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The Cost Effectiveness of Counseling Strategies to Improve Adherence to Highly Active Antiretroviral Therapy (HAART) Among Men Who Have Sex with Men

Gregory S. Zaric, Ph.D.[1,*], **Ahmed M. Bayoumi, M.D., M.Sc.**[2], **Margaret L. Brandeau, Ph.D.**[3], and **Douglas K. Owens, M.D., M.S.**[4,5]

[1]Ivey School Of Business, University of Western Ontario, London, Ontario, Canada N6A 5X4

[2]Inner City Health Research Unit and Department of Medicine St. Michael's Hospital, Toronto, Canada M5B 1W8 and Departments of Medicine and Health Policy, Management, and Evaluation, University of Toronto

[3]Department of Management Science and Engineering, Stanford University, Stanford, CA 94305

[4]VA Palo Alto Health Care System, Palo Alto, CA 94304

[5]Center for Primary Care and Outcomes Research, Department of Medicine, and Department of Health Research and Policy, Stanford University Medical School, Stanford, CA 94305

Abstract

Objective—Inadequate adherence to highly active antiretroviral therapy (HAART) may lead to poor health outcomes and the development of HIV strains that are resistant to HAART. We developed a model to evaluate the cost effectiveness of counseling interventions to improve adherence to HAART among men who have sex with men (MSM).

Methods—We developed a dynamic compartmental model that incorporates HIV treatment, adherence to treatment, and infection transmission and progression. All data estimates were obtained from secondary sources. We evaluated a counseling intervention given prior to initiation of HAART and before all changes in drug regimens, combined with phone-in support while on HAART. We considered a moderate-prevalence and a high-prevalence population of MSM.

Results—If the impact of HIV transmission is ignored, the counseling intervention has a cost-effectiveness ratio of $25,500 per QALY gained. When HIV transmission is included, the cost-effectiveness ratio is much lower: $7,400 and $8,700 per QALY gained in the moderate- and high-prevalence populations, respectively. When the intervention is twice as costly per counseling session and half as effective as we estimated (in terms of the number of individuals who become highly adherent, and who remain highly adherent), then the intervention costs $17,100 and $19,600 per QALY gained in the two populations, respectively.

Conclusions—Counseling to improve adherence to HAART increased length of life, modestly reduced HIV transmission, and cost substantially less than $50,000 per QALY gained over a wide range of assumptions, but did not reduce the proportion of drug-resistant strains. Such counseling provides only modest benefit as a tool for HIV prevention, but can provide significant benefit for individual patients at an affordable cost.

Keywords

Cost Effectiveness; Adherence; HIV; Counseling; Computer Simulation

[*]Corresponding Author. Tel: 1.519.661.3415, Fax: 1.519.661.3485, gzaric@ivey.uwo.ca.

A number of strategies have been proposed to improve adherence to highly active antiretroviral therapy (HAART), including electronic reminders (1), easier-to-follow regimens (1–3), medication under supervised settings (4, 5), self-monitoring (6), counseling sessions (6), and other strategies (7, 8). Recent reviews have identified aspects of successful strategies to improve adherence (9–15). However, some strategies to improve HIV adherence "require considerable resources, and adherence is typically not sustained after the intervention is withdrawn" (15).

Since resistant HIV strains can be transmitted to others, improved adherence to HAART benefits not only those whose adherence is increased, but also those whom they may infect. Two recent papers examined the effectiveness (16) and cost effectiveness (17) of interventions to improve adherence to HAART, but did not account for changes in HIV transmission. To estimate the impact of improved adherence on the development and transmission of resistant strains of HIV, a model that incorporates mixing and infection transmission is needed. Recent papers have highlighted the importance of considering HIV transmission, resistance, and viral load when evaluating the effects of improved adherence (18–20) and have demonstrated the relationship between adherence and resistance (21) and viral load suppression (22, 23). An evaluation of the cost effectiveness of adherence interventions that does not include the benefits related to transmission may substantially underestimate cost effectiveness.

We evaluated the cost effectiveness of counseling to improve adherence to HAART. The analysis is based on a model of the HIV epidemic that incorporates infection transmission, disease progression, treatment and adherence to treatment. We included costs of HIV testing, viral load monitoring, resistance testing, counseling to improve adherence, HIV treatment, and non-HIV-related health care. We measured total quality-adjusted life years of survival (QALYs) experienced by the population, number of new HIV infections, and proportion of HIV cases in each resistance category.

METHODS

Model Overview

We constructed a dynamic compartmental model of HIV transmission and progression (Figure 1). We modeled an open population of men who have sex with men (MSM) aged 18–65. We constructed moderate- and high- prevalence (10% and 20%, respectively) HIV populations to reflect levels of HIV prevalence among MSM in different US cities (24–26). Key data and sources are shown in Table 1.

We modeled three different types of transitions. First, we modeled the progression from uninfected to HIV-infected receiving treatment (active therapy and non-suppressive therapy), incorporating resistance (Figure 1a). Second, we modeled the transitions between adherence levels and therapeutic regimens during active therapy (Figure 2). Third, we modeled the progression from HIV to AIDS to death. Each of these is detailed below.

Uninfected individuals become infected through sexual contact with infected individuals. Once infected, individuals remain unaware of their infection until either they develop HIV-related symptoms or opportunistic infections, or they are identified through routine screening. Once identified, individuals begin a HAART regimen.

While on HAART, individuals who achieve viral load suppression remain on that regimen until they either experience a treatment failure due to the development of a resistant strain or

they develop a toxicity. Following three HAART regimens, individuals enter non-suppressive therapy.

Individuals whose viral load is suppressed are assumed to be asymptomatic, while those who experience a failure or toxicity while on HAART will be temporarily symptomatic until they switch regimens. Individuals can experience a declining CD4 count and a risk of both AIDS and AIDS-related death once they enter non-suppressive therapy.

The model was simulated for 20 years. For the first 20 years, costs and benefits were estimated directly through the model simulation. Costs and benefits beyond the first 20 years were estimated as the future expected costs and QALYs experienced by individuals in each model compartment assuming no more disease transmission or population growth. Costs are expressed in 2004 dollars. Costs and benefits were discounted at 3% (27).

Resistance

Clinically, HIV resistance is determined by specific mutations in the viral genome (which can confer resistance to single drugs or cross-resistance to other drugs in the same class), the number of mutations, and interactions between mutations. Rather than model specific drugs and resistance mutations, we classified individuals into four resistance groups reflecting their probability of sustaining virologic suppression with antiretroviral therapy. Resistance can be acquired at the time of infection or can develop during drug exposure (most frequently due to non-adherence). Accordingly, we assumed that resistance patterns are cumulative (and nondecreasing) and persist indefinitely.

The lowest resistance level (level 1) represents no resistant HIV strains. Individuals in this resistance class respond to all HAART regimens and derive the maximum benefit from HAART. Individuals with intermediate resistance levels (levels 2 and 3) have accumulated resistance mutations from past regimens or by being infected by an individual with a high resistance level, and therefore have restricted options for subsequent treatment. Because of cross-resistance between antiretroviral drugs, these individuals experience treatment failures at a higher rate than individuals with no resistant strains. Individuals with the highest resistance level (level 4) were assumed to have less than a 50% chance of achieving virologic suppression with HAART. We assumed that an individual's resistance level changes only as a result of exposure to HAART (vertical arrows in Figure 1a).

In the base case, 14.3% of the population carried a resistant strain of HIV at the beginning of the time horizon; among these individuals, we estimated that 90.8% were in resistance level 1, 9.0% were in resistance level 2, and 0.2% were in resistance level 3. The distribution of individuals among compartments with resistant individuals was derived by starting with a model in which there were no resistant individuals and simulating forward until approximately 13% of the population was in resistance level 1 (comparable to (28)). The proportion initially resistant was varied in sensitivity analysis to reflect wide variations in the observed prevalence of resistant strains (29, 30).

HIV Transmission

Infection transmission occurs via sexual contacts. We assumed random mixing, which is a reasonable approximation for a homogenous population of MSM (31–33). We assumed that a newly infected individual has the same resistance level as the person who infected him. We calculated HIV incidence based on the average number of sexual partners (estimated from studies of MSM (34–47)), the condom usage rate, the reduction in transmission associated with condom use (34), and changes in infectivity associated with HAART (48–63).

A wide range of estimates of the probability of HIV transmission per unprotected sexual partnership have appeared (49–63). We estimated that the probability of sexual transmission was 14.7% per sexual partnership when the infected partner had AIDS (59) and that it would be reduced to 6.6% (a factor of 0.45) for infected individuals without AIDS whose viral load was not suppressed (64). Several studies have observed reduced sexual HIV transmission risk associated with reduced viral load (52, 53, 57, 58, 61). Studies of vertical HIV transmission have also observed reduced transmission risk associated with reduced viral load: a 25.5% chance of transmission when no antiretroviral treatment is received during pregnancy (65); less than 2.5% among those mothers whose viral load was less than 1730 (66); and 0% among mothers whose viral load was less than 1000 (67). We used a formula given elsewhere (48) to estimate the ratio of the probability of transmission when viral load is suppressed to the probability of transmission when viral load is not suppressed as being 0.21. When switching to subsequent regimens, the transmission rate rises slightly when the individual is in a viral load rebound state. We assumed that the average transmission probability among individuals on their first HAART regimen would be slightly higher than for individuals on later HAART regimens, reflecting the delay between HAART initiation and viral load suppression. Thus, we estimated that the chance of transmission to an uninfected partner was 1.4% for an individual on his first HAART regimen, and 1.0% for an individual on his second or third HAART regimen.

Treatment before HAART

We assumed that all newly infected individuals are untreated and unaware of their status. They may become aware of their HIV status through routine HIV screening or through the development of symptoms. CDC guidelines call for annual screening (68), although in practice not all at-risk individuals are screened. We estimated that 75% of individuals whose HIV status is unknown are screened each year (69–72). We assumed that individuals whose CD4 count is greater than 350 cells/mm^3 are asymptomatic. Individuals initiate HAART if their CD4 count drops below 350 (73) or if they develop opportunistic infections. The expected time from infection until initiation of HAART was set to 7.3 years, consistent with another study (48).

HAART

We defined HAART as a treatment regimen that includes three or more antiretroviral drugs taken in combination according to recent guidelines (73). Individuals on HAART (Figure 1b) continue on their first HAART regimen until they experience a viral load rebound or toxicity. If the regimen changes due to a viral load rebound, an individual progresses to the next regimen at a higher resistance level; if the regimen changes due to a toxicity, the individual progresses to the next regimen at the same resistance level. We assumed that individuals changing regimens receive genotypic resistance testing to identify an appropriate new drug regimen and undergo additional viral load testing to establish the new level prior to regimen change (after intolerance) or to confirm rebound (after failure). We assumed that viral load monitoring would occur every three months, so the average time in a treatment failure state is 1.5 months. We assumed that, while on HAART, viral load is suppressed except during temporary viral load rebounds; CD4 cell counts increase; and no one develops AIDS.

Viral Load Suppression and Treatment Change

Individuals who achieve viral load suppression can experience increased survival and quality-of-life gains from HAART. The probability of achieving viral load suppression on HAART and the probability of a HAART regimen failing within two years varied with the HAART regimen, the adherence level, and the resistance level (Table 2). We estimated that 80% of individuals on their first regimen, 65% of individuals on their second regimen, and

30% of individuals on their third regimen would achieve viral load suppression for both the high- and intermediate-adherence groups (74–122). These values are averages over all resistance levels. Mutations from early failures may persist, thus contributing to lower success rates for later regimens (123, 124). We estimated that 18% of individuals in the low-adherence group would achieve viral load suppression for all treatment regimens (125).

Baseline Adherence

Adherence was defined as the percentage of prescribed doses of medicine taken. We defined three levels of adherence to HAART: high (> 90% adherence, averaged to be 95%), intermediate (70–90% adherence, averaged to be 80%), and low (< 70% adherence, averaged to be 45%).

The proportion of individuals in each adherence level at a given point in time is a function of the proportion who initiate HAART at each adherence level and the rate at which individuals change adherence levels. A review of studies to improve adherence found baseline rates ranging from 37% to 92%, with a median value of 62% (126, 127). We estimated the initial proportion of individuals in the high-adherence group to be 62%, and assumed that the remaining 38% would be split evenly between the intermediate- and low-adherence groups (19% in each group). Evidence suggests that adherence decreases over time (128). We estimated that, of 100 individuals with high adherence (with 95% average adherence), 28.2 would switch to intermediate adherence (with 80% average adherence) each year in the absence of any intervention (129), and 1 of every 100 persons would switch between other groups each year.

Adherence has an indirect impact on health outcomes in the model. Compared to individuals with high adherence, individuals with intermediate adherence are less likely to experience viral load suppression, and if they do, they experience treatment failure at a faster rate. Thus, they spend less time in asymptomatic states in which quality of life is high and they progress to non-suppressive therapy at a faster rate.

Toxicities and Treatment Failures

We assumed that, among individuals who achieve viral load suppression, 25% experience a toxicity within two years. Additionally, 15% of individuals with high adherence, 22.5% of individuals with intermediate adherence, and no individuals with low adherence would experience a treatment failure caused by the development of resistant strains within two years. The corresponding proportions of individuals who achieved viral load suppression and were still on their initial regimen are shown in Table 2. The values in Table 2 were used to calculate continuous rates of treatment failure and development of toxicities.

Non-suppressive Therapy

Individuals progress to non-suppressive therapy following three failed HAART regimens. We assumed that the rate of developing additional resistant strains in non-suppressive therapy was the same as on the third HAART regimen. We modeled three stages of HIV infection defined by CD4 cell counts (> 200, 50–200, < 50 cells/mm^3). We estimated the amount of time on non-suppressive therapy based on a pre-HAART model of HIV progression (130).

Counseling to Improve Adherence

We assumed that the intervention to improve adherence to HAART would consist of individual counseling sessions provided by a registered nurse or similar skilled health-care professional and would be given to all individuals prior to HAART initiation and following all changes in HAART regimens. We assumed that patients would also have access to

"phone-in" support services, provided by a registered nurse, throughout their treatment. Individuals not receiving counseling may still practice other techniques to improve adherence. We measured the improvement in adherence relative to the base case of no counseling. Two recent systematic reviews examined the effectiveness of interventions aimed at improving adherence to HAART (126, 127). The reviews differed with respect to inclusion criteria and analytical approach, but both found a wide range of intervention effectiveness. Amico et al. (126), including all comparison trials, found that interventions targeted to non-adherent patients were most effective. Rueda et al. (127), including only randomized trials, did not identify such a trend but did find that interventions targeted to individuals (rather than groups), interventions provided over a longer period of time (12 or more weeks), and interventions targeting practical skills (rather than psychological factors) seemed most successful. Amico et al. (126) estimated that the overall effect of interventions, measured by improvement in adherence, was modest.

In our analysis, we used the estimated odds ratio of 1.41 from Amico et al. (126) corresponding to untargeted interventions, but considered a 95% confidence interval (1.20, 1.63), recognizing the considerable heterogeneity in included studies. We modeled increases in adherence by estimating a baseline rate of adherence (with no intervention) and applying the odds ratios, converting between probabilities and odds as appropriate. Accordingly, we estimated that without a counseling intervention, 62% of participants would be highly adherent at baseline, and that with an intervention, this proportion would increase to 69.7% (range 66.2% to 72.3%). We estimated that the intervention would also reduce the annual rate of switching from high to intermediate adherence to 14.8 per 100 (129).

Neither of the systematic reviews reported the costs of (nor resources required for) the interventions. For our base case estimate, we assumed that the counseling would be provided by a registered nurse (average national wage rate of $26.87/hour in 2004 (131)). Schackman et al. (132) found that sessions provided by a registered nurse lasted 31.88 minutes on average, and that labor represented 65.7% of the total cost. Thus, we estimated the cost per counseling session to be (31.88/60)×($26.87)×(1/.657) = $21.73. Additionally, we assumed that patients used phone-in support costing an average of $5.42/month. We considered a wide range of cost estimates in sensitivity analysis.

Health Outcomes and Costs

We measured the number of new HIV infections, proportion of HIV cases in each resistance category, and QALYs experienced by the population. We included costs of HIV testing, viral load monitoring, resistance testing, counseling, HIV treatment, and non-HIV-related health care (Table 1). We estimated total costs (and health benefits) as the sum of the discounted costs (health benefits) experienced over the first 20 years in all model compartments plus the discounted value of the expected future lifetime healthcare costs (quality-adjusted life expectancy) for all individuals at the end of the initial 20 years.

We used the model to calculate lifetime future costs and quality-adjusted life expectancy for individuals in each model compartment. For example, for a newly infected individual with no resistant strains, we initialized the model with a cohort of 100,000 individuals in the compartment corresponding to "infected, unaware, no treatment, no resistant strains". The populations of all other compartments were set to zero, as was the rate of migration into the population. We then projected the model forward for 100 years and calculated the total discounted cost and QALYs experienced. This results in a future discounted cost of $306,985 for a newly infected individual with no resistant strains, which is close to the estimate of $303,100 obtained by Schackman et al. (133). We repeated this process for all model compartments.

We present all results as total costs and health benefits accrued for a population initially consisting of 100,000 individuals. We present the results in this way because the adherence intervention affects HIV transmission and mortality, and thus affects population size.

Model Implementation

We implemented the model in an Excel spreadsheet. We calculated net present costs and QALYs for the base case (Table 1), with and without the effects of HIV transmission in the population. We performed one-way sensitivity analysis on all model parameters, a variety of two-way sensitivity analyses on important related variables, and a stochastic sensitivity analysis in which all parameters were varied simultaneously (details in Figure 2 legend).

RESULTS

Adherence

We first considered a cohort of 100,000 infected individuals. This analysis captures the benefits of the intervention only for those who receive the intervention: everyone in the population is infected, so no one avoids infection as a result of the intervention. In this case, the counseling intervention had an incremental cost-effectiveness ratio of $25,500 per QALY gained (13,847 QALYs gained at an incremental cost of $353.2 million). At the end of 20 years, 1,168 more people were alive and 65.9% of the population was infected with a resistant strain (an increase of less than 0.1% compared to no intervention).

Adherence and HIV Transmission

We next analyzed the effect of the intervention in a cohort of infected and uninfected individuals (Table 3). This analysis captures the impact of the intervention not only among those who receive the intervention, but also among those whom they might infect. In the moderate-prevalence population, the counseling intervention cost $7,400 per QALY gained (3,967 additional QALYs at a cost of $29.3 million). In the high-prevalence population, the intervention cost $8,700 per QALY gained (6,920 QALYs gained at a cost of $60.1 million). The contrast between these results and the individual-level results highlights the impact of considering mixing and population dynamics: the intervention to improve adherence appears more cost effective when its impact on disease transmission is considered. In the moderate-prevalence population, at the end of 20 years, approximately 57.7% of the population had a resistant strain of HIV without the intervention, compared to 57.8% with the intervention. In the high-prevalence population, the corresponding numbers are 58.5% and 58.6%, respectively.

Although the cost-effectiveness ratios are favorable in both populations, the intervention is slightly more cost effective in the moderate-prevalence population. This is because relatively more infections are prevented in the moderate-prevalence population than in the high-prevalence population. In absolute terms, more infections are prevented in the high-prevalence population, but the impact of the intervention relative to the pre-intervention number of infections is larger in the moderate-prevalence population.

Improved adherence leads to more viral load suppression and thus reduced HIV transmission. In the moderate-prevalence population, the counseling intervention led to 309 fewer new HIV infections over a 20-year period and a 0.1% reduction in HIV prevalence at the end of 20 years. In the high-prevalence population, the intervention led to 498 fewer infections and a 0.2% reduction in prevalence. The total QALYs gained can be split into two groups: QALYs gained by the cohort during the 20 years of the simulation, and expected future QALYs among all members of the population who are alive at the end of 20 years. The latter increase in QALYs is due to fewer infections occurring during the simulation

period, resulting in a healthier population at the end of 20 years. For both populations, this latter increase represents approximately 85% of the total QALYs gained.

In both populations, the counseling intervention reduced the total number of HIV infections that occurred over 20 years (by approximately 2.8% and 2.6% in the moderate-and high-prevalence populations, respectively) and reduced the total number of individuals infected with a resistant strain of HIV (by approximately 1.1% and 0.8% in the moderate- and high-prevalence populations, respectively), but slightly increased the proportion of infected individuals who were infected with a resistant HIV strain at the end of 20 years (by about . 1% in both populations). The intervention can be thought of as shifting 3.9% of individuals on HAART from initial intermediate adherence to initial high adherence, and shifting an additional 3.9% from initial low adherence to initial high adherence. Shifting patients from initial intermediate adherence to high adherence causes the proportion of resistant strains to decrease because patients temporarily move from a state where resistant strains develop rapidly to one where they develop slowly. Shifting patients from initial low adherence to high adherence causes the proportion of resistant strains to increase because low-adherence patients, who would normally develop resistant strains very slowly, are moved to a state where they may eventually become intermediate-adherence patients who develop resistant strains rapidly. For the base case, these two effects approximately offset each other, leading to a slight increase in the proportion of resistant strains at the end of 20 years.

Sensitivity Analysis

In sensitivity analysis, for the case of no HIV transmission, we considered a cohort of newly infected individuals with no resistant strains. In this case, the intervention cost $24,900 per QALY gained (14,972 QALYs gained at an incremental cost of $373.0 million). At the end of 20 years, 63.5% of the population was infected with a resistant strain of HIV, an increase of less than 0.1% compared to the case of no intervention. The remaining sensitivity analyses were all conducted for the base model, moderate-prevalence scenario, which did include consideration of HIV transmission.

In one-way sensitivity analysis, the cost-effectiveness ratio remained below $50,000 per QALY gained over the entire range for all variables. The annual screening rate was varied from 25% to 99%; at 25% the intervention cost $7,500 per QALY gained, and at 99% the intervention cost $7,300 per QALY gained. In the base case we assumed no survival advantage associated with partial suppression in non-suppressive therapy. If there is a 50% survival advantage associated with non-suppressive therapy, then the cost-effectiveness ratio decreases to $6,400 per QALY gained. Base case incidence was approximately 1.6%. When we increased this to 2.1%, the cost-effectiveness ratio fell to $4,600 per QALY gained; when we decreased incidence to 1.0%, the ratio increased to $11,800 per QALY gained. In the base case, 62% of the population initially entered the high-adherence state when initiating treatment. We varied this number while holding the odds ratio for treatment constant. If only 50% enter the high-adherence state, then the cost-effectiveness ratio decreases to $6,700 per QALY gained; if the proportion initially adherent increases to 75%, then the ratio increases to $8,700 per QALY gained.

When we simultaneously varied the cost per counseling session and the ongoing cost of phone-in support (up to $200 per counseling session and $100 per patient per month), the intervention cost $54,300 per QALY gained. When the intervention is twice as costly per session and half as effective as we estimated (in terms of the number of individuals who move into the high-adherence state, and the annual rate of remaining in the high-adherence state), then the intervention cost $17,100 per QALY gained (and $19,600 per QALY gained in the high-prevalence population).

We conducted multi-way sensitivity analysis in which we varied the parameters related to the cost and effectiveness of the intervention (Table 4). In most instances considered, the incremental cost-effectiveness ratio was less than $50,000 per QALY gained, although for the most pessimistic combinations of parameter estimates, the incremental cost-effectiveness ratio exceeded $100,000 per QALY gained. The intervention would need to increase the proportion of individuals entering the high-adherence state to at least 65% (from the pre-intervention value of 62%, corresponding to shifting 1.5% of the population from intermediate to high adherence, and 1.5% from low to high adherence) in order for it to cost less than $50,000 per QALY gained.

We considered the possibility that 50% of individuals would inherit the same resistance level as the person who infected them, and 50% would inherit the next lower level. We also considered the possibility of no inherited resistance (i.e., all newly-infected individuals started at resistance level 1 regardless of the level of the person who infected them). In both cases, the incremental cost-effectiveness ratio remained at $7,400 per QALY gained, and the proportion of newly infected individuals with any level of resistance at the end of 20 years was reduced by 0.1%.

In stochastic sensitivity analysis (Figure 2), the intervention had a 20% chance of costing less than $10,000 per QALY gained, an 89% chance of costing less than $50,000 per QALY gained, and a 97% chance of costing less than $100,000 per QALY gained.

DISCUSSION

Counseling to improve adherence to HAART cost less than $10,000 per QALY gained in the base cases considered, and less than $50,000 per QALY gained over a wide range of sensitivity analyses. The cost-effectiveness ratio was most sensitive to the monthly cost of maintaining improved adherence. More than two-thirds of the QALYs gained were due to averted HIV infections.

A recent analysis of the cost effectiveness of improved adherence to HAART reported cost-effectiveness ratios as low as $22,400 per QALY gained in a cohort with late disease and as low as $27,100 per QALY gained in a cohort with early disease, but did not consider HIV transmission (17). When we ignored HIV transmission, we found that counseling to improve adherence had a cost-effectiveness ratio between $24,900 and $25,500 per QALY gained, depending on the prevalence of resistant HIV already in the population. When we included the impact of the intervention on HIV transmission, we found lower cost-effectiveness ratios: $7,400 and $8,700 per QALY gained in the moderate- and high-prevalence populations, respectively. Although the cost-effectiveness ratios are lower when we consider transmission, the counseling intervention appears cost effective when using common benchmarks regardless of whether transmission is considered.

We based our estimates of cost and effectiveness on one type of intervention for improving adherence. Numerous other interventions to improve adherence have been studied (e.g., (129, 134, 135)). Additionally, interventions that treat depression and alcohol abuse may improve adherence (136, 137). Evaluations of the costs and benefits of such programs that fail to include HIV transmission may significantly underestimate their cost effectiveness.

Our analysis suggests that modest gains can be expected from counseling interventions that improve adherence to HAART. The gains are modest because some of the benefits offset each other. For instance, individuals who receive the counseling intervention may live longer. They will spend more time in a state with reduced viral load, but the increased length of life leads to increased opportunities for infection transmission. As another example, the intervention prevents a small number of infections, thus reducing HIV treatment costs, but

this reduction is offset by the increased survival and time in treatment among those who receive the intervention.

Our analysis suggests that improved adherence would lead to a very small increase in the proportion of resistant HIV strains after 20 years. The magnitude of the increase may depend on the adherence level of those receiving the counseling. Counseling interventions targeted to individuals expected to have only intermediate adherence may not produce this effect. Either with or without the counseling intervention we predict that approximately 58% of HIV infections would contain a resistant strain of HIV after 20 years. This compares with other models which suggest that the proportion resistant could be as high as 40% after 10 years (20); 60% after 10 years (138); or 100% after 30 years (139). This motivates continued drug development as well as research on drug dosing strategies that may reduce the rates at which resistant strains emerge.

In contrast to some existing research, our analysis suggests that improved adherence would lead only to a small reduction in HIV prevalence after 20 years. One model suggests reductions in prevalence of up to 10% after 30 years (139); another suggests that viral eradication may be possible if risky activity decreases (20). However, those analyses consider the impact of changing from limited to widespread use of HAART, whereas we considered the impact of changing adherence in a population of MSM who would have high access to HAART as part of usual HIV care.

Our model was restricted to MSM, a group that typically has higher adherence to HAART than other at-risk populations. Other populations would likely benefit from improved adherence to HAART. Further analysis is needed to evaluate the cost effectiveness of adherence interventions targeted to groups other than MSM.

Our analysis has several limitations. We assumed random mixing in the population. To the extent that individuals mix non-randomly, our analyses may overstate the benefits of improved adherence on HIV transmission (although, as we showed, counseling to improve adherence is cost effective even if there is no transmission benefit). We assumed that counseling is given to all individuals beginning a HAART regimen. Interventions to improve adherence may be most effective if targeted to those most likely to have low adherence. However, identifying such individuals may be difficult. While adherence interventions may become less important as new regimens are introduced that are easier to follow (including once-daily drug dosing), our model indicates that even at relatively high baseline levels of adherence, counseling to improve adherence remains cost effective. We modeled resistance categories, rather than focusing on single antiretrovirals or classes of drugs, recognizing that resistance-associated mutations frequently confer cross-resistance to other drugs in the same class, especially as mutations accumulate. With the development of new classes of drugs, individuals may have more treatment options than we modeled. However, effective interventions to support sustained adherence will still be needed. Existing research on adherence interventions shows mixed support for the hypothesis that adherence interventions improve adherence.

Our analyses show that counseling efforts to improve adherence to HAART among MSM are likely to be cost effective. Such counseling provides only modest benefit as a tool for HIV prevention, but can provide significant benefit for individual patients at an affordable cost.

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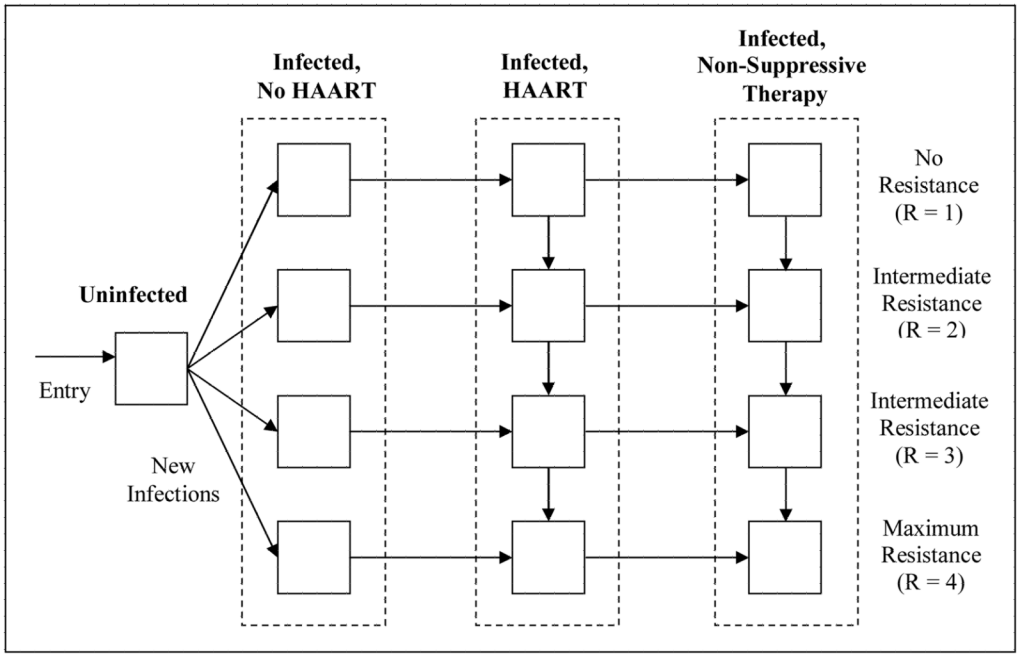

Figure 1a. Overview of compartmental model (R denotes resistance level)

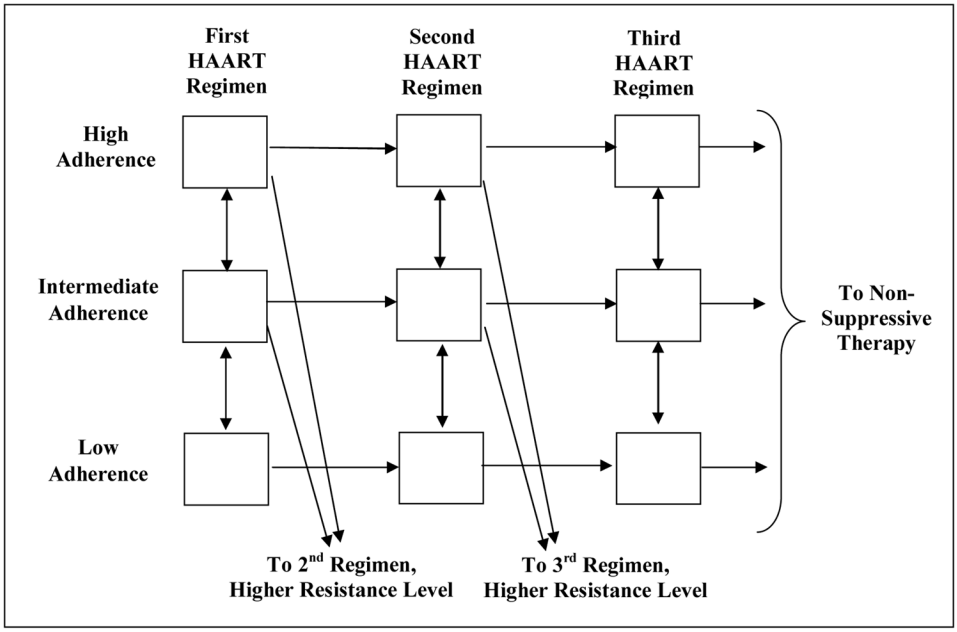

Figure 1b. Disease progression on HAART

Figure 1. Schematic of model

The model is divided into four sub-models: Uninfected; Infected, No HAART; Infected, HAART; and Infected, Non-suppressive Therapy (Figure 1a). Among infected individuals we considered four resistance levels. Infected individuals not receiving HAART are divided into three health states: asymptomatic and unaware of HIV status, asymptomatic and aware of HIV status, and symptomatic. Individuals receiving HAART (Figure 1b) are divided into

three adherence levels high, intermediate, and low and six treatment states first, second, and third HAART regimens, and viral rebound states after each regimen (Figure 1b).

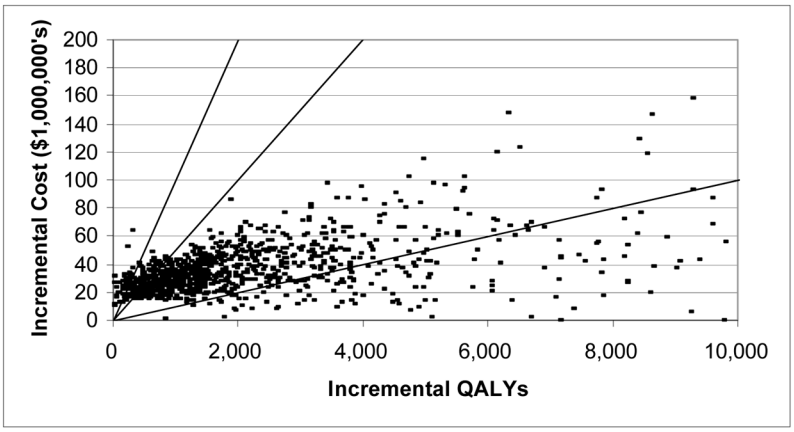

Figure 2a. Incremental costs and QALYS gained for 1000 instances

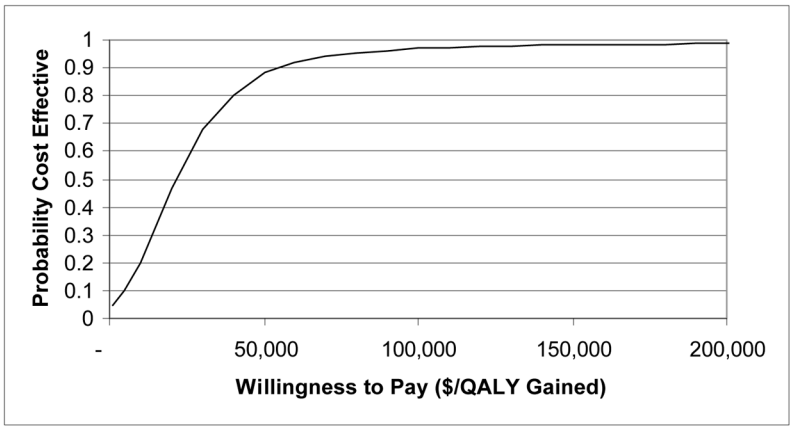

Figure 2b. Cost-effectiveness acceptability curve

Figure 2. Results of stochastic sensitivity analysis for a moderate-prevalence population*

* We modeled all rates and probabilities as beta distributions, all costs as normal distributions, and all other parameters as uniform distributions. For the uniform random variables, we used the upper and lower limits shown in Table 1. For the beta and normal variables, we assumed that the width of each range in Table 1 was equal to four times the standard deviation of the distribution. All failure and toxicity rates were varied within ± 20% of their base case values. Figure 2a shows the results of 1000 simulations. The x-axis shows incremental QALYs gained for each simulation instance and the y-axis shows the associated incremental cost. The three diagonal lines show thresholds of $10,000 per QALY gained (lower line), $50,000 per QALY gained (middle line), and $100,000 per QALY gained (upper line). Figure 2b shows the resulting cost-effectiveness acceptability curve.

Table 1

Parameter Estimates and Data Sources

Parameter	Base Value [Range]*	Source
Demographic factors		
Annual population growth rate	4% [3–5%]	Derived§
Annual maturation rate¶	2% [0–4%]	Calculated
Annual death rates		
Uninfected individuals£	0.35% [.0–.5%]	(140)
Incremental mortality, asymptomatic HIV infection	0% [0–1%]	(141, 142)
Incremental mortality, AIDS	47% [35%–55%]	(130)
Baseline HIV prevalence	10%, 20%	(24, 143)
Baseline HIV incidence	1.6%, 3.2% [1.0%–2.1%]	(24)
Initial fraction of individuals with a resistant HIV strain¤	13% [0–25%]	(28–30)
Annual fraction of individuals with unknown HIV status who are screened each year	75% [25%–99%]	(69–72)
HIV transmission		
Number of new sexual partners per year	3 [1–5]†	(45, 46)
Activity multiplier if aware of HIV infection	1 [.5, 2]	(144–146)
Condom usage rate	.7 [.5–.9]	(35–37, 39–47, 147)
Condom effectiveness in preventing transmission	87% [70%–99%]	(34)
Transmission probability from a partner with#		
No AIDS, no viral suppression or viral load rebound	6.6% [1.44%–7.35%]	(49–51, 53–56, 59, 60, 62, 63)
No AIDS, viral suppression due to HAART	1.4% [0%–3.0%]‡	(49–63)
AIDS	14.7% [5%–20%]	(49–51, 53–56, 59, 60, 62, 63)
Proportion of patients on first HAART regimen who have not experienced viral load suppression	.10 [0–.14]	(48)
HIV progression (years)		
Average time in Infected, No HAART sub-model	7.3 [5.5–10]	(48)
Average time from AIDS to death in non-suppressive therapy sub-model	2.1Ψ	
Average time from infection to death	24	Calculated

Parameter	Base Value [Range]*	Source
Adherence to HAART**		
Average level of adherence		
High-adherence group	.95	Estimated based on (125, 148, 149)
Intermediate-adherence group	.80	“
Low-adherence group	.45	“
Fraction of individuals who are initially in		
High-adherence group	.62 [0–.75]	(126, 127)
Intermediate-adherence group	.19 [0–.38]††	Assumed
Low-adherence group	.19 §§	“
Annual rate of switching		
From high- to intermediate-adherence group	.331 [.148–.5]¶¶	(129)
Between all other groups	.01 [0–.10]	Assumed
Effect of counseling intervention		
Fraction of individuals who are initially in:		
High-adherence group	.697 [.50–.75]¥¥	Estimated based on (126, 127)
Intermediate-adherence group	.1515¤¤	“
Low-adherence group	.1515¤¤	“
Annual rate of switching from high- to intermediate-adherence group	.148 [0–0.331]	(129)
Quality-of-life multipliers		
Uninfected	1.00	Assumed
Asymptomatic, untreated	0.87 [.79–.95]	(150–153)
Symptomatic, untreated	0.79 [.70–.87]	(150–153)
HIV, treated	0.83 [.79–.87]	(150–153)
AIDS	0.73 [.50–.79]	(150–153)
Costs ($)		
Annual non-HIV healthcare costs, all individuals##	1,620 [1,200–1,750]	(140)
Ongoing annual HIV treatment costs		
Pre-HAART, Asymptomatic	1,976 [1,580–2,371]	(154)

Parameter	Base Value [Range]*	Source
Pre-HAART, Symptomatic	14,944 [11,955–17,938]	(154)
HAART, Asymptomatic	14,249 [11,399–17,099]	(154)
HAART, Symptomatic	14,944 [11,955–17,938]	(154)
Non-suppressive therapy, CD4 >350	7,104 [5,683–8,525]	(154)
Non-suppressive therapy, CD4 200–350	12,353 [9,882–14,824]	(154)
Non-suppressive therapy, AIDS	31,303 [25,042–37,567]	(154)
Viral load monitoring§§	456 [228–684]	(155)
One-time counseling and testing costs		
HIV counseling and testing, positive test	131.82 [105–158]	(156)
HIV counseling and testing, negative test	42.41 [34–51]	(156)
Viral load test following treatment failure	114 [220–660]	(155)
Resistance testing	541 [433–649]	(157)
Enhanced counseling to improve adherence	21.73 [21.73–200]	(131, 132) (See text)
Enhanced counseling provided with each viral load test	21.73 [21.73–200]	(131, 132) (See text)
Monthly phone-in cost per patient for counseling intervention	5.42 [0–100]	Estimated$^{\Psi\Psi}$
Discount factor for QALYs and costs	3%	(27)

*This column shows the base value assumed for each parameter, and the range of values considered in sensitivity analysis. When two base values are shown, they correspond to the moderate- and high-prevalence populations, respectively. Sensitivity analysis was performed for the moderate-prevalence population and ranges thus correspond to estimates for the moderate-prevalence population.

§ Derived to ensure approximately 1% growth per year in the MSM population.

¶Maturation into and out of population. Individuals enter the population by turning 18, and leave the population through death and maturation. All individuals entering the population begin in the Uninfected state and progress through the remaining model compartments according to disease progression, treatment, and adherence. Assuming an equal age distribution among individuals age 18–65, approximately 1/(65–18) = 1/47 ~ 2.0% age out of the population every year. The maturation rate was set to zero for the scenarios that did not incorporate HIV transmission.

£Average mortality rate among 18–65 year old men.

¤We assumed that initially 13% of all HIV-infected individuals were infected with a resistant strain of HIV (28). We derived the distribution of individuals among resistance categories by projecting forward with a model that initially has no resistant HIV until the prevalence of resistant strains was 13%. In sensitivity analysis we considered higher and lower prevalence of individuals with resistant strains (29, 30).

†Wide ranges for annual number of sexual partners have been reported in studies of MSM (34–47). We selected an intermediate value.

#A wide range of estimates of the probability of HIV transmission per unprotected sexual partnership have appeared (49–63) We assumed that the probability of sexual transmission was 14.7% per sexual partnership when the infected partner had AIDS (59) and that it would be reduced to 6.6% (a factor of 0.45) for infected individuals without AIDS whose viral load was not suppressed (64). Several studies

have observed reduced risk sexual HIV transmission risk associated with reduced viral load (52, 53, 57, 58, 61). Studies of vertical HIV transmission estimate 25.5% chance of transmission when no antiretroviral treatment is received during pregnancy (65); less than 2.5% among those mothers whose viral load was less than 1730 (66); and 0% among mothers whose viral load was less than 1000 (67). We used a formula given elsewhere (48) to estimate the ratio of the probability of transmission when viral load is suppressed to the probability of transmission when viral load is not suppressed as being 0.21. When switching to subsequent regimens the transmission rate rises slightly when the individual is in a viral load rebound state. We assumed that the average transmission probability among individuals on their first HAART regimen would be slightly higher, reflecting the delay between HAART initiation and viral load suppression.

‡We estimated that the chance of transmission to an uninfected partner was 1.4% if the individual is on his first HAART regimen, and 1.0% if the individual is on his second or third HAART regimen; the chance of transmission is likely to be higher during the first HAART regimen than during later regimens due to the delay between HAART initiation and viral load suppression.

ΨThis is the inverse of the incremental mortality associated with AIDS and was not varied separately.

**All estimates related to adherence to HAART were derived so that average adherence over the entire population and the rate of switching from high adherence to a lower adherence state closely approximated estimates in existing studies (125, 148, 149).

††Varied as the proportion of those who did not enter the high-adherence state who entered the intermediate-adherence state, and assumed to be 50% in the base case.

§§This value automatically varies as the above two values vary.

¶¶The value ρ=.331 corresponds to $e^{-.331}$ = 71.8% of individuals who initially enter the high-adherence state moving to the intermediate-adherence state per year. Thus, 28.2% of those who initially are non-adherent for 0–3 days per month become non-adherent for 6 days per month after one year.

¥¥In stochastic sensitivity analysis, the number entering the high-adherence state following the intervention was fixed at the maximum of this number and the pre-intervention proportion.

¤¤In stochastic sensitivity analysis, when the fraction of individuals in the high-adherence group changed, the distribution of the remaining individuals between the intermediate- and low-adherence groups was assumed to be the same as in the base case.

##Average annual healthcare expenditure among 18–65 year old men.

Table 2

Chance of Viral Load Suppression and HAART Regimen Failure Within Two Years for Individuals on HAART

Fraction of individuals on each HAART regimen and in each resistance level who experience initial viral load suppression*					
	Average	**R = 1†**	**R = 2**	**R = 3**	**R = 4**
High or Intermediate Adherence					
First regimen	0.80	0.90	0.80	0.55	0.45
Second regimen	0.65	0.79	0.71	0.48	0.40
Third regimen	0.30	0.46	0.41	0.28	0.23
Low Adherence					
All regimens	0.18	0.18	0.18	0.18	0.18

Fraction of individuals who remain on a HAART regimen two years after starting§				
	R = 1	**R = 2**	**R = 3**	**R = 4**
High Adherence				
First regimen	0.54	0.48	0.33	0.27
Second regimen	0.48	0.42	0.29	0.24
Third regimen	0.27	0.24	0.17	0.14
Intermediate Adherence				
First regimen	0.47	0.42	0.29	0.24
Second regimen	0.42	0.37	0.25	0.21
Third regimen	0.24	0.21	0.15	0.12
Low Adherence				
All regimens	0.09	0.09	0.09	0.09

* Let α_{ij} denote the fraction of individuals in HAART regimen i and resistance level j who experience initial viral load suppression. We estimated the average values of α_{ij} for the first, second, and third regimens as 80%, 65% and 30%, respectively (48). The values of α_{11}, α_{12}, α_{13} and α_{14} were estimated elsewhere (48). We estimated all otherα_{ij} by assuming that the ratio $\alpha_{i,j+1}:\alpha_{i,j}$ was the same for i = 2 and i = 3 as for i = 1.

† R denotes resistance level. R = 1 is the lowest resistance level and R = 4 is the highest resistance level (see text).

§ Among those who achieve viral load suppression, let p_1 be the proportion who experience a viral load rebound within two years of initiating HAART, and let p_2 be the proportion of individuals who discontinue their HAART regimen within two years due to a toxicity. We assumed that p_1 would be different for the high- and intermediate-adherence groups, consistent with numerous studies that have shown a relationship between adherence and viral load (22, 125, 128, 149, 158–162). The fraction of individuals who remain on a HAART regimen is calculated as $\alpha_{ij}\times(1-p_1-p_2)$, where p_1 = .15 for high-adherence individuals, p_1 = .225 for intermediate- and low-adherence individuals, and p_2 = .25 for all groups. To implement the compartmental model, we estimated continuous rates of failure and toxicity based on α_{ij}, p_1, and p_2.

Table 3

Base Case Results

	Moderate-Prevalence Population			High-Prevalence Population		
	Pre-Intervention	**Post-Intervention**	**Incremental**	**Pre-Intervention**	**Post-Intervention**	**Incremental**
Health Outcomes						
New infections	11,162	10,854	−309	18,930	18,432	−498
HIV infections after 20 years						
Number resistant	6,106	6,039	−67	10,859	10,773	−86
Number not resistant	4,473	4,408	−66	7,707	7,616	−91
Total	10,580	10,447	−133	18,566	18,389	−177
HIV prevalence after 20 years	8.0%	7.9%	−0.1%	14.8%	14.6%	−0.2%
Proportion resistant						
All HIV cases	57.7%	57.8%	0.1%	58.5%	58.6%	0.1%
New HIV cases	57.2%	57.6%	0.4%	58.2%	58.6%	0.4%
QALYs experienced						
In 20 years	1,692,000	1,692,000	566	1,624,000	1,625,000	1,045
After 20 years	1,531,000	1,534,000	3,400	1,395,000	1,401,000	5,875
Total	3,223,000	3,227,000	3,967	3,019,000	3,026,000	6,920
Costs ($1,000)						
Intervention	-	15,461	15,461	-	29,714	29,714
Total	10,629,000	10,659,000	29,320	12,345,000	12,405,000	60,077
Cost per QALY gained ($)			7,392			8,682

Table 4

Sensitivity Analysis on Cost and Effectiveness of the Enhanced Counseling Program in a Moderate-Prevalence Population: Cost per QALY Gained ($)*

Proportion Initially in High-Adherence† (Post-Intervention)	Annual Rate of Switching from High to Intermediate Adherence (Post-Intervention)	Proportion of Individuals Not in High-Adherence State Who Are in Intermediate-Adherence State§								
		25%			50%			100%		
		Cost per Counseling Session			Cost per Counseling Session			Cost per Counseling Session		
		$21.73	$50	$100	$21.73	$50	$100	$21.73	$50	$100
62.0% (OR = 1.00)	0.083	13,100	16,300	22,000	13,100	16,300	21,900	13,000	16,200	21,900
	0.148	15,900	21,400	31.100	15,900	21,400	31,100	15,800	21,400	31,100
	0.248	29,800	46,000	74,500	29,800	46,000	74,700	29,900	46,100	74,900
	0.331	No Benefit	No Benefit	No Benefit	No Benefit	No Benefit	No Benefit	No Benefit	No Benefit	No Benefit
66.1% (OR = 1.20)	0.083	8,600	10,900	14,900	9,800	12,200	16,600	12,700	15,600	20,700
	0.148	8,300	11,600	17,500	10,0200	13,800	20,400	15,000	19,900	28,500
	0.248	7,900	13,700	24,000	11,200	18,300	31,000	25,100	37,800	60,100
	0.331	7,400	16,800	33,400	13,400	26,800	50,500	99,200	167,800	289,200
69.7% (OR = 1.41)	0.083	6,400	8,200	11,500	7,900	10,000	13,700	12,400	15,100	19,900
	0.148	5,300	7,900	12,300	7,400¶	10,400	15,600	14,500	18,900	26,700
	0.248	3,500	7,300	14,100	6,500	11,300	20,000	22,600	33,200	52,000
	0.331	1,800	6,900	15,900	5,400	12,700	25,600	58,000	95,400	161,500
72.3% (OR = 1.63)	0.083	5,100	6,700	9,500	6,800	8,600	11,900	12,200	14,800	19,300
	0.148	3,800	5,800	9,600	5,900	8,400	12,900	14,100	18,200	25,500
	0.248	1,700	4,600	9,800	4,300	8,200	15,000	21,000	30,300	46,900
	0.331	CS	3,600	10,100	2,700	8,000	17,300	44,400	71,300	119,100

†We varied the proportion of individuals initially entering the high-adherence state (post-intervention) from 62% to 72.3% (base case 69.7%); the annual rate of switching from the high-adherence state to the intermediate-adherence state from 0.083 to 0.331 (base case .148); the proportion of individuals initially not entering the high-adherence state who would enter the intermediate-adherence state from 25% to 100% (base case 50%); and the cost of each counseling session from $21.73–$100 (base case $21.73). All cost-effectiveness ratios are rounded to the nearest $100. OR = Odds Ratio, CS = Cost Saving (more effective and less costly than no program).

ξξBased on viral load monitoring every 3 months.

ψψWe assumed that the phone-in support line would need to provide adequate resources for each patient to call once every two months for 30 minutes per call, leading to a cost of $5.42 per patient per month (assuming an hourly wage rate of $21.68 for the phone counselor).

[†]This column shows the proportion initially in high adherence and the corresponding odds ratio comparing post-intervention and pre-intervention proportions in high-adherence.

[§]This number refers to the proportion of individuals with intermediate adherence among those whose adherence is not high, following the intervention. For example, if this proportion is 25% and the proportion in the high-adherence group is 70%, then the proportions of the population with intermediate and low adherence are 7.5% and 22.5%, respectively. In the absence of the intervention we assumed that this proportion would be 50%, and in the base case we assumed that the intervention would not change this proportion.

[¶]Base case.

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