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Cost-effectiveness Analysis of *UGT1A1* Genetic Testing to Inform Antiretroviral Prescribing in HIV Disease

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Abstract

Background—Homozygosity for *UGT1A1**28/*28 (Gilbert's variant) has been reported to be associated with atazanavir-associated hyperbilirubinemia and premature atazanavir discontinuation. We assessed the potential cost-effectiveness of *UGT1A1* testing to inform choice of an initial protease inhibitor-containing regimen in antiretroviral therapy (ART)-naïve individuals.

Methods—We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) computer simulation model to project quality-adjusted life years (QALYs) and lifetime costs (2009 US dollars) for atazanavir-based ART with or without *UGT1A1* testing, using darunavir rather than atazanavir when indicated. We assumed *UGT1A1*-associated atazanavir discontinuation rates reported in the Swiss HIV Cohort Study, a *28/*28 frequency of 14.9%, equal efficacy and cost of atazanavir and darunavir, and genetic assay cost of \$107. Sensitivity analyses varied these parameters and hyperbilirubinemia impact on quality of life and loss to follow-up (LTFU). Costs and QALYs were discounted at 3% annually.

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Results—Initiating atazanavir-based ART at CD4 <500/μl without *UGT1A1* testing had an average discounted life expectancy of 16.02 QALYs and \$475,800 discounted lifetime cost. Testing for *UGT1A1* increased QALYs by 0.49 per 10,000 patients tested, and was not cost-effective (>\$100,000/QALY). Testing for *UGT1A1* was cost-effective (<\$100,000/QALY) if assay cost decreased to \$10, or if avoiding hyperbilirubinemia by *UGT1A1* testing reduced LTFU by 5%. If atazanavir and darunavir differed in cost or efficacy, testing for *UGT1A1* was not cost-effective under any scenario.

Conclusions—Testing for *UGT1A1* may be cost-effective if assay cost is low and if testing improves retention in care, but only if the comparator ART regimens have the same drug cost and efficacy.

INTRODUCTION

Homozygosity for *UGT1A1**28/*28 confers decreased hepatic expression of *UGT1A1* (UDP-glucuronosyltransferase1 family, polypeptide A1) as compared to the *1 allele, and is required although not sufficient to manifest the mild unconjugated hyperbilirubinemia of Gilbert's syndrome [1,2]. Such bilirubin elevations reflect decreased bilirubin clearance from plasma, not hepatic injury, but can still cause icterus. The HIV-1 protease inhibitor atazanavir is metabolized by *UGT1A1*, and in most patients causes plasma bilirubin concentrations to increase from pre-treatment values. Among patients prescribed atazanavir-containing antiretroviral therapy (ART), the *UGT1A1**28/*28 variant is associated with greater increases from baseline in plasma bilirubin concentrations [3].

In a retrospective analysis of patients initiating ART in the Swiss HIV Cohort Study, *UGT1A1* genotype was reported to be associated with the likelihood of atazanavir discontinuation, with discontinuation rates of 62.5% (33.3% due to toxicity), 23.8%, and 14.6% among 18 patients homozygous for *28/*28, 48 patients heterozygous for *1/*28, and 55 patients homozygous for *1/*1, respectively [4]. The overall atazanavir discontinuation rate due to toxicity was 10.7% and due to all causes was 25.4%. This may be clinically relevant as atazanavir-containing regimens are among the preferred initial options recommended by the U.S. Department of Health and Human Services Guidelines Panel [5].

Genetic testing for *HLA**B-5701 has been shown to be cost-effective to avoid abacavir hypersensitivity reactions in HIV-infected individuals [6]. Cost-effectiveness of genetic testing for other ART drugs and outcomes beyond abacavir hypersensitivity have not been investigated [7]. Among HIV-negative patients with colorectal cancer, testing for *UGT1A1* may be cost-effective prior to cancer therapy with irinotecan because individuals who are homozygous for the *UGT1A1**28 variant are at increased risk of irinotecan-related adverse events due to greater plasma concentrations of SN-38, the active metabolite of irinotecan [8].

Economic considerations increasingly affect how antiretroviral drugs are incorporated into clinical care, particularly given the availability of several initial ART options. In this context, we sought to identify factors that would most influence cost-effectiveness of *UGT1A1* testing to inform first-line ART prescribing and prevent atazanavir discontinuation in the United States.

METHODS

Analytic overview

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model, a widely published state transition simulation model of HIV disease [6,9–11] to identify key

determinants of cost-effectiveness of *UGT1A1**28 testing to guide selection of first-line ART. We compared ‘universal testing’ with ‘no testing’ of hypothetical patients for whom atazanavir-based ART was determined by the physician and patient to be the preferred initial regimen (Figure 1). In the universal testing strategy, all patients were tested for *UGT1A1**28 homozygosity prior to ART initiation, atazanavir-containing ART was prescribed for all patients who were not homozygous for *UGT1A1**28/*28 or who lacked *UGT1A1* test results, and darunavir-containing ART was prescribed for patients homozygous for *UGT1A1**28/*28. In the no testing strategy, all patients initiated atazanavir-based ART. With both strategies, patients who discontinued atazanavir were assumed to require an extra outpatient visit, and were switched from atazanavir to darunavir. This switch was considered a medically supervised drug substitution within the first-line therapy regimen.

Results are reported as quality-adjusted life years (QALYs) and lifetime direct medical costs in 2009 US dollars, discounted to present value at a 3% annual rate [12]. All cost-effectiveness ratios (\$/QALY) are calculated by comparing the incremental costs and QALYs of the universal testing strategy to the no testing strategy. A cost-effectiveness ratio <\$100,000/QALY was considered cost-effective [8,11,13].

HIV Disease Model

We projected the 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 cell count, plasma HIV-1 RNA level, and presence or absence of opportunistic infections [6,10,14]. Without treatment, patients’ CD4 counts decline at a rate dependent on their HIV-1 RNA level [15]. As their CD4 counts decline, patients are more likely to develop opportunistic infections and are subject to an increased HIV-related mortality rate. Probabilities of opportunistic infections and HIV-related deaths are also dependent on prior history of opportunistic infections [9,15–17]. Patients receive quarterly CD4 and HIV-1 RNA tests and become eligible for treatment according to US guidelines. ART is initiated at CD4 > 500 cells/μl as recommended by US guidelines, and opportunistic infection prophylaxis is initiated at the appropriate CD4 counts according to the type of prophylaxis [5,18]. Patients also face an age- and sex-based risk of non-HIV-related mortality [19].

Upon ART initiation, patients are subject to a probability of viral suppression and subsequent CD4 count increase, with the greatest CD4 count gain during the first two months on therapy [20]. With increasing CD4 counts, patients are less likely to develop opportunistic infections or die of HIV-related causes. If a patient experiences virologic rebound, he or she is switched to the next available ART regimen. Table 1 specifies the six lines of therapy used in the simulation [21–25]. In the current analysis, we assume that first-line and second-line regimens are equally efficacious, and that substituting darunavir for atazanavir in the first-line regimen does not reduce or increase efficacy.

Data

Characteristics of the hypothetical cohort including age, sex, HIV-1 RNA distribution, and baseline quality of life (QOL) are from published sources (Table 1). On this QOL scale, 0.00 is death or worst possible health, and 1.00 is equivalent to best possible health. Base case model inputs for genetic risk and associations with atazanavir discontinuation are based on results from the Swiss HIV Cohort Study [4]. These include a 14.9% probability of testing homozygous for *UGT1A1**28/*28, an 84.8% probability of testing either heterozygous for *UGT1A1**28/*1 or non-carrier for *UGT1A1**28, and a 0.3% probability of failed genotype testing. We assumed that the probability of discontinuing atazanavir for drug-associated toxicity is 33.3% among patients homozygous for *UGT1A1**28/*28, and 6.8% among

patients heterozygous for *UGT1A1**28 or non-carrier for *UGT1A1**28. We assumed 100% accuracy of genotyping for those with a successful test.

We applied a quality-of-life multiplier of 0.97 for patients experiencing hyperbilirubinemia so that these patients would have a QOL value equal to 97% of the QOL value they would have otherwise been assigned without the side effect, and varied the multiplier in sensitivity analyses. The multiplier had no effect on life expectancy. The multiplier was applied to baseline QOL for 14 days in the base case based on clinical judgment, and both the magnitude and the duration of this hyperbilirubinemia impact were varied in sensitivity analyses.

We used a *UGT1A1**28 test cost of \$107, derived from the Medicare fee schedule and Medicare reimbursement codes [8]. We also evaluated a hypothetical cost of \$10 (as may occur if *UGT1A1* testing were to be included in a multiplex testing panel). The monthly cost of antiretroviral regimens are published average wholesale prices adjusted to reflect institutional discounts [26,27]. We assumed that the darunavir-containing regimen cost was equivalent to that of the atazanavir-containing regimen, and varied this assumption in sensitivity analyses. Costs of HIV care are presented from a health system perspective and are based on HIV Research Network data and Medicare fee schedules [10,26,28–30]. For the cost of evaluating a case of drug-induced hyperbilirubinemia, we used a \$114 single clinic visit cost, which includes associated laboratory tests [29,31].

Analysis

We first projected quality-adjusted life expectancy and lifetime costs for hypothetical cohorts initiating a first-line ART regimen with either atazanavir or darunavir, both prescribed in combination with ritonavir, tenofovir and emtricitabine. In the base case, hypothetical patients entered the model with a CD4 count of 500/ μ l. These results were then applied to the universal testing and no testing strategies based on the probabilities that patients would be assigned to atazanavir-containing or darunavir-containing ART, or switch to darunavir-containing ART after experiencing hyperbilirubinemia. Finally, the quality-of-life decrement and additional cost associated with hyperbilirubinemia were applied to determine the expected outcomes for each strategy and the incremental cost-effectiveness ratio for universal testing versus no testing.

In sensitivity analyses we evaluated the assumption that atazanavir-containing ART and darunavir-containing ART had equal efficacy as first-line regimens by varying the efficacy of darunavir-containing ART, using the same efficacy when darunavir is administered initially or substituted for atazanavir. We also varied the cost of darunavir relative to atazanavir to reflect the possibility of higher or lower cost depending on negotiated discounts [27]. In scenarios where darunavir-containing ART had superior efficacy or lower cost, we also considered initiating darunavir-containing ART in all patients and assumed that these efficacy or cost advantages might outweigh the provider considerations that led to initial prescribing of atazanavir rather than darunavir.

We examined the impact of varying the frequency of *UGT1A1**28/*28 homozygosity based on known frequency variation by ancestry, from 9% (the lowest reported prevalence among Caucasians) to 33% (the highest reported prevalence among individuals of African ancestry) [32]. We also examined the impact of lowering by one half the rates of atazanavir discontinuation due to toxicity for individuals with and without *UGT1A1**28/*28 homozygosity, to reflect the overall rate of discontinuation due to toxicity without virologic failure observed in a clinical trial conducted in the US [21]. To test the impact of the QOL multiplier associated with hyperbilirubinemia, we varied the duration of symptoms from 7 to 28 days and the QOL multiplier from 0.99 to 0.92 (equivalent to the utility decrement for all

symptoms patients felt were definitely attributable to ART in the Veterans Aging Cohort Study [13]). In probabilistic sensitivity analyses, we varied the symptom duration and QOL multiplier across these ranges and simultaneously varied the cost of evaluating a case of drug-induced hyperbilirubinemia based on assumptions about the duration of the outpatient visit. We conducted 1,000 probabilistic simulations using triangular distributions to represent the uncertainty in these 3 parameters with the base case value considered most likely [33].

We also explored the possibility that hyperbilirubinemia would cause some patients to completely discontinue ART and be lost to follow-up. We conducted a sensitivity analysis in which 5% of patients experiencing hyperbilirubinemia were lost to follow up and only returned to care upon development of an opportunistic infection or at a more advanced stage of disease (represented by crossing a specified CD4 count threshold). Additional sensitivity analyses included varying baseline CD4 count, age, baseline quality of life, and likelihood of failed genotyping (Table 1).

RESULTS

Using the CEPAC model, we found that initiating atazanavir-containing ART without *UGT1A1* testing had an average projected discounted life expectancy of 16.02 QALYs and \$475,800 discounted lifetime cost. At current *UGT1A1* genotyping cost of \$107 per assay, *UGT1A1* testing increased QALYs by 0.49 per 10,000 patients tested with a cost-effectiveness ratio of over \$2 million/QALY. At a hypothetical *UGT1A1* genotyping cost of \$10 per assay, this cost-effectiveness ratio dropped to \$88,500/QALY (Table 2). If atazanavir-containing ART had either lower efficacy or higher cost than darunavir-containing ART, then the optimal strategy was always to initiate darunavir-containing ART. If atazanavir-containing ART had higher efficacy than darunavir-containing ART, then the “no test” strategy was preferred (cost-effectiveness ratio <\$100,000/QALY) because of the greater efficacy despite slightly higher cost. If atazanavir-containing ART had lower cost than darunavir-containing ART, then the cost-effectiveness ratio of *UGT1A1* testing was > \$100,000/QALY at any test cost (e.g. approximately \$50 million/QALY with a 10% cost advantage for atazanavir-containing ART).

At a cost of \$10 per *UGT1A1* assay, the cost-effectiveness of testing became sensitive to the frequency of *UGT1A1**28/*28 homozygosity, varying from \$220,600/QALY at a *UGT1A1**28/*28 frequency of 9% to cost-saving at a *UGT1A1**28/*28 frequency of 33% (Figure 2). When the discontinuation rates associated with the presence and absence of *UGT1A1**28/*28 homozygosity were both reduced by one half, the cost-effectiveness ratio increased to \$290,700/QALY at the homozygosity prevalence in the base case and varied from \$560,100/QALY at 9% prevalence to \$69,100/QALY at 33% prevalence. At \$10 per assay, the cost-effectiveness of testing was also sensitive to the duration and magnitude of the impact of hyperbilirubinemia on quality of life and the cost of evaluating a case of drug-induced hyperbilirubinemia. The cost-effectiveness ratio for testing exceeded \$100,000/QALY when the duration of hyperbilirubinemia was reduced from 14 to 7 days, when the quality-of-life multiplier for patients experiencing hyperbilirubinemia was increased from 0.97 to 0.99, and when the cost of case evaluation was reduced from \$114 to \$45. In contrast, the cost-effectiveness ratio for testing was \$44,300/QALY when the duration of hyperbilirubinemia was increased to 28 days, \$33,200/QALY when the quality-of-life multiplier was reduced to 0.92, and \$49,300/QALY when the cost of case evaluation was increased to \$153. In probabilistic sensitivity analyses, 76% of simulations that simultaneously varied the quality of life and cost parameters across these ranges had a cost-effectiveness ratio below \$100,000/QALY (Figure 3).

When we assumed that 5% of patients experiencing hyperbilirubinemia were lost to follow up and returned after their disease had progressed further, the cost-effectiveness ratio for testing generally decreased. For example, when we assumed patients who are lost to follow up return either when they experience an opportunistic infection or when their CD4 count decreases to 200/ μ l, the cost-effectiveness ratio of testing was \$70,000/QALY at the \$107 assay cost, and \$56,600/QALY at the hypothetical \$10 assay cost. Results were similar for a hypothetical cohort with an initial CD4 count of 350/ μ l (Table 2). Results were sensitive, however, to the CD4 count at which patients return to care. When we assumed patients lost to follow up return either when experiencing an opportunistic infection or reaching a CD4 count of 350/ μ l, the cost-effectiveness ratio of testing was >\$100,000/QALY at the current assay cost for a hypothetical cohort with initial CD4 count of 500/ μ l. Results were not substantially affected by varying age, baseline quality of life, or the proportion with failed genotyping.

DISCUSSION

We conducted simulation model analyses to identify factors that would determine the cost-effectiveness of *UGT1A1* pharmacogenetic testing to inform prescribing of first-line protease inhibitor-containing ART in the United States. In a hypothetical cohort of patients who would otherwise initiate atazanavir-containing ART at CD4 500/ μ l, the cost-effectiveness of *UGT1A1* testing was most sensitive to *UGT1A1* assay cost and whether atazanavir-associated hyperbilirubinemia caused patients to be lost to follow-up only to return with substantially more advanced HIV disease. At low *UGT1A1* assay cost, the cost-effectiveness of *UGT1A1* testing was also sensitive to the population frequency of *UGT1A1**28/*28. However, if atazanavir-containing ART and darunavir-containing ART differed in either cost or efficacy, *UGT1A1* testing was not cost-effective under any scenario. That is, the benefits of higher efficacy or lower cost outweighed the benefits of testing. These findings highlight the areas in which model-based analyses can inform priorities for translating pharmacogenetics into HIV clinical care.

Previous model-based analyses have shown that *HLA**B-5701 testing to prevent abacavir hypersensitivity reactions is cost-effective [6,34], but *HLA**B-5701 testing is far more sensitive and specific for abacavir hypersensitivity than *UGT1A1* testing is for atazanavir discontinuation. Moreover, abacavir hypersensitivity is potentially life-threatening, while atazanavir-associated hyperbilirubinemia is a relatively mild adverse event with minimal impact on quality of life. Our finding, that *UGT1A1* testing is not cost-effective if an alternative drug that does not require pharmacogenetic testing is either more effective or less expensive, is consistent with what has been reported for *HLA**B-5701 testing [6].

Testing for *UGT1A1* was not cost-effective at the current stand-alone test cost of \$107 unless hyperbilirubinemia resulted in loss to follow-up that could be prevented by *UGT1A1* testing. Loss to follow-up represents a critical gap in HIV care in the US [35,36], where currently an estimated one-third of HIV-infected individuals linked to care are not retained in care [37]. Future evaluations of pharmacogenetic tests for HIV regimen selection should consider the clinical implications of test results for retention in care, as well as the feasibility of genetic test panels that substantially reduce the cost attributable to each marker tested. Electronic health records increase the feasibility of integrating such large scale pharmacogenetic testing with clinical care [38].

Our analysis is subject to several limitations. We used as model inputs reported results of a retrospective analysis of 121 patients initiating ART in the Swiss HIV Cohort Study, among whom *UGT1A1* homozygosity was associated with atazanavir discontinuation rates of 62.5%, 23.8%, and 14.6% among patients homozygous for *28/*28, heterozygous for *1/

*28, and homozygous for **1/*1*, respectively [4]. Such data may not be generalizable to the U.S. or other populations. When we varied genetic risk to reflect variation in *UGT1A1**28 frequency by ancestry, the cost-effectiveness ratios varied considerably at a hypothetical \$10 assay cost and similar variation was observed if we assumed lower discontinuation rates. Furthermore, a recent analysis of data from a clinical trial conducted in the U.S. suggested that *UGT1A1**28*28 was associated with atazanavir discontinuation in Hispanics, but not in whites or blacks [39]. In the base case, we assumed atazanavir and darunavir had equivalent efficacy and cost. A clinical trial comparing atazanavir-containing and darunavir-containing first-line ART is ongoing [40], and drug costs may vary depending on manufacturer discounts. Our assumption that clinicians or patients might prefer to initiate atazanavir was not captured in base case QALYs or costs. The range of quality-of-life effects of hyperbilirubinemia that we considered may not capture the full spectrum of clinical situations. For example, icterus may more adversely affect quality of life in certain groups (e.g. adolescents, or individuals in jobs where their appearance affects their ability to work). We did not consider the potential future benefit of *UGT1A1* testing to inform prescribing of other non-HIV drugs.

To determine the cost-effectiveness of *UGT1A1* and other pharmacogenetic testing to guide ART regimen selection, it will be important to better understand the associations between genotype, adverse events, and loss to follow-up. Cost-effectiveness of initial ART, however, will remain primarily driven by regimen efficacy and cost.

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REFERENCES

1. Monaghan G, Ryan M, Seddon R, Hume R, Burchell B. Genetic variation in bilirubin UDP-glucuronosyltransferase gene promoter and Gilbert's syndrome. *Lancet*. 1996; 347:578–581. [PubMed: 8596320]
2. Bosma PJ, Chowdhury JR, Bakker C, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *N Engl J Med*. 1995; 333:1171–1175. [PubMed: 7565971]
3. Zhang D, Chando TJ, Everett DW, Patten CJ, Dehal SS, Humphreys WG. In vitro inhibition of UDP-glucuronosyltransferases by atazanavir and other HIV protease inhibitors and the relationship of this property to in vivo bilirubin glucuronidation. *Drug Metab Dispos*. 2005; 33:1729–1739. [PubMed: 16118329]
4. Lubomirov R, Colombo S, di Iulio J, et al. Association of pharmacogenetic markers with premature discontinuation of first-line anti-HIV therapy: an observational cohort study. *J Infect Dis*. 2011; 203:246–257. [PubMed: 21288825]
5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services; Updated 27 March 2012. Available from: <http://www.aidsinfo.nih.gov/contentfiles/adultandadolescentGL.pdf> [Accessed 6 August 2012]
6. Schackman BR, Scott CA, Walensky RP, Losina E, Freedberg KA, Sax PE. The cost-effectiveness of HLA-B*5701 genetic screening to guide initial antiretroviral therapy for HIV. *AIDS*. 2008; 22:2025–2033. [PubMed: 18784465]

7. Haas DW, Kuritzkes DR, Ritchie MD, et al. Pharmacogenomics of HIV therapy: summary of a workshop sponsored by the National Institute of Allergy and Infectious Diseases. *HIV Clin Trials*. 2011; 12:277–285. [PubMed: 22180526]
8. Gold HT, Hall MJ, Blinder V, Schackman BR. Cost effectiveness of pharmacogenetic testing for uridine diphosphate glucuronosyltransferase 1A1 before irinotecan administration for metastatic colorectal cancer. *Cancer*. 2009; 115:3858–3867. [PubMed: 19517472]
9. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med*. 2001; 344:824–831. [PubMed: 11248160]
10. Schackman BR, Gebo KA, Walensky RP, et al. The lifetime cost of current human immunodeficiency virus care in the United States. *Med Care*. 2006; 44:990–997. [PubMed: 17063130]
11. Morris BL, Scott CA, Wilkin TJ, et al. Cost-effectiveness of adding an agent that improves immune responses to initial antiretroviral therapy (ART) in HIV-infected patients: guidance for drug development. *HIV Clin Trials*. 2012; 13:1–10. [PubMed: 22306583]
12. Gold, MR.; Seigel, JE.; Russell, LB.; Weinstein, MC. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
13. Braithwaite RS, Goulet J, Kudel I, Tsevat J, Justice AC. Quantifying the decrement in utility from perceived side effects of combination antiretroviral therapies in patients with HIV. *Value Health*. 2008; 11:975–979. [PubMed: 18225989]
14. Schackman BR, Scott CA, Sax PE, et al. Potential risks and benefits of HIV treatment simplification: a simulation model of a proposed clinical trial. *Clin Infect Dis*. 2007; 45:1062–1070. [PubMed: 17879926]
15. Mellors JW, Muñoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997; 126:946–954. [PubMed: 9182471]
16. Freedberg KA, Scharfstein JA, Seage GR 3rd, et al. The cost-effectiveness of preventing AIDS-related opportunistic infections. *JAMA*. 1998; 279:130–136. [PubMed: 9440663]
17. Multicenter AIDS Cohort Study (MACS) Public Dataset: Release P04. Springfield, VA: National Technical Information Service; 1995.
18. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009; 58:1–207. quiz CE1–4.
19. United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2008 Revision, Highlights. 2009 Working Paper No. ESA/P/WP.210.
20. Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naïve patients: virologic, immunologic, and morphologic changes--a 96-week analysis. *J Acquir Immune Defic Syndr*. 2006; 43:535–540. [PubMed: 17057609]
21. Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med*. 2011; 154:445–456. [PubMed: 21320923]
22. Nelson M, Arasteh K, Clotet B, et al. Durable efficacy of enfuvirtide over 48 weeks in heavily treatment-experienced HIV-1-infected patients in the T-20 versus optimized background regimen only 1 and 2 clinical trials. *J Acquir Immune Defic Syndr*. 2005; 40:404–412. [PubMed: 16280694]
23. Johnson M, Grinsztejn B, Rodriguez C, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. *AIDS*. 2005; 19:685–694. [PubMed: 15821394]
24. Grinsztejn B, Nguyen BY, Katlama C, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. *Lancet*. 2007; 369:1261–1269. [PubMed: 17434401]
25. Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med*. 2008; 359:1429–1441. [PubMed: 18832244]
26. Red Book. Montvale, NJ: Thompson PDR; 2009.

27. Medicaid Drug Price Comparisons: Average Manufacturer Price to Published Prices. Department of Health and Human Services. Office of Inspector General; 2005. Available from: <http://oig.hhs.gov/oei/reports/oei-05-05-00240.pdf>
28. Losina E, Schackman BR, Sadownik SN, et al. Racial and sex disparities in life expectancy losses among HIV-infected persons in the United States: impact of risk behavior, late initiation, and early discontinuation of antiretroviral therapy. *Clin Infect Dis*. 2009; 49:1570–1578. [PubMed: 19845472]
29. Medicare Physician Fee Schedule. [Accessed 6 August 2012] Centers for Medicare and Medicaid Services. 2009. Updated 27 March 2012. Available from: <https://www.cms.gov/apps/physician-fee-schedule/>
30. Gebo KA, Moore RD, Fleishman JA. The HIV Research Network: a unique opportunity for real time clinical utilization analysis in HIV. *Hopkins HIV Rep*. 2003; 15:5–6. [PubMed: 14974424]
31. Clinical laboratory fee schedule 2009. [Accessed 6 August 2012] Centers for Medicare and Medicaid Services. Updated 23 March 2012. Available from: <http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/clinlab.html>
32. Hall D, Ybazeta G, Destro-Bisol G, Petzl-Erler ML, Di Rienzo A. Variability at the uridine diphosphate glucuronosyltransferase 1A1 promoter in human populations and primates. *Pharmacogenetics*. 1999; 9:591–599. [PubMed: 10591539]
33. Hunink, MGM.; Glasziou, PP.; Siegel, JE., et al. Decision making in health and medicine: integrating evidence and values. Cambridge: Cambridge University Press; 2001.
34. Kauf TL, Farkouh RA, Earnshaw SR, Watson ME, Maroudas P, Chambers MG. Economic efficiency of genetic screening to inform the use of abacavir sulfate in the treatment of HIV. *Pharmacoeconomics*. 2010; 28:1025–1039. [PubMed: 20575592]
35. Christopoulos KA, Das M, Colfax GN. Linkage and retention in HIV care among men who have sex with men in the United States. *Clin Infect Dis*. 2011; 52(Suppl 2):S214–S222. [PubMed: 21342910]
36. Horstmann E, Brown J, Islam F, Buck J, Agins BD. Retaining HIV-infected patients in care: Where are we? Where do we go from here? *Clin Infect Dis*. 2010; 50:752–761. [PubMed: 20121413]
37. Vital signs: HIV prevention through care and treatment--United States. *MMWR Morb Mortal Wkly Rep*. 2011; 60 1618-23.
38. Wilke RA, Xu H, Denny JC, et al. The emerging role of electronic medical records in pharmacogenomics. *Clin Pharmacol Ther*. 2011; 89:379–386. [PubMed: 21248726]
39. Ribaud, HJ.; Daar, ES.; Tierney, C., et al. Premature Discontinuation of Atazanavir/ritonavir and UGT1A1 Variants: ACTG Protocol A5202; Seattle, Washington. 19th Conference on Retroviruses and Opportunistic Infections (CROI); Mar 5–8. 2012 Abstract 597
40. AIDS Clinical Trials Group, National Institute of Allergy and Infectious Diseases (NIAID), Bristol-Myers Squibb, Gilead Sciences, Merck, Tibotec Therapeutics. Comparative Study of Three NNRTI-Sparing HAART Regimens. Bethesda, MD: National Library of Medicine (US); Updated 6 October 2011. Available from: <http://clinicaltrials.gov/ct2/show/NCT00811954?term=NCT00811954&rank=1> [Accessed 22 May 2012]
41. Schackman BR, Goldie SJ, Freedberg KA, Losina E, Brazier J, Weinstein MC. Comparison of health state utilities using community and patient preference weights derived from a survey of patients with HIV/AIDS. *Med Decis Making*. 2002; 22:27–38. [PubMed: 11833663]

Figure 1. Schema for first-line antiretroviral regimes evaluated
 ATV: atazanavir, DRV: darunavir

Figure 2. Cost-effectiveness ratio varying frequency of risk genotype (with test cost of \$10)
 QALY: quality-adjusted life year, Low Case: lowest reported prevalence among Caucasians,
 High Case: highest reported prevalence among individuals of African ancestry

Figure 3. Results of probabilistic sensitivity analysis varying hyperbilirubinemia duration, evaluation cost, and quality-of-life multiplier
QALY: quality-adjusted life year

Table 1Model variable inputs for an analysis of *UGT1A1* genetic testing before initiation of antiretroviral therapy

Variable	Base Case	Range	Reference
Baseline cohort characteristics			
CD4 count at initiation, cells/ μ l	500	200–500	Assumption
Age, mean years (standard deviation)	44.0 (9.7)	37.0 (9.7)–50.0 (9.7)	[4]
Percent male	73	---	[4]
HIV RNA distribution (%)			[17]
>100,000 copies/ml	12.9	---	
30,001–100,000 copies/ml	12.9	---	
10,001–30,000 copies/ml	25.0	---	
3,001 – 10,000 copies/ml	25.2	---	
501 – 3,000 copies/ml	16.3	---	
<500 copies/ml	7.7	---	
Baseline quality of life	0.87	0.83–0.87	[41]
Genotype association			
Percent with risk genotype	14.9	9.0–33.0	[4,32]
Percent with failed genotype	0.3	0.0–2.4 ^a	[4]
Adverse events in absence of genetic testing (%)			
With risk genotype	33.3	---	[4]
Without risk genotype	6.8	---	[4]
Genotyping test cost			
Cost per test (\$)	107	10–107	[31], Assumption
Atazanavir adverse event evaluation cost			
Clinic visit and lab test costs ^b (\$)	114	45–153	[29,31]
Atazanavir adverse event quality of life			
Adverse event quality-of-life multiplier ^c	0.97	0.92 –0.99	Assumption, [13]
Days of adverse event	14	7–28	Assumption
Variable	Base Case	Monthly Cost (\$)	Reference
Antiretroviral therapy regimens: % HIV RNA suppression at 24 weeks, mean increase in CD4 cell count at 48 weeks, and monthly cost			
First-line, atazanavir-based	93.2%	1,841	[21,26]
	175/ μ l		
First-line, darunavir-based ^d	93.2%	1,841	[21,26]
	175/ μ l		
Second-line	93.2%	1,276	[21,26]
	175/ μ l		
Third-line	61.3%	1,822	[23,26]
	121/ μ l		
Fourth-line	64.5%	2,385	[24,26]
	102/ μ l ^e		

Variable	Base Case	Range	Reference
Fifth-line	40.0%	4,306	[22,25,26]
	119/ μ l		
Sixth-line	15.0%	1,593	[22,26]
	45/ μ l ^e		

^a Includes no genotype due to a failed test (0.3%) or lack of consent or biomaterial (2.1%).

^b Outpatient follow-up visit (base case 20 minutes, range 5–40 minutes), complete blood count, urinalysis and chemistries including renal function and liver enzymes.

^c Base case value selected based on expert opinion; minimum value selected based on quality-of-life reduction for all symptoms patients believed were definitely attributable to antiretroviral therapy in a study of the Veterans Aging Cohort Study population [13]; maximum value is the smallest quality-of-life impact appropriate to consider.

^d Ranges of 83.9%–99.0% HIV RNA suppression and \$1,841 $\pm$ 10% examined in sensitivity analyses.

^e At 24 weeks.

Table 2

Results of an analysis of *UGT1A1* genetic testing before initiation of antiviral therapy

Strategy	Total Lifetime QALYs	Δ QALY	Test Cost \$107			Test Cost \$10		
			Total Lifetime Cost (\$)	Δ Cost (\$)	\$/QALY	Total Lifetime Cost (\$)	Δ Cost (\$)	\$/QALY
Base Case								
No testing	16.02		475,800			475,800		
Universal testing	16.02	0.000049	475,910	100	2,058,200	475,810	<10	88,500
Atazanavir efficacy lower (darunavir efficacy 99% suppressed at 24 weeks)								
No testing	16.02		476,120			476,120		
Universal testing	16.03	0.004003	476,510	390	dominated ^a	476,410	290	dominated ^a
No testing, treat all with darunavir	16.06	0.035810	478,700	2,590	72,200	478,700	2,590	72,200
Atazanavir cost higher (darunavir cost 10% lower)								
No testing	16.02		473,010			473,010		
Universal testing	16.02	0.000049	470,550	-2,460	Dominated ^b	470,450	-2,560	Dominated ^b
No testing, treat all with darunavir	16.02	0.000108	449,820	-23,190	Cost-saving	449,820	-23,190	Cost-saving
Atazanavir efficacy higher (darunavir efficacy 10% lower)								
No testing	16.01		475,300			475,300		
Universal testing	16.01	-0.005880	474,950	-360	Less effective	474,850	-460	Less effective
Atazanavir cost lower (darunavir cost 10% higher)								
No testing	16.02		478,600			478,600		
Universal testing	16.02	0.000049	481,260	2,670	53,957,300	481,170	2,570	51,987,600
Initial CD4 500/μl, 5% with adverse event lost to follow up, return to care with opportunistic infection or CD4 <200/μl								
No testing	16.01		475,020			475,020		
Universal testing	16.01	0.007270	475,530	510	70,000	475,430	410	56,600
Initial CD4 350/μl, 5% with adverse event lost to follow up, return to care with opportunistic infection or CD4 <200/μl								
No testing	15.85		472,990			472,990		
Universal testing	15.85	0.006794	473,380	390	56,900	473,280	290	42,600
Initial CD4 500/μl, 5% with adverse event lost to follow up, return to care with opportunistic infection or CD4 <350/μl								

Strategy	Total Lifetime QALYs	Δ QALY	Test Cost \$107			Test Cost \$10		
			Total Lifetime Cost (\$)	Δ Cost (\$)	\$/QALY	Total Lifetime Cost (\$)	Δ Cost (\$)	\$/QALY
No testing	16.01		475,360			475,360		
Universal testing	16.02	0.002836	475,690	330	117,600	475,590	240	83,200

^a Less efficient (higher cost-effectiveness ratio compared to the 'no testing' strategy) than the 'no testing, treat all with darunavir' strategy (extended dominance).

^b Less effective and more costly than the 'no testing, treat all with darunavir' strategy (Dominance). QALY: quality-adjusted life year