied the HIV RNA suppression rate of regimens containing lower dose efavirenz and the availability of generic efavirenz as described above. In additional sensitivity analyses, we varied the cost of \textit{CYP2B6} genotyping, the likelihood of early treatment discontinuation due to efavirenz toxicity, the quality of life effect and cost of efavirenz toxicity leading to treatment discontinuation, possible care discontinuation by patients experiencing treatment limiting efavirenz toxicity, and population characteristics, including proportion eligible for the 600 mg dose, mean age and mean CD4 count at treatment initiation (Tables 1 & 2). Finally, we conducted threshold analyses to explore the impact on our findings of possible ongoing quality-of-life decrements for patients who received efavirenz 600 mg in the standard care scenario (i.e., without \textit{CYP2B6} genotyping) but who could have received a lower dose in the other two scenarios [25].

\textbf{Results}

With \textit{CYP2B6} genotyping, we estimate that approximately 3% of patients initiating efavirenz-based regimens switch to a substitute regimen due to early treatment-limiting
toxicity on efavirenz. These patients experience a 10% reduction in quality of life for 1 month, which is equivalent to an average 0.00021 QALY loss across the entire population. The average monthly regimen cost reflecting this switch and lower costs for lower dose efavirenz regimens is $1700. With standard care, approximately 5% of patients initiating efavirenz-based regimens switch to a substitute regimen, there is a 0.00037 QALY loss across the entire population, and the average monthly regimen cost is $1870. Assuming no reduction in HIV RNA suppression on lower dose efavirenz regimens, genotyping is the more efficient strategy (i.e., dominates) because standard care results in a very small per person QALY loss and $18,500 additional lifetime cost (Table 3). If the efficacy of lower dose efavirenz regimens is decreased from an HIV RNA suppression rate of 91% to 85, 80, or 75%, standard care results in 0.02–0.05 higher QALYs but still incurs $15,900–$9600 higher lifetime costs. The resulting cost–effectiveness ratios for standard care versus genotyping are all >$100,000/QALY (Table 3), indicating that genotyping remains the preferred strategy.

Results are similar when we consider the availability of generic efavirenz (Table 3). Although the additional lifetime cost in the standard care compared with the genotyping strategy is lower ($7600 with generic efavirenz versus $18,500 without generic efavirenz), genotyping remains the dominant strategy assuming an equal HIV RNA suppression rate with lower dose efavirenz. Standard care becomes the preferred strategy (cost–effectiveness ratio <$100,000/QALY) when the HIV RNA suppression rate is decreased from 91% to approximately 85%. When the suppression rate is decreased to 80%, standard care is more effective and cost-saving compared with the genotyping strategy. In this scenario, genotyping results in a large number of individuals who do not achieve HIV RNA suppression and move on to more expensive regimens, resulting in a higher overall lifetime cost than standard care.

Results are not sensitive to variations in genotype test cost, the likelihood of early treatment discontinuation due to efavirenz toxicity, the quality of life effect and cost of efavirenz toxicity leading to treatment discontinuation, the proportion of the population eligible for lower dose efavirenz, mean age, or mean CD4 count (Supplementary Table 1). When we assume that some patients who experience treatment-limiting toxicity are lost to care for 6–24 months, standard care becomes even less attractive, such that genotyping is dominant even with generic efavirenz availability and HIV RNA suppression decreased to 80% on lower dose efavirenz. Similarly, if we decrease the quality of life in the standard care scenario by 1% or more for patients who could have received lower dose efavirenz with genotyping, then genotyping results in higher QALYs than standard care and is cost-saving.

When standard care, genotyping and universal lower dose strategies are compared, universal lower dose is the preferred strategy if generic efavirenz is not available. Slightly fewer than 3% of patients switch to a substitute regimen and the average monthly regimen cost is lower compared with the genotyping strategy ($1650 versus $1700). The cost–effectiveness ratio of genotyping versus universal lower dose remains >$100,000/QALY unless HIV RNA suppression is decreased by more than 15%, from 91% to approximately 76% (Figure 2 & Supplementary Table 2). Sensitivity analysis results are generally consistent with these findings (Supplementary Table 3). With generic efavirenz availability, universal lower dose
is still preferred to both other strategies if there is no change in HIV RNA suppression. When the HIV RNA suppression rate is decreased to 85%, however, genotyping results in higher QALYs than universal lower dose and is cost-saving. Standard care has a cost-effectiveness ratio <$100,000/QALY when the HIV RNA suppression rate is decreased to 80% and is cost-saving when the HIV suppression rate is decreased to 75%, consistent with the results of the genotyping versus standard care comparison assuming generic efavirenz availability (Supplementary Table 2).

**Discussion & conclusion**

Human genotyping to inform medication prescribing will become more common with increasing knowledge of genetic associations for many diseases and decreasing cost of genotyping. In the future, prescribing of generic efavirenz-based regimens may be promoted if its cost is lower than alternatives. Our results show that dosing of efavirenz to treat HIV disease based on *CYP2B6* genotyping is cost-effective compared with standard care under reasonable assumptions, both without and with generic efavirenz available.

In previous studies we used the CEPAC model to evaluate the cost-effectiveness of genotyping to inform selection of initial ART when the primary benefit was to avoid a medication adverse effect [28,43]. Results varied depending on the strength of association between genotype and adverse effect outcomes, severity of adverse effects and costs of medications and the genetic test. We found that genotyping for *HLA*B-*5701* to avoid abacavir hypersensitivity was cost-effective [28]. In contrast, *UGT1A1* genotyping to avoid atazanavir-related hyperbilirubinemia was cost-effective only if the assay cost was low, testing improved retention in care, and comparator ART regimens had similar drug costs [43].

In contrast to those analyses, *CYP2B6* genotyping has two potential benefits: decreased early treatment-limiting efavirenz toxicity and lower average regimen cost. We found that *CYP2B6* genotyping lowered lifetime cost and slightly increased QALYs compared with standard care. Even if lower dose efavirenz was assumed to less effectively control HIV replication, differences in QALYs between genotyping and standard care were small enough that genotyping was still preferred at a cost-effectiveness threshold of $100,000/QALY. These findings were generally consistent when we assumed availability of generic efavirenz as long as lower dose efavirenz achieved a viral suppression rate of greater than 85%. Although lower dosing of efavirenz without genotyping may also be an acceptable alternative, based on results of the ENCORE1 trial [11,12], genotyping prior to making a decision to prescribe a lower dose has the potential to alleviate provider concerns that a lower dose may result in suboptimal plasma efavirenz exposure among some individuals with extensive metabolizer genotypes. While ENCORE1 results suggest that once-daily ART with efavirenz 400 mg will likely maintain virologic efficacy with extensive metabolizer genotypes, the relatively small sample size (~50) with *CYP2B6* genotypes that predict the lowest efavirenz exposure stratum and the exceptionally high virologic response rate in ENCORE1 overall (97–98%) indicate the need for caution regarding such a claim.
Our analysis has several limitations. While the impact of genotype-guided efavirenz dosing on virologic control has not been assessed in a large clinical trial, findings from genetic association studies that correlate genotype with plasma efavirenz exposure are robust [4–9]. Providers may not be comfortable, however, prescribing efavirenz at doses lower than the 400-mg dose evaluated in the ENCORE1 study [11,12]. Model inputs included data from a genetic association study involving participants in clinical trials of various ancestries [7]. Our results were not sensitive, however, to the variation in the proportion of patients eligible for dose reduction that would be expected based on differences in genotype prevalence by ancestry. The few efavirenz dose reduction studies to date have shown no decrease in virologic efficacy and some evidence of a decrease in side effects [10–12,20]. Nevertheless, we conservatively considered a range of efficacies associated with lower dose, and in the base case did not assume worse quality of life for patients in the standard care scenario who could have received a lower dose with genotyping. Additionally, we only considered CYP2B6 variants. In individuals with slow metabolizer genotypes for both CYP2B6 and CYP2A6 (<1% of the population), daily doses of even <200 mg may maintain therapeutic plasma concentrations. However, relatively few individuals with slow metabolizer genotypes in both genes have been studied for efavirenz pharmacokinetics [49–51]. Moreover, we assumed a hypothetical price reduction for generic efavirenz. If the actual price reduction is less than we assumed, results with generic efavirenz will be more similar to results without generic efavirenz. However, unless generic efavirenz becomes available in fixed-dose combination tablets, all once-daily regimens with generic efavirenz will require multiple pills, reducing potential adherence differences between 600 mg and lower dose regimens requiring multiple pills that might affect efficacy [52]. Although pharmacokinetic drug monitoring of lower dose regimens could reduce the probability of virologic failure while increasing the cost of these regimens, we did not consider this strategy because HIV drug monitoring is not routinely conducted or reimbursed by health insurance in the USA.

We also considered scenarios with an increased likelihood of virologic failure with lower efavirenz doses. In the USA, effective control of HIV replication is a major priority in HIV therapy, especially as ART has become better tolerated with less chronic toxicity. Importantly, the correlation between CYP2B6 genotype and plasma efavirenz exposure is strong [7], indicating that efavirenz dosing based on genotype would maintain sufficient plasma efavirenz levels to control HIV replication and that increased virologic failure would be unlikely if medication adherence is similar to standard care. In contrast, universal lower dose without genotyping may lower plasma efavirenz $C_{\text{min}}$ values to below those achieved in clinical trials, particularly in individuals with CYP2B6 genotypes predicting the lowest plasma efavirenz concentration stratum [7].

In summary, genotyping of CYP2B6 can inform efavirenz dosing strategies and lower HIV therapy cost in the USA. This strategy will have value even after generic efavirenz becomes available. In this context, genotyping can increase both provider and patient acceptance of a lower dose as an alternative to using more expensive regimens for initial HIV treatment.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.
Acknowledgements

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References

Papers of special note have been highlighted as:

• of interest;

•• of considerable interest


12•. Encore1 Study Group. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1
study. Lancet Infect. Dis. 2015; 15(7):793–802. [PubMed: 25877963] [This study compared the efficacy and safety of reduced dose efavirenz with standard dose efavirenz in combination with tenofovir and emtricitabine as first-line treatment for HIV infection at 48 weeks. This 96-week follow-up of the trial assessed the durability of efficacy and safety of this treatment over 96 weeks.]


Executive summary

Rationale

• Efavirenz-based antiretroviral therapy (ART) is an alternative first-line regimen for HIV infection. Recent evidence suggests lower efavirenz doses may be effective with potentially fewer side effects.

• Economic considerations may affect ART prescribing, particularly because multiple options with varying costs are now available for initial ART.

• Frequent CYP2B6 polymorphisms predict approximately tenfold interindividual variability in plasma efavirenz exposure with standard 600 mg/day dosing.

Simulation model

• We used the Cost–Effectiveness of Preventing AIDS Complications (CEPAC) microsimulation model to project quality-adjusted life years (QALYs) and lifetime costs (2014 US dollars) for initiating efavirenz-based ART with or without CYP2B6 genotyping.

• We assumed that with genotyping 47 and 13% of patients would be eligible to receive 400 mg/day and 200 mg/day, respectively.

• In sensitivity analyses we varied lower dose treatment efficacy, standard and lower dose treatment-limiting toxicity and availability of generic efavirenz.

CYP2B6 genotyping cost–effectiveness

• Assuming equal efficacy, current standard care (i.e., 600 mg/day without CYP2B6 genotyping) increases lifetime cost by $18,500 with a slight decrease in QALYs compared with CYP2B6 genotyping.

• Standard care has an incremental cost–effectiveness ratio >$100,000/QALY compared with genotype-guided dosing even if lower dosing reduces efficacy. An incremental cost–effectiveness ratio >$100,000/QALY is frequently considered not cost–effective by US standards.

• When we assumed availability of generic efavirenz, standard care has an incremental cost–effectiveness ratio >$100,000/QALY compared with genotype-guided dosing unless lower dosing reduces efficacy by 6% or more.

Conclusion

• CYP2B6 genotyping can inform efavirenz dosing strategies and decrease cost of HIV therapy in the USA. This strategy will have value even when generic efavirenz becomes available.
Figure 1. Schema for evaluation of CYP2B6 genotyping before initiation of efavirenz-based initial HIV therapy

All antiretroviral therapy regimens also include emtricitabine (200 mg) and tenofovir disoproxil fumarate (300 mg).

Conclusive: Genotype result can be interpreted in order to assign a dosing strategy; EFV: Efavirenz; Inconclusive: Genotype result cannot be interpreted (e.g., genotyping fails on the sample).
Figure 2. Clinical and economic outcomes of standard care, CYP2B6 genotyping for efavirenz dosing, and universal lower dose

The solid line shows the decrease in total discounted lifetime cost (horizontal axis) with the universal lower dose strategy (triangle) and the genotyping strategy (rectangle) compared with the standard care strategy (circle), assuming equal efficacy among strategies. The difference in quality-adjusted life expectancy among strategies (vertical axis) is minimal. When the efficacy of the lower dose is assumed to be lower compared with 600 mg, the dashed (6% lower) and dotted (11% lower) lines show the lower lifetime cost and quality-adjusted life expectancies for the universal lower dose and genotyping strategies. The cost-effectiveness ratios for these strategies are represented by the slopes of the lines.
Table 1

Selected model inputs for an analysis of genotyping to inform efavirenz dosing in HIV.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base case</th>
<th>Range</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td><strong>Cohort characteristics at ART initiation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– CD4 count, mean cells/μl (SD)</td>
<td>317 (283)</td>
<td>135–517</td>
<td>[39]</td>
</tr>
<tr>
<td>– Age (years)</td>
<td>43</td>
<td>34–50</td>
<td>[39]</td>
</tr>
<tr>
<td>– Male (%)</td>
<td>84</td>
<td></td>
<td>[39]</td>
</tr>
<tr>
<td>– HIV RNA distribution post-acute infection (%):</td>
<td></td>
<td></td>
<td>Derived from [3]</td>
</tr>
<tr>
<td>– &gt;100,000 copies/ml</td>
<td>25.1</td>
<td></td>
<td></td>
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<tr>
<td>– 30,001–100,000 copies/ml</td>
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<td>– 10,001–30,000 copies/ml</td>
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<td>– 3001–10,000 copies/ml</td>
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<tr>
<td>– &lt;3000 copies/ml</td>
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<td><strong>Baseline ART adherence:</strong></td>
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<tr>
<td>– Adherence &lt;50%</td>
<td>3.1</td>
<td></td>
<td>[35,40]</td>
</tr>
<tr>
<td>– 50% adherence &lt;95%</td>
<td>50.7</td>
<td></td>
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<tr>
<td>– Adherence ≥95%</td>
<td>46.2</td>
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<td><strong>First-line ART efficacy:</strong></td>
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<tr>
<td>– HIV RNA suppressed at 6 months, overall (%)</td>
<td>91</td>
<td>See Table 2</td>
<td>[37]</td>
</tr>
<tr>
<td>– Adherence &lt;5%; &gt;95%</td>
<td>0.96</td>
<td></td>
<td>Derived from [41]</td>
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<tr>
<td>– Virologic failure rate after 6 months, per 100 PY</td>
<td>93.3; 1.6</td>
<td></td>
<td>Derived from [41]</td>
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<tr>
<td>– Loss to follow-up rate on ART, per 100 PY</td>
<td>7.5</td>
<td></td>
<td>[42]</td>
</tr>
<tr>
<td>– Adherence &lt;50%; &gt;95%</td>
<td>84.5; 0.1</td>
<td></td>
<td>Derived from [41]</td>
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<tr>
<td>– Return to care rate, per 100 PY</td>
<td>16.9</td>
<td></td>
<td>[42]</td>
</tr>
<tr>
<td><strong>First-line ART monthly cost (US$):</strong></td>
<td></td>
<td></td>
<td>[38]</td>
</tr>
<tr>
<td>– Branded EFV 600mg/FTC/TDF</td>
<td>1,850</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Branded EFV 400mg/FTC/TDF</td>
<td>1,630</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Branded EFV 200mg/FTC/TDF</td>
<td>1,410</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Generic EFV 600mg with branded FTC/TDF</td>
<td>1,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Generic EFV 400mg with branded FTC/TDF</td>
<td>1,330</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Generic EFV 200mg with branded FTC/TDF</td>
<td>1,260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Substitute 1st-line ART regimen</td>
<td>2,190</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subsequent ART regimen monthly costs (US$)</strong></td>
<td>2520–3,570</td>
<td></td>
<td>[38]</td>
</tr>
<tr>
<td><strong>Genotyping test cost (US$)</strong></td>
<td>349</td>
<td>10–500</td>
<td>Assumption based on [43]</td>
</tr>
<tr>
<td><strong>Efavirenz treatment-limiting adverse event:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Duration (days)</td>
<td>30</td>
<td>30–100</td>
<td>[44]</td>
</tr>
</tbody>
</table>

Pharmacogenomics. Author manuscript; available in PMC 2016 April 15.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Base case</th>
<th>Range</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation cost for clinical visits and lab test (US$)</td>
<td>202</td>
<td>100–400</td>
<td>Calculated from [45]</td>
</tr>
<tr>
<td>Quality-of-life multiplier</td>
<td>0.9</td>
<td>0.8–1.0</td>
<td>Assumption</td>
</tr>
<tr>
<td>Discontinue care after experiencing adverse event (% of those experiencing event, time to return to care)</td>
<td>0</td>
<td>50–100% for 6–24 months</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

ART: Antiretroviral therapy; EFV: Efavirenz; FTC: Emtricitabine (200 mg); PY: Person-years; SD: Standard deviation; TDF: Tenofovir disoproxil fumarate (300 mg).

*Loss to follow-up is defined as an interruption in care of at least 12 months.

†Branded costs are 77% of average wholesale price reflecting discounts to institutional purchasers, and generic costs are 25% of average wholesale price.

§Weighted average cost of substitute options, including integrase inhibitor-based regimens (75%), nonnucleoside reverse transcriptase inhibitor-based regimens (15%), and protease inhibitor-based regimens (10%).

¶Sensitivity analysis based on assumption.
Table 2

Efficacy and toxicity of efavirenz-based regimen.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base case (%)</th>
<th>Range (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients without risk genotype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of all patients</td>
<td>39.7</td>
<td>39.7–90.0 †</td>
<td>Derived from [7,39]</td>
</tr>
<tr>
<td>Efficacy: EFV(600 mg) FTC/TDF regimen</td>
<td>91</td>
<td></td>
<td>[37]</td>
</tr>
<tr>
<td>Efficacy: EFV(400 mg) FTC/TDF regimen</td>
<td>91</td>
<td></td>
<td>[37]</td>
</tr>
<tr>
<td>Toxicity: EFV(600 mg) FTC/TDF regimen</td>
<td>3</td>
<td>Assumption based on [3,48]</td>
<td></td>
</tr>
<tr>
<td>Toxicity: EFV(400 mg) FTC/TDF regimen</td>
<td>2</td>
<td>0–4</td>
<td></td>
</tr>
<tr>
<td><strong>Patients with risk genotype requiring EFV 400 mg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of all patients</td>
<td>47.1</td>
<td>47.1–8.0 †</td>
<td>Derived from [7,39]</td>
</tr>
<tr>
<td>Efficacy: EFV(600 mg) FTC/TDF regimen</td>
<td>91</td>
<td></td>
<td>[37]</td>
</tr>
<tr>
<td>Efficacy: EFV(400 mg) FTC/TDF regimen</td>
<td>91</td>
<td>75 †–91</td>
<td>[37]</td>
</tr>
<tr>
<td>Toxicity: EFV(600 mg) FTC/TDF regimen</td>
<td>6</td>
<td>3–9</td>
<td>Assumption based on [3,48]</td>
</tr>
<tr>
<td>Toxicity: EFV(400 mg) FTC/TDF regimen</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients with risk genotype requiring EFV 200 mg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of all patients</td>
<td>13.2</td>
<td>13.2–2.0 †</td>
<td>Derived from [7,39]</td>
</tr>
<tr>
<td>Efficacy: EFV(600 mg) FTC/TDF regimen</td>
<td>91</td>
<td></td>
<td>[37]</td>
</tr>
<tr>
<td>Efficacy: EFV(400 mg) FTC/TDF regimen</td>
<td>91</td>
<td>75 †–91</td>
<td>[37]</td>
</tr>
<tr>
<td>Toxicity: EFV(600 mg) FTC/TDF regimen</td>
<td>9</td>
<td>6–12</td>
<td>Assumption based on [3,48]</td>
</tr>
<tr>
<td>Toxicity: EFV(400 mg) FTC/TDF regimen</td>
<td>6</td>
<td>3–9</td>
<td></td>
</tr>
</tbody>
</table>

EFV: Efavirenz; FTC: Emtricitabine (200 Mg); TDF, Tenofovir disoproxil fumarate (300 mg).

†Sensitivity analysis based on assumption.
Table 3

Results of an analysis of *CYP2B6* genotyping before initiation of efavirenz-based initial HIV therapy comparing standard care (without genotyping) to genotyping: incremental cost–effectiveness ratios of genotyping (US$/QALY).

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Total lifetime QALYs</th>
<th>Incremental QALYs</th>
<th>Total lifetime cost (US$)</th>
<th>Incremental cost (US$)</th>
<th>$/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efavirenz lower dose efficacy equal to full dose (91% suppressed at 24 weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotyping 13.4688</td>
<td>386,000</td>
<td>349,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard care 13.4686</td>
<td>404,500</td>
<td>18,500</td>
<td>Dominated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Efavirenz lower dose efficacy less than full dose (85% suppressed at 24 weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotyping 13.4474</td>
<td>388,600</td>
<td>355,300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard care 13.4686</td>
<td>404,500</td>
<td>15,900</td>
<td>747,500</td>
<td>356,600</td>
<td>1300</td>
</tr>
<tr>
<td><strong>Efavirenz lower dose efficacy less than full dose (80% suppressed at 24 weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotyping 13.4316</td>
<td>391,800</td>
<td>356,700</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard care 13.4686</td>
<td>404,500</td>
<td>12,700</td>
<td>342,800</td>
<td>356,600</td>
<td>(200)</td>
</tr>
<tr>
<td><strong>Efavirenz lower dose efficacy less than full dose (75% suppressed at 24 weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotyping 13.4210</td>
<td>394,900</td>
<td>360,400</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard care 13.4686</td>
<td>404,500</td>
<td>9600</td>
<td>201,700</td>
<td>356,600</td>
<td>(380)</td>
</tr>
</tbody>
</table>

Dominated: Strategy is more expensive and less effective than another strategy; QALY: Quality-adjusted life year.

*Due to rounding, this number does not reflect the difference between total lifetime costs as shown in the table.*