Published in final edited form as:

HIV Clin Trials. 2012 ; 13(1): 1–10. doi:10.1310/hct1301-001.

Cost-effectiveness of Adding an Agent That Improves Immune Responses to Initial Antiretroviral Therapy (ART) in HIV-Infected Patients: Guidance for Drug Development

Bethany L. Morris¹, Callie A. Scott¹, Timothy J. Wilkin⁵, Paul E. Sax^{3,4}, Roy M. Gulick⁵, Kenneth A. Freedberg^{1,2,4,7}, and Bruce R. Schackman⁶

¹Division of General Medicine Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

²Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

³Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts, USA

⁴Harvard University Center for AIDS Research, Harvard Medical School, Boston, Massachusetts, USA

⁵Division of Infectious Diseases, Department of Medicine, Weill Cornell Medical College, New York, New York, USA

⁶Division of Health Policy, Department of Public Health, Weill Cornell Medical College, New York, New York, USA

⁷Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts, USA

Abstract

Purpose—Adding an immune-enhancing agent to initial antiretroviral therapy (ART) for HIV is a potential strategy to ensure that patients achieve optimal immune response.

Method—Using a mathematical model of HIV disease and treatment, we evaluated the treatment benefits and cost-effectiveness of adding a hypothetical immune-enhancing agent to the initial 6 months of ART. We assumed that the additional agent would result in a higher CD4 increase that would provide clinical benefit. The additional cost (\$1,900/month) was based on the cost of a drug currently under investigation for immune enhancement. Outcomes included projected life expectancy and cost-effectiveness in 2009 US dollars/quality-adjusted life year (QALY) with costs and QALYs discounted at 3% annually.

Results—Compared to standard ART, immune-enhanced ART resulting in an additional 40 CD4 cell/ μ L increase at 6 months yields a 2.4 month projected undiscounted life expectancy increase with a cost-effectiveness ratio of \$107,600/QALY. Achieving a cost-effectiveness ratio <

© 2012 Thomas Land Publishers, Inc.

Address for correspondence: Bethany L. Morris, 50 Staniford Street, 9th Floor, Boston, MA 02144 USA; phone: 617-724-2835; fax: 617-726-2691; blmorris@partners.org.

Conflicts of Interest Dr. Wilkin has served as a paid consultant to Pfizer and Quest Diagnostics. Dr. Sax has served as a consultant to Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, and Tibotec and has received grant support from Gilead, Merck, GlaxoSmithKline, and Tibotec. Dr. Gulick has served as an ad-hoc consultant to GlaxoSmithKline, Merck, Pfizer, and ViiV and has received grant support from Merck and Pfizer.

\$100,000/QALY requires a >43 CD4 cell/ μ L improvement, or >19 cells/ μ L if immune-enhancing agent costs are halved.

Conclusions—In addition to showing clinical efficacy, investigational immune enhancement agents need to increase CD4 counts more than has been previously observed or have a lower cost to be considered cost-effective in the United States.

Keywords

ART-naïve; HIV; immune-enhanced

Antiretroviral therapy (ART) has 2 primary benefits when used to treat HIV: HIV RNA viral load suppression and restoration of immune function. However, not all patients who begin ART experience an immunologic benefit from therapy.^{1,2} Approximately 20% have suboptimal immunologic response despite HIV RNA suppression and are at significantly higher risk of clinical progression in the first year after starting ART.^{2,3} The SILCAAT and ESPRIT randomized trials of interleukin-2 have recently investigated the merits of administering immune-enhancing agents to boost CD4 counts of patients with suboptimal immunologic response.⁴ Despite showing a significant increase in CD4 counts with immune-enhanced ART, these studies concluded that the additional IL-2-induced CD4 cells did not provide clinical benefits.⁴ Several pilot studies of other agents to increase CD4 counts, such as the approved CCR5 antagonist maraviroc, have been reported.^{5,6}

Each of these studies was conducted among ART-experienced patients after they had been identified as suboptimal immune responders. An alternative strategy would be to provide immune-enhanced ART to all patients initiating ART with lower pretreatment CD4 counts in order to prevent suboptimal immune response among patients at the highest risk of adverse outcomes; one clinical study is currently evaluating this strategy using maraviroc as an immune-enhancing agent.⁷ There are indications in the clinical literature that this strategy may be effective. For example, in the MERIT trial of antiretroviral-naïve patients, CD4 count increases after 48 weeks were significantly higher in patients treated with maraviroc + zidovudine/lamivudine than with efavirenz/zidovudine/lamivudine (+170 vs +144 cells/ μ L; difference +26 [95% CI, +7 to +46]), despite a lower degree of virologic suppression (65% vs 69% with HIV RNA <50 copies/mL), and the CD4 count difference was maintained at 96 weeks.^{8,9} The clinical benefit of this additional CD4 count improvement is not known and will need to be tested in future clinical studies.⁹ Similarly, the cost of immune-enhanced initial ART will depend on whether the immune-enhancing agent can be subsequently withdrawn without losing this clinical benefit.

With resources for current HIV treatment already severely constrained, new HIV treatment advances will need to be evaluated in economic as well as clinical terms. Our objective was to assess the potential cost-effectiveness of immune-enhanced initial ART as a strategy to prevent suboptimal immune response in patients with low pretreatment CD4 counts. We sought to define thresholds of effectiveness and cost at which such an agent might be cost-effective to guide drug development and the design of future clinical trials to test this strategy.

METHODS

Analytic Overview

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) simulation model of HIV disease progression and treatment,^{10–12} along with data from relevant peer-reviewed literature,^{4,5} to project the long-term outcomes and evaluate the cost-effectiveness

of a potential immune-enhanced ART regimen for ART-naïve patients. The advantage of a model-based Monte Carlo simulation is that it allows projections of lifetime benefits and costs that are not observable in a clinical trial.

We compared a strategy in which simulated patients initiate a first-line ART regimen consisting of efavirenz, tenofovir, and emtricitabine with the addition of an immune-enhancing agent for 6 months (immune-enhanced ART) to a strategy in which simulated patients initiate this first-line antiretroviral regimen without an immune-enhancing agent (standard ART); we also included a no antiretroviral treatment strategy (no ART) for comparison purposes only. We assumed that the addition of the immune-enhancing agent would result in a higher CD4 cell increase after 6 months than would occur with standard ART and that this increase would provide sustained clinical benefit. The clinical benefit, duration, and cost of the immune-enhanced treatment were varied in sensitivity analyses.

Simulated patients were followed in the model until death, and results are reported in life years, quality-adjusted life years (QALYs), and lifetime costs in 2009 US dollars; both QALYs and costs are discounted at a 3% annual rate in accordance with established guidelines for cost-effectiveness analysis.¹³ Incremental cost-effectiveness ratios (\$/QALY) are reported and compared to a ratio of \$100,000/QALY, because many evidence-based treatments in the United States fall below this threshold.^{14,15}

Cost-effectiveness Threshold

We use a cost-effectiveness threshold of \$100,000/QALY, which reflects current reimbursement practice in the United States more accurately than the \$50,000/QALY threshold from the mid 1990s,¹⁶ although the threshold value varies among decision makers.¹⁷ Nevertheless, some have argued that \$100,000/QALY remains too low and that an incremental cost-effectiveness ratio that lies between \$100,000/QALY and \$300,000/QALY may be appropriate.^{14,15,18} Conversely, \$100,000/QALY is substantially higher than the cost-effectiveness ratios that have been reported for many HIV treatment and prevention interventions, even after adjustment for medical inflation.¹⁹

CEPAC Model

In the CEPAC state transition model, simulated HIV-infected patients are characterized by health states that are defined by CD4 count, HIV RNA level, and presence or absence of opportunistic infections.^{10–12} In the absence of treatment, patients' CD4 counts decline according to a specified trajectory that depends on their HIV RNA level.²⁰ As the CD4 count declines, patients are at increased risk for developing opportunistic infections and HIV-related death based on an incidence density analysis of natural history data.^{20–24} Patients' HIV RNA levels and CD4 counts are routinely monitored, and patients are eligible for ART at CD4 $\leq$ 500 cells/ μ L, which is consistent with current US guidelines.²⁵ Opportunistic infection prophylaxis is initiated at the recommended CD4 counts according to the type of prophylaxis.²⁶ Once initiated on ART, patients have a probability of virologic suppression and subsequent CD4 count gain that is specified based on current literature and divided into 3 time periods, with the greatest benefit occurring in the first 2 months on ART.²⁷ CD4 count gains are associated with reductions in the risk of developing opportunistic infections and of HIV-related death that also depend on prior history of opportunistic infections and ART treatment status. Upon virologic rebound, patients are switched to the next available ART regimen. Six efficacious ART regimens, each with decreasing efficacy, are specified in the model.^{27–34} All patients also face a risk of non-HIV-related mortality that depends on age and sex,³⁵ adjusted for race/ethnicity and other risk factors as has been previously described.^{35–37} Cost of HIV treatment and care is from

the health system perspective and is derived from HIV Research Network data and Medicare fee schedules.^{10,38–41}

Model Inputs and Analysis

Mean age of the simulated patients is 43 years, and 84% of patients are male,⁴² with a mean (*SD*) CD4 count of 175 (77) cells/ μ L based on median CD4 counts for patients entering the A5256 and SILCAAT clinical trials (**Table 1**).^{4,5} Initial ART with efavirenz, tenofovir, and emtricitabine in the absence of an immune-enhancing agent has an immunologic benefit averaging 167 CD4 cells/ μ L at 24 weeks, based on 48-week results reported in the literature and adjusted for loss to follow-up.²⁸ We examine alternative levels of additional CD4 count benefit with a hypothetical immune-enhancing agent, modeled as an absolute gain for patients that is varied from 5 to 100 CD4 cells/ μ L. We assume that the additional CD4 increase would provide an additional clinical benefit by reducing the probability of opportunistic infections and HIV-related death. In the base case, we assume that the immune-enhancing agent was added to initial ART for the first 6 months and then withdrawn and that the additional CD4 count gain would be maintained thereafter, but there would be no further CD4 count improvement compared to standard ART. In sensitivity analyses, we vary the duration of treatment and benefit and explore differences in benefit depending on initial CD4 count. The cost of the hypothetical immune-enhancing agent is \$1,900 per month based on the current price of maraviroc, adjusted for estimated discounts and dispensing fees,^{10,39} and is also varied in sensitivity analyses.

RESULTS

In this simulated cohort with an initial mean CD4 count of 175 cells/ μ L, compared to no ART, standard ART increases undiscounted life expectancy from 3.02 years (2.29 discounted QALYs) to 14.75 years (8.97 discounted QALYs), increases discounted lifetime cost from \$125,140 to \$345,990, and has a cost-effectiveness ratio of \$33,100/QALY (Table 2). The addition of an immune-enhancing agent not only increases CD4 count response to initial ART by an additional 40 CD4 cells/ μ L, but also increases undiscounted life expectancy to 14.95 years, an additional 0.20 years (2.4 undiscounted life months, or 1.3 quality-adjusted life months), compared to the current standard of care. The discounted lifetime cost is \$357,220 or \$11,230 higher than standard ART, including the cost of the agent for 6 months and the cost of treatment for the additional life months gained. The cost-effectiveness ratio for immune-enhanced ART with this level of benefit compared to standard ART is \$107,600/QALY. As immunologic benefit increases, the immune-enhanced ART becomes both more effective and more cost-effective. With an additional CD4 count gain of 60 cells/ μ L at 6 months, there is an added benefit of 3.4 undiscounted life months and 1.9 quality-adjusted life months, with a cost-effectiveness ratio of \$77,000/QALY. The threshold immunologic benefit, or breakeven point, for a cost-effectiveness ratio <\$100,000/QALY is an additional 43 CD4 cells/ μ L.

When the cost of the immune-enhancing agent is halved, the threshold immunologic benefit to achieve a cost-effectiveness ratio <\$100,000/QALY is immune-enhanced ART with an additional 19 CD4 cells/ μ L increase (Figure 1). The cost-effectiveness ratios for immune-enhanced ART are higher as the duration of therapy increases, assuming the same monthly cost (Table 2). The threshold benefit to achieve a cost-effectiveness ratio <\$100,000/QALY is an additional 79 CD4 cells/ μ L with 12 months of immune-enhanced therapy and an additional 165 CD4 cells/ μ L with 24 months of immune-enhanced therapy.

When the initial cohort CD4 count was lowered to a mean of 75 cells/ μ L, the cost-effectiveness ratios of immune-enhanced therapy were similar to those for a cohort with a mean CD4 count of 175 cells/ μ L. Results were also similar when the degree of CD4 count

increase was varied depending on initial CD4 count. For example, if an immune-enhancing agent provides a CD4 count increase of approximately 20% to all patients, instead of 40 cells/ μ L to all patients, the mean CD4 count increase remains 40 cells/ μ L, but the lowest quintile increases by 24 cells/ μ L and the highest quintile increases by 56 CD4 cells/ μ L. The cost-effectiveness ratio for immune-enhanced ART is \$81,000/QALY in this scenario versus \$107,600/QALY, with a uniform increase of 40 cells/ μ L for all quintiles.

DISCUSSION

Nearly one-third of all patients in the United States have a CD4 count <200 cells/ μ L when presenting for care.⁴³ Using a mathematical model of HIV disease and treatment, we evaluated the potential treatment benefits, costs, and cost-effectiveness of immune-enhanced initial ART as a strategy to prevent suboptimal immune response in patients with low pretreatment CD4 counts. This assumes that immune-enhanced ART would result in a higher CD4 increase that in turn would provide clinical benefit leading to increased life expectancy. To achieve a cost-effectiveness ratio $<\$100,000/\text{QALY}$ compared to standard ART in a cohort with a mean CD4 count of 175 cells/ μ L, we found that the CD4 count improvements need to be an additional 43 cells/ μ L over 6 months if the cost of the hypothetical immune-enhancing agent is \$1,900 per month. This is a higher CD4 count increase than previously reported for immune-enhanced ART in treatment-experienced patients.^{4,5} If the cost of such an agent can be reduced by 50%, however, the CD4 count increase required would be 19 cells/ μ L, which is closer to the additional increase reported in the MERIT study of a maraviroc-based regimen (compared to an efavirenz-based regimen) in treatment-naïve patients.⁸

Despite recent findings that have not shown clinical benefit for immune-enhanced ART (such as IL-2)⁴ in treatment-experienced HIV-infected patients, there remains a strong rationale for identifying agents that can prevent suboptimal immune response after treatment initiation currently experienced by a substantial minority of patients. This need is particularly great for patients with lower CD4 counts who have a suboptimal immune response during their first 6 months on ART, when the risk of adverse outcomes is highest.^{2,3} To benefit these patients, however, an immune-enhancing agent would need to be included in the initial regimen for all patients, because patients who will have a suboptimal immune response cannot yet be identified reliably in advance despite some high-risk indicators such as older age, pretreatment CD4 <200 cells/ μ L, and prior AIDS diagnosis.³ This analysis suggests that for such a strategy to be considered cost-effective, investigational agents will need to reach a higher level of CD4 count increase than has been previously observed or need to be priced lower than about \$1,000 per month for 6 months. Antiretroviral drug doses required for immune enhancement may be different (and could be lower) than those required for antiretroviral activity.

These model-based findings provide a guide for drug development and the design of clinical trials to test the strategy of immune-enhanced initial ART. There are, however, several limitations to the analysis. First, we intentionally make assumptions favorable to the efficacy of immune-based therapy, because only drugs with substantial immuno-logical efficacy would be considered for further development. Although recognizing that in previous studies of immune-based therapy CD4 cell increases were not associated with clinical benefit, we assume in this analysis that this would be for an immune-enhancing agent with clinical benefit. We also assume that this one-time benefit will endure throughout the remainder of a patient's time on ART, even after the agent is no longer part of the ART regimen. If ongoing or lifelong treatment were required to maintain the immunological benefit, then the cost of the immune-enhancing agent would need to be implausibly low compared to current ART drug costs.³⁹ Additionally, we assume that all patients in the cohort are eligible for treatment

(ie, no restrictions based on viral tropism) and that after initial regimen failure patients remain on subsequent lines of ART and continue to receive guideline-concordant care. Finally, we assume that patients with persistently low CD4 counts despite virologic suppression remain at higher risk for HIV-related complications, although the highest risk occurs in the first 6 months. If the prognosis of immunologic nonresponse is in fact reasonably good after 1 year, as suggested by one recent study,³ then we may have provided an overly optimistic estimate of the cost-effectiveness of this intervention.

Designing clinical trials to evaluate agents for immune enhancement will be challenging. Enrollment will need to target treatment-naïve individuals with low CD4 counts who are most likely to achieve benefit from such an intervention. Long-term follow-up will be necessary to determine the extent to which CD4 count improvements are associated with sustained clinical benefit, and sample sizes will need to be large enough to show such a benefit compared to standard care. If these challenges can be met and these agents identified, the benefits of immune reconstitution could be experienced by a larger number of HIV-infected patients on suppressive ART at a reasonable cost to the US health care system.

Acknowledgments

Financial Support This research was funded by the National Institute for Allergy and Infectious Diseases: R37 AI042006, AI51966, U01 AI 069472 (Partners/Harvard Clinical Trials Unit), U01 AI068636 (Central AIDS Clinical Trials Group) and U01 AI069419 (Cornell Clinical Trials Unit).

REFERENCES

1. Chêne G, Sterne JA, May M, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. *Lancet*. 2003; 362(9385):679–686. PMID:12957089. [PubMed: 12957089]
2. Grabar S, Le Moing V, Goujard C, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. *Ann Intern Med*. 2000; 133(6):401–410. PMID:10975957. [PubMed: 10975957]
3. Zoufaly A, an der Heiden M, Kollan C, et al. Clinical outcome of HIV-infected patients with discordant virological and immunological response to antiretroviral therapy. *J Infect Dis*. 2011; 203(3):364–371. PMID:21208929. [PubMed: 21208929]
4. Abrams D, Levy Y, Losso MH, et al. Interleukin-2 therapy in patients with HIV infection. *N Engl J Med*. 2009; 361(16):1548–1559. PMID:19828532. [PubMed: 19828532]
5. Wilkin, TJ.; Lalama, C.; Tenorio, A., et al. Maraviroc (MVC) intensification for suboptimal CD4+ response despite sustained virologic suppression: ACTG 5256. Program and abstracts of the 17th Conference of Retroviruses and Opportunistic Infections (CROI); San Francisco, CA, USA. February 16–19, 2010; Abstract 285
6. Hunt, P.; Shulman, N.; Hayes, T., et al. Immunomodulatory effects of MVC intensification in HIV-infected individuals with incomplete CD4+ T cell recovery during suppressive ART. Program and abstracts of the 18th Conference on Retroviruses and Opportunistic Infections (CROI); Boston, MA, USA. February 27–March 2, 2011; Abstract 153LB
7. [Accessed March 12, 2011] Maraviroc (CCR5) antagonism to decrease the incidence of the Immune Reconstitution Inflammatory Syndrome in HIV-infected patients (CADIRIS). US National Institutes of Health. [ClinicalTrials.gov](http://clinicaltrials.gov/ct2/show/results/NCT00988780)http://clinicaltrials.gov/ct2/show/results/NCT00988780.
8. Cooper DA, Heera J, Goodrich J, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naïve subjects with CCR5-tropic HIV-1 infection. *J Infect Dis*. 2010; 201(6):803–813. PMID:20151839. [PubMed: 20151839]
9. Sierra-Madero J, Di Perri G, Wood R, et al. Efficacy and safety of maraviroc versus efavirenz, both with zidovudine/lamivudine: 96-week results from the MERIT study. *HIV Clin Trials*. 2010; 11(3): 125–132. PMID:20736149. [PubMed: 20736149]

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(11):990–997. PMID: 17063130. [PubMed: 17063130]
11. 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(8):1062–1070. PMID:17879926. [PubMed: 17879926]
12. 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(15):2025–2033. PMID:18784465. [PubMed: 18784465]
13. Gold, MR.; Siegel, JE.; Russell, LB.; Weinstein, MC., editors. *Cost Effectiveness in Health and Medicine*. Oxford University Press; New York: 1996.
14. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the \$50,000 per quality-adjusted life-year decision rule? *Med Care*. 2008; 46(4):349–356. PMID:18362813. [PubMed: 18362813]
15. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? *Arch Intern Med*. 2003; 163(14):1637–1641. PMID:12885677. [PubMed: 12885677]
16. Grosse SD. Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY threshold. *Expert Rev Pharmacoecon Outcomes Res*. 2008; 8(2):165–178. PMID:20528406. [PubMed: 20528406]
17. Schackman BR, Gold HT, Stone PW, Neumann PJ. How often do sensitivity analyses for economic parameters change cost-utility analysis conclusions? *Pharmacoeconomics*. 2004; 22(5): 293–300. PMID:15061679. [PubMed: 15061679]
18. Kim JJ, Ortendahl J, Goldie SJ. Cost-effectiveness of human papillomavirus vaccination and cervical cancer screening in women older than 30 years in the United States. *Ann Intern Med*. 2009; 151(8):538–545. PMID:19841455. [PubMed: 19841455]
19. Walensky RP, Freedberg KA, Weinstein MC, Paltiel AD. Cost-effectiveness of HIV testing and treatment in the United States. *Clin Infect Dis*. 2007; 45(Suppl 4):S248–254. PMID:18190295. [PubMed: 18190295]
20. 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(12):946–954. PMID:9182471. [PubMed: 9182471]
21. Multicenter AIDS Cohort Study (MACS). Public Dataset: Release P04 [database on the Internet]. National Technical Information Service; Springfield, VA: 1995.
22. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med*. 2001; 344(11):824–831. PMID:11248160. [PubMed: 11248160]
23. Freedberg KA, Scharfstein JA, Seage GR 3rd, et al. The cost-effectiveness of preventing AIDS-related opportunistic infections. *JAMA*. 1998; 279(2):130–136. PMID:9440663. [PubMed: 9440663]
24. Samet JH, Freedberg KA, Savetsky JB, Sullivan LM, Stein MD. Understanding delay to medical care for HIV infection: the long-term non-presenter. *AIDS*. 2001; 15(1):77–85. PMID:11192871. [PubMed: 11192871]
25. [Accessed March 22, 2011] Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services. January 10, 2011 <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.
26. 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(RR-4):1–207. PMID:19357635.
27. Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in anti-retroviral-naïve patients: virologic, immunologic, and morphologic changes—a 96-week analysis. *J Acquir Immune Defic Syndr*. 2006; 43(5):535–540. PMID:17057609. [PubMed: 17057609]

28. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med*. 2006; 354(3):251–260. PMID: 16421366. [PubMed: 16421366]
29. 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(9569):1261–9. PMID:17434401. [PubMed: 17434401]
30. 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(7):685–694. PMID:15821394. [PubMed: 15821394]
31. Johnson MA, Gathe JC Jr, Podzamczar D, et al. A once-daily lopinavir/ritonavir-based regimen provides noninferior antiviral activity compared with a twice-daily regimen. *J Acquir Immune Defic Syndr*. 2006; 43(2):153–160. PMID:16951643. [PubMed: 16951643]
32. Lalezari, J.; Goodrich, J.; DeJesus, E., et al., editors. Efficacy and safety of maraviroc plus optimized background therapy in viremic ART-experienced patients infected with CCR5-tropic HIV-1: 24-week results of a phase 2b/3 study in the US and Canada [Abs: 104bLB]. Program and abstracts of the 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, CA. February 25–28, 2007;
33. 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(4):404–412. PMID:16280694. [PubMed: 16280694]
34. Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med*. 2008; 359(14):1429–1441. PMID:18832244. [PubMed: 18832244]
35. Arias, E. United States Life Tables, 2004: National Vital Statistics Reports. Centers for Disease Control and Prevention; 2007.
36. Texas Department of State Health Services. [Accessed March 22, 2011] Texas vital statistics: life tables. 2005. <http://www.dshs.state.tx.us/chs/vstat/annrpts.shtm>.
37. 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 anti-retroviral therapy. *Clin Infect Dis*. 2009; 49(10):1570–1578. PMID: 19845472. [PubMed: 19845472]
38. Centers for Medicare and Medicaid Services. [Accessed October 3, 2011] Medicare Physician Fee Schedule. <http://www.cms.hhs.gov/physicianfeesched/downloads/RVU08D.zip>.
39. Red Book. Thomson Reuters; Montvale, NJ: 2009.
40. 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(6):5–6. PMID:14974424. [PubMed: 14974424]
41. University HealthSystems Consortium. [Accessed July 27, 2011] CDP online report. 2008. www.uhc.edu.
42. Althoff KN, Gange SJ, Klein MB, et al. Late presentation for human immunodeficiency virus care in the United States and Canada. *Clin Infect Dis*. 2010; 50(11):1512–1520. PMID:20415573. [PubMed: 20415573]
43. Vital signs: HIV testing and diagnosis among adults—United States, 2001–2009. *MMWR Morb Mortal Wkly Rep*. 2010; 59(47):1550–1555. PMID:21124295. [PubMed: 21124295]

Figure 1.

Cost-effectiveness threshold analysis for adding a hypothetical immune-enhancing agent to first-line antiretroviral therapy for 6 months. The solid, black line represents the \$1,900 base case monthly cost of the hypothetical immune-enhancing agent. The dark gray dashed line represents a 25% reduction in monthly cost for the same drug, the medium gray dashed and dotted line represents a 50% reduction in monthly cost, and the light gray dotted line represents a 75% reduction in monthly cost, assuming the same efficacy and clinical benefit. To have a cost-effectiveness ratio less than \$100,000/QALY compared to standard of care, the agent must provide at least an additional 43 CD4 cell/μL increase in CD4 count above standard therapy (solid diamond) with no price reduction, or a 19 CD4 cell/μL increase with a 50% cost reduction (open circle).

Figure 2.

Cost-effectiveness and quality-adjusted life expectancy by CD4 increase due to immune-enhancing agent. The solid bars represent incremental cost-effectiveness ratios for adding a hypothetical immune-enhancing agent for the first 6 months of therapy. The solid black line corresponds to the quality-adjusted life expectancy for a 6-month duration of immune-enhanced therapy. The dashed bars and dashed line represent the cost-effectiveness and quality-adjusted life expectancy, respectively, for 12 months of immune-enhanced therapy. The cost-effectiveness and quality-adjusted life expectancy of immune-enhanced therapy for 24 months are represented by the dotted bars and dotted line, respectively.

Table 1A

Baseline cohort characteristics for a simulation of treatment of ART-naïve HIV-infected patients with an immune-enhancing agent

Variable	Base case	Reference
Distribution of initial CD4, mean cells/ μ L (<i>SD</i>)		
Chronic HIV infection	175 (77) ^a	4, 5
Mean age, years (<i>SD</i>)	43 (11.9)	42
Sex		42
Male (%)	84	
Discount rate (annual)	3% ^b	
HIV RNA distribution in untreated chronic HIV infection (%)		21, 24
>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	
Mean monthly CD4 cell decline by HIV RNA level (cells/ μ L)		20
>30,001–100,000 copies/mL	6.4	
10,001–30,000 copies/mL	5.4	
3,001–10,000 copies/mL	4.6	
501–3,000 copies/mL	3.7	
<500 copies/mL	3.0	

^aRange examined: 75 (19) to –175 (77).

^bRange examined: 0% to 3%.

Table 1B

Cost input parameters for a simulation of treatment of ART-naïve HIV-infected patients with an immune-enhancing agent^a

Variable	Base case	Reference
Routine care (range by CD4, monthly), off ART	290–2,380	10, 40, 41
Routine care (range by CD4, monthly), on ART	240–1,080	10, 40, 41
CD4 test	70	38
HIV RNA test	120	38
Acute OI events		10, 40, 41
<i>Pneumocystis jiroveci</i> pneumonia	13,120	
<i>Mycobacterium avian</i> complex	5,620	
Toxoplasmosis	31,320	
Cytomegalovirus	8,010	
Fungal infections	8,930	
Other opportunistic infections	6,010	
Mortality (treated and untreated patients)		10, 40, 41
Any OI event	93,990	
Chronic AIDS	59,670	

Note: OI = opportunistic infection.

^a Costs are listed in 2009 US\$.

Table 1C

ART input parameters for a simulation of treatment of ART-naïve HIV-infected patients with an immune-enhancing agent

Variable	Base case Value	Monthly cost (\$)	Reference
ART efficacy: % HIV RNA suppression at 24 weeks, mean increase in CD4 count at 48 weeks			
First line, without immune-enhancing agent (standard of care)	86.0% 190 cells/ μ L	1,430	27, 28, 39
Second line	73.3% 110 cells/ μ L	2,050	30, 31, 39
Third line	61.3% 121 cells/ μ L	2,040	30, 31, 39
Fourth line	65.0% 102 cells/ μ L ^a	2,630	29, 39
Fifth line	40.0% 121 cells/ μ L	4,000	32–34, 39
Sixth line	15.0% 45 cells/ μ L	1,740	33, 39

Note: ART = antiretroviral therapy.

^a At 24 weeks.

Table 2

Results at alternative rates of efficacy

Strategy	Undiscounted life expectancy (years)	Discounted quality-adjusted life years (QALYs)	Discounted cost (2009 US\$)	Incremental cost-effectiveness ratio (\$/QALY) ^a
No ART	3.02	2.29	125,140	–
Standard of care	14.75	8.97	345,990	33,100
6 months of immune-enhancing agent ^b				
5 cell/μL increase	14.77	8.99	356,110	854,100
10 cell/μL increase	14.80	9.00	356,430	353,400
20 cell/μL increase	14.85	9.03	356,610	200,100
40 cell/μL increase	14.95	9.08	357,220	107,600
60 cell/μL increase	15.03	9.13	357,840	77,000
80 cell/μL increase	15.11	9.17	358,270	62,600
100 cell/μL increase	15.18	9.20	358,470	54,800
12 months of immune-enhancing agent ^b				
5 cell/μL increase	14.79	8.99	365,090	1,076,200
10 cell/μL increase	14.81	9.01	365,320	557,900
20 cell/μL increase	14.87	9.03	365,510	322,900
40 cell/μL increase	14.98	9.09	366,240	168,000
60 cell/μL increase	15.05	9.14	366,750	122,800
80 cell/μL increase	15.15	9.19	367,370	98,000
100 cell/μL increase	15.22	9.23	367,720	85,200
24 months of immune-enhancing agent ^b				
5 cell/μL increase	14.80	8.99	379,280	1,580,900
10 cell/μL increase	14.83	9.02	379,820	703,900
20 cell/μL increase	14.89	9.05	379,930	464,500
40 cell/μL increase	15.01	9.11	380,740	250,700
60 cell/μL increase	15.10	9.17	381,490	180,100
80 cell/μL increase	15.19	9.21	381,780	150,600
100 cell/μL increase	15.28	9.24	381,940	133,500

^a Cost-effectiveness ratios may not exactly match costs and QALYs due to rounding.^b Each compared to the standard of care.