Expanding access to HAART: a cost-effective approach for treating and preventing HIV

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Objective: HIV continues to present a substantial global health burden. Given the high direct medical costs associated with the disease, prevention of new transmission is an important element in limiting economic burden. In addition to providing therapeutic benefit, treatment with HAART has potential to prevent transmission of HIV. The objective in this study was to perform an economic evaluation of the incremental net benefit associated with an intervention to expand treatment with HAART in British Columbia, Canada.

Design: A mathematical model describing transmission of HIV, integrated with a microsimulation model describing the clinical and economic course of HIV.

Methods: The primary outcome was the incremental net benefit of expanding treatment with HAART from 50 to 75% of clinically eligible individuals in British Columbia, assuming a willingness-to-pay threshold of US$ 50 000 per quality-adjusted life year. Direct medical costs included were antiretroviral and nonantiretroviral medications, hospitalizations, physician visits, and laboratory tests. The mathematical and microsimulation models were based on patient characteristics observed in British Columbia. Longitudinal data described health services utilization, clinical progression, and survival for all individuals receiving treatment for HIV in British Columbia.

Results: Over 30 years, the HAART expansion scenario was associated with a net benefit of US$ 900 million (95% confidence interval US$ 493 million to 1.45 billion).

Conclusion: Increasing the HAART treatment rate from 50 to 75% of clinically eligible individuals in British Columbia appears to be a cost-effective strategy based on this model. These cost-effectiveness results are consistent with public health objectives: all individuals who are eligible for an established life-saving treatment should receive it.

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Introduction

HIV presents a major burden to healthcare systems throughout the world, including British Columbia, Canada. At the end of 2005, it was estimated that 58 000 Canadians were living with HIV, a 16% increase since 2002 [1]. Of these, an estimated 13 000 (22.4%) are estimated to be in British Columbia, although only 13% of Canada's population resides in British Columbia [2]. Whereas British Columbia is not home to a generalized

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epidemic, particular demographic groups have experienced concentrated epidemics of similar magnitude to sub-Saharan Africa and other developing regions [3,4]. Within British Columbia, the subpopulations most affected by HIV include some of the most marginalized segments of society [5–7]. Following HIV infection, these marginalized subgroups are least likely to receive optimal treatment for their disease [8]. Although treatment with antiretroviral medications is successful in reducing morbidity and mortality [9], it does not eradicate the infection within infected individuals [10], making prevention of new infections a priority in curbing epidemic growth.

It has been suggested that increasing coverage with HAART among persons infected with HIV with medical indication for HAART may help to prevent new infections [11]. The mechanism is through a reduction in HIV-1 viral load among treated individuals [12], which reduces the likelihood of HIV transmission to uninfected persons [13,14]. A mathematical model describing transmission of HIV in sub-Saharan Africa has been used to show that universal screening coupled with immediate HAART for those testing positive could result in dramatic decreases in HIV incidence and long-term treatment costs in this setting [15].

Given the lifetime cost of treating individuals infected with HIV [16], an effective prevention strategy may be a cost-effective measure [11]. Simplified costing analyses, which included only the costs of HIV testing and HAART have supported this empirically [15]. However, there are additional expenses associated with increased use of HAART that must be accounted for. These include the provision of medical services to individuals infected with HIV who are now living longer due to the increase in life expectancy conferred by HAART, and thus requiring medical care for an extended period [17]. A formal economic evaluation is required to fully quantify the cost implications of a strategy to increase use of HAART.

In British Columbia, Canada, the HIV epidemic can be characterized as being mature and relatively stable, with comparatively consistent annual incidence of new positive tests over the past 10 years [18]. Using the proposed definition of a concentrated epidemic to be one in which transmission is primarily restricted to particular HIV-vulnerable groups [19], British Columbia can be classified as having a concentrated epidemic with the majority of infections occurring within the subpopulations of men who have sex with men, sex trade workers, and injection drug users [1]. Medical costs in British Columbia, including inpatient, outpatient, and HAART costs, are covered centrally by a government payer. The objective of this study was to perform a comprehensive economic evaluation of a program to increase the uptake of HAART in British Columbia. A payer perspective was taken, as only direct medical costs were considered.

Methods

The model utilized in this study was designed as an integration of a microsimulation model of the clinical and economic course of HIV with a series of difference equations describing HIV transmission in discrete time steps. The microsimulation is described in the Appendix, http://links.lww.com/QAD/A51, and summarized in Table 1. All processes were modeled using statistical analyses of individual-level data for all individuals in British Columbia receiving treatment with HAART [20]. In particular, CD4 and viral load trajectories following the initiation of HAART were described by nonlinear statistical models [21], and direct medical costs were described by random effects models that incorporated both utilization and level of use of particular health services [22]. The microsimulation described individual disease trajectories to account for random variability between individuals. Based on British Columbia data, it was assumed that 81.6% of individuals were men, 72.3% were injection drug users, and average medication adherence (defined as the proportion of months receiving HAART) was 79.1%.

Individuals who did not access treatment were assumed to experience CD4 cell count trajectories associated with the natural untreated history of HIV [23]. Following primary infection, untreated viral load trajectories were characterized by a 'set-point' that was randomly generated

Table 1. Statistical methods used to describe processes included in microsimulation.

Process	Statistical methods used
CD4 cell count trajectories	Nonlinear statistical model
Plasma viral load trajectories	Nonlinear statistical model
Medication resistance[a]	Weibull time-to-event model with frailty terms due to correlation between resistance to different classes of medication
Accumulation of direct medical costs	Series of two-stage random effects models
HIV-related mortality following HAART initiation	Cox proportional hazards model incorporating CD4 cell count as a time-dependent covariate

All models fit using individual-level data from British Columbia.
[a]Defined as developing a first resistance mutation to each of four categories of antiretrovirals: protease inhibitors, nonnucleoside reverse transcriptase inhibitors, lamivudine, and nucleoside reverse transcriptase inhibitors (excluding lamivudine).

with a mean of 4 log-copies [24] and an assumed increase of 0.1 log-copies per year in the absence of treatment. HIV-related mortality in the untreated group was based on data collected prior to the introduction of HAART [25].

The disease transmission model was based on a published model [26], updated to be integrated with the microsimulation. We considered a population of susceptible individuals at high risk for acquiring HIV infection and a population of individuals infected with HIV at varying disease stages. The baseline infected population was assumed to consist of 8000 individuals, 50% of whom were assumed to have accessed treatment. The population size was chosen through a process of empirical calibration, as it resulted in model-predicted numbers of new infections and new treatment initiations that were consistent with observed data [26]. The structure of the transmission model is shown in Appendix Fig. A1, http://links.lww.com/QAD/A52, and further technical details are given in Appendix, http://links.lww.com/QAD/A51.

Newly infected individuals were randomly assigned to one of two categories: the first category of individuals would remain untreated throughout the course of their disease, whereas the second category would access treatment with HAART. Individuals assigned to the second category were then randomly assigned a point in their disease history (between zero and 10 years following infection) at which they would present for routine clinical monitoring. These individuals were assumed to initiate treatment with HAART once they had presented for monitoring and their CD4 cell count first dropped below 350 cells/μl. This allowed us to account for the fact that some individuals may not present for treatment until their CD4 cell count has dropped well below the threshold for clinical eligibility.

A 1000-iteration probabilistic sensitivity analysis [27] was performed to assess the impact of uncertainty in microsimulation and transmission model parameters on cost-effectiveness results. Nested within each iteration of the sensitivity analysis, individual life histories were generated to account for heterogeneity in clinical and economic processes. Parameter values used in the transmission model and associated distributions for the probabilistic sensitivity analysis are given in Appendix Table A1, http://links.lww.com/QAD/A53.

Costs incurred by infected individuals included costs associated with physician visits, hospitalizations, HAART, non-HAART medications, laboratory tests, and emergency room visits. These costs were generated randomly based on statistical models, adjusted for treatment status, medication adherence, and CD4 cell count [22]. The statistical models were fit using comprehensive health services data for a population-based cohort of individuals in British Columbia. Predicted direct medical costs varied by current CD4 cell count and ranged between approximately US$ 300 and 2500 per month for non-HAART costs. In the base-case analysis, HAART costs were based on actual costs incurred by infected individuals in British Columbia, including individuals with sub-optimal adherence and were approximately US$ 900 per month for protease inhibitor-based regimens and US$ 1100 per month for nonnucleoside reverse transcriptase inhibitor regimens. In a sensitivity analysis, we assumed 100% adherence to an arbitrary regimen of ritonavir-boosted atazanavir and tenofovir with lamivudine (US$ 1438 per month), which has been a commonly used first-line regimen in British Columbia.

Costs incurred by susceptible individuals were assumed to be US$ 4133 per year, the average Canadian healthcare cost reported for 2005 [28]. To account for health-related quality of life, life years were converted to quality-adjusted life years by applying utilities to time spent in various health states. The utility associated with a health state is a number between zero and one that is used to weight time spent in the state, with one representing perfect health and zero representing death [29]. Health state utilities for infected individuals were assumed to follow published estimates [30]. For the susceptible state, a utility of 0.87 was assumed, as this was the highest observed utility for asymptomatic HIV patients. All costs were converted to 2005 Canadian dollars, using healthcare-specific cost inflators [31].

We considered two scenarios regarding treatment with HAART. In both scenarios, it was assumed that the infected population at baseline was based on a historical treatment rate of 50%. In the first scenario, it was assumed that this treatment rate would remain at 50% for the entire simulated period. In the second scenario, it was assumed that treatment uptake would immediately increase to 75% and that 75% of newly infected individuals would continue to seek treatment throughout the simulated period.

The primary outcome compared between the two scenarios was incremental cost-effectiveness, assessed using the incremental net benefit approach [32] based on a willingness-to-pay threshold of US$ 50 000 per quality-adjusted life year [33]. The net benefit is a synthetic economic quantity, simultaneously incorporating costs, survival, and quality of life. For a given willingness-to-pay threshold, a positive incremental net benefit indicates that the proposed intervention is cost-effective. Further mathematical details are given in Appendix, http://links.lww.com/QAD/A51. Net benefit was considered at both the overall population level, in which costs and quality-adjusted life years were aggregated across all infected and susceptible individuals over time, and the patient-centered level, in which the only costs and quality-adjusted life years considered were

those accrued by the subgroup of individuals who were infected at baseline. Patient-centered net benefit reflects the direct health benefits due to expanding HAART use, whereas overall population net benefit further incorporates benefits due to reducing new infections. Uncertainty in the model was expressed using empirical 95% confidence bounds for the incremental net benefit [34] and a cost-effectiveness acceptability curve [35].

Results

Figure 1 displays the cumulative incremental net benefit over time for the HAART expansion scenario relative to a continuing coverage rate of 50%. The incremental net benefit is based on a willingness-to-pay threshold of US$ 50 000 per quality-adjusted life year; an incremental net benefit greater than zero indicates that the intervention is considered cost-effective at this threshold [32]. The HAART expansion scenario was estimated to reach cost-effectiveness – indicated by a positive incremental net benefit – within 4 years. Prior to the 4-year point, the immediate cost outlay associated with treatment uptake was not yet offset by health benefits or reduced infections. The cumulative net benefit increased steadily over time, reaching approximately US$ 900 million [95% confidence interval (CI) US$ 493 million to 1.45 billion) after 30 years. As an alternative to the net benefit approach, the results of the probabilistic sensitivity analysis are also shown in a cost-effectiveness acceptability curve in Fig. 2.

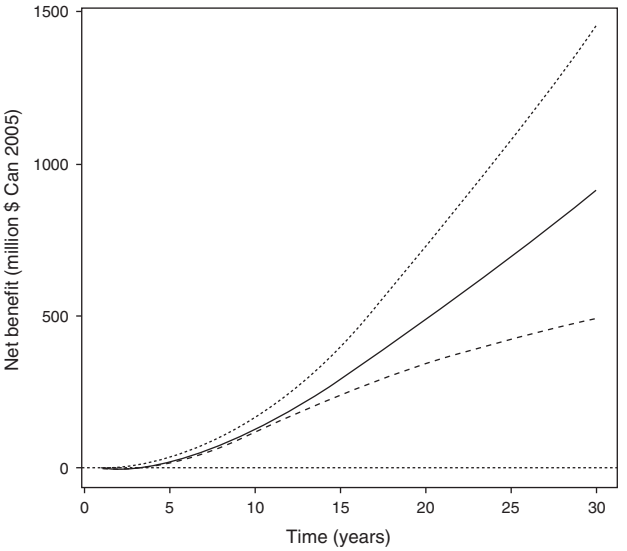

Fig. 1. Incremental net benefit of immediately increasing HAART from 50 to 75% and measuring costs and benefits over a simulated period of 30 years, based on a willingness-to-pay thresholds of US$ 50 000 per quality-adjusted life year. Solid line represents mean of empirical distribution of probabilistic sensitivity analysis results, whereas dashed lines represent a 95% confidence interval.

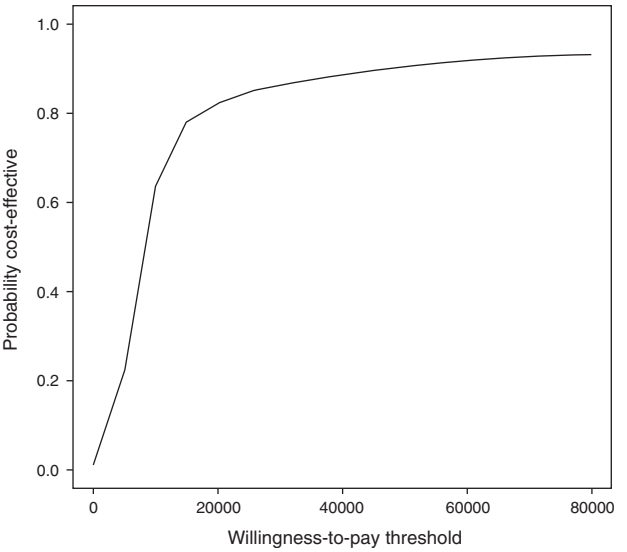

Fig. 2. Cost-effectiveness acceptability curve. Cost-effectiveness acceptability curve associated with immediately increasing HAART from 50 to 75% and measuring costs and benefits over a simulated period of 30 years shows the proportion of probabilistic sensitivity analysis iterations that were cost-effective for willingness-to-pay thresholds between US$ 0 and 80 000.

For a willingness-to-pay threshold of US$ 20 000, over 80% of iterations indicated cost-effectiveness of the HAART expansion scenario, whereas over 90% of iterations indicated cost-effectiveness for a willingness-to-pay threshold of US$ 50 000.

When we assumed US$ 1438 for monthly HAART costs, the scale of cumulative net benefit was reduced, reaching a plateau of approximately US$ 760 million over 30 years. However, a similar pattern of cost-effectiveness was observed, with the HAART expansion scenario reaching cost-effectiveness within 7 years and remaining cost-effective throughout the 30-year duration of simulated time.

The overall population and patient-centered incremental net benefits are shown in Fig. 3. For the first 5 years of expanded HAART, it is estimated that overall population net benefit is comprised largely of net benefits accrued by the initial group of individuals infected at baseline. The general trend continues for approximately 10 years, with the overall population net benefits gradually increasing beyond the patient-centered net benefits. After 10 years, there is a widening divergence, with overall population net benefits increasingly explained by averted infections. After 30 years, patient-centered net benefits account for approximately half of overall population net benefits.

Cumulative new infections under each scenario are shown in Fig. 4. During the 30-year period, the HAART

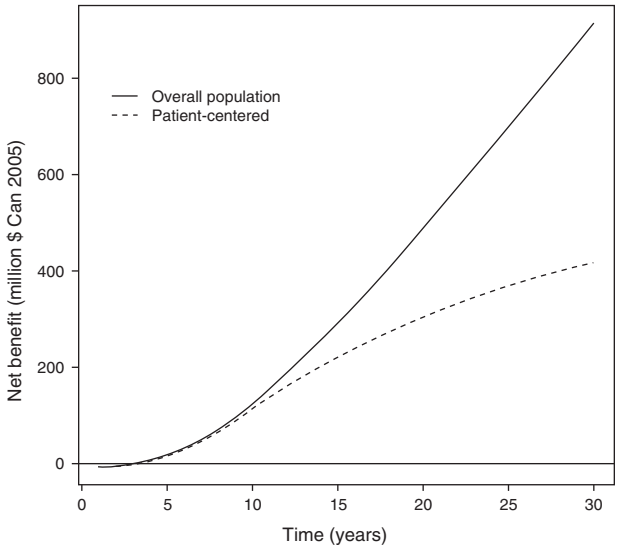

Fig. 3. Overall population and patient-centered incremental net benefit associated with immediately increasing HAART from 50 to 75% and measuring costs and benefits over a simulated period of 30 years, based on a willingness-to-pay threshold of US$ 50 000 per quality-adjusted life year.

expansion scenario was predicted to yield 26% fewer new infections.

Discussion

In this study, we demonstrated the potential cost-effectiveness of expanding the use of HAART – as defined by increasing the proportion of HIV-infected individuals with CD4 cell counts below 350 cells/μl receiving HAART from 50 to 75% – in British Columbia. Increased treatment was found to reduce the incidence of new infections and, despite the up-front acquisition costs associated with an increase in HAART use, the strategy was estimated to become cost-effective within 4 years.

Several other mathematical models have been used to assess the impact of HAART on HIV transmission. Relative to the results presented here, some models have resulted in similar or more dramatic effects on HIV incidence [15,26,36], whereas others have resulted in more conservative estimates [37,38]. All investigators have reported some reduction in the incidence of new infections when treatment rates are increased. Differences across studies are due in part to varying assumptions regarding the impact of HAART on infectivity, although when evaluating infectious disease prevention strategies, the current phase of the particular epidemic being modeled is an important factor [39], so some discordance between studies undertaken in different settings is to be expected. To our knowledge, ours is the first study to incorporate a comprehensive economic evaluation in this context.

The microsimulation component of the model, which described the clinical course and economic implications of HIV disease, was based on high-quality population-based data for British Columbia and is thus expected to be accurate for British Columbia and other areas with similar healthcare systems. Because this component of the model

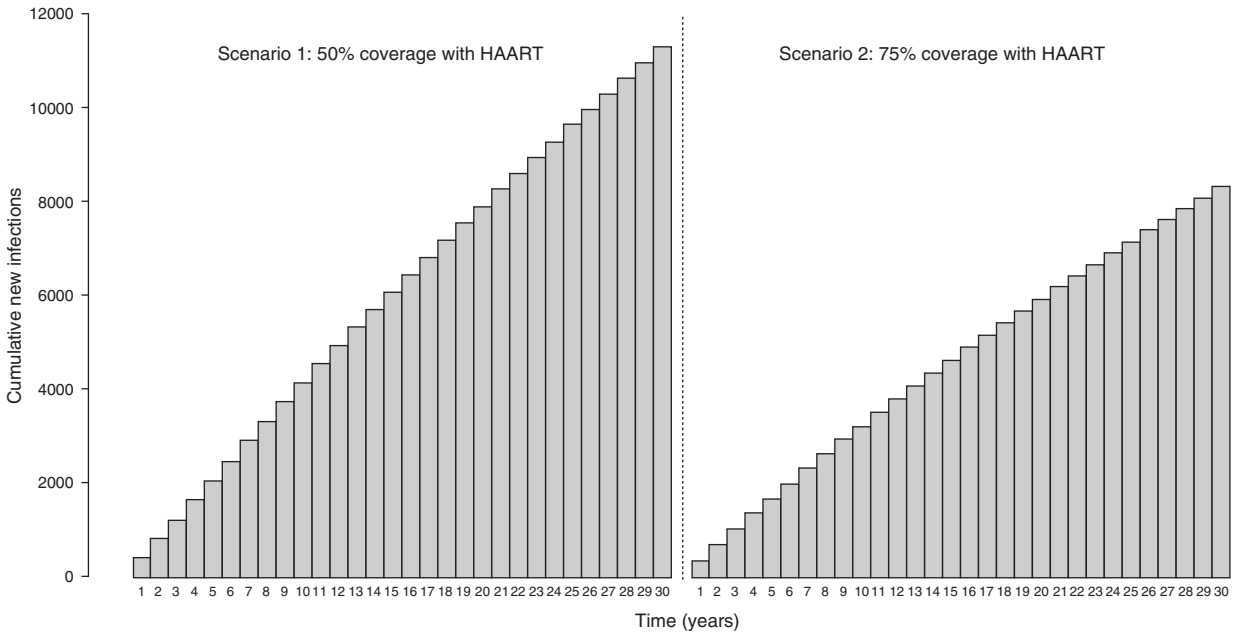

Fig. 4. Estimated cumulative number of new infections over time. Scenario1: increasing uptake of HAART from 50 to 75%. Scenario 2: uptake of HAART consistent at 50% over a simulated period of 30 years.

was based on observational data, it describes actual clinical and virological outcomes observed in practice, rather than idealized outcomes based on the assumption of optimal medication adherence. Comprehensive direct medical costs were available so that costs associated with treating HIV symptoms, HAART toxicity, and background medical issues were included.

The model addressed multiple sources of complexity of HIV disease through the integration of microsimulation and transmission models. Because HIV is an infectious disease, a dynamic modeling method, such as the transmission model used here, is required to quantify the impact of a prevention program. Due to the relatively long clinical course of HIV, it also displays properties of a chronic disease, and lifetime direct medical costs may vary substantially across individuals. Microsimulation methods based on statistical models have been well developed within the health economics literature for describing the costs associated with a chronic disease [40]. Microsimulation methods provide a framework for quantifying the impact of HAART use at the individual level. By combining the two modeling techniques, we were able to exploit the strengths of two complementary methods: one for addressing the infectious nature of HIV transmission and the other for addressing the chronic nature and individual-level variability associated with HIV clinical processes and medical costs.

A limitation of the study was the paucity of data available for assigning parameters to the disease-transmission component of the model. Parameters for which limited empirical data were available were based on a combination of expert opinion and calibration to historical incidence and treatment rates [26]. We allowed parameters to vary across a relatively wide range of plausible values in the probabilistic sensitivity analysis (Appendix Table A1, http://links.lww.com/QAD/A53). The results of this sensitivity analysis were consistent with the base-case analysis regarding cost-effectiveness over time.

When considering a 30-year time horizon, long-term changes in diagnostics, treatment options, clinical indication for treatment initiation, and treatment costs may influence the future cost-effectiveness profile. Although some medication costs may decrease as product patents expire, there is also the possibility for more efficacious and more costly medications to be brought to market. The results reported here do not reflect any such hypothetical changes. Under the assumption that a favorable economic profile would be required for any future guideline changes to be made, it is not expected that they would prevent the proposed intervention of increasing HAART from achieving a positive incremental net benefit within a time frame similar to that reported here.

In order to not overestimate the net benefit associated with the HAART expansion scenario, wherever possible, we made conservative assumptions to make increased uptake of HAART appear less effective. A recent meta-analysis provides data that suggest that the impact of reduced viral load on infectivity may be larger than the figures used here [13], particularly at very low levels of viral load [41]. We chose to use the more conservative figure to be certain that the impact was not overestimated. We also made the conservative choice of 0.87 as the utility value associated with individuals susceptible for HIV infection, equivalent to the highest utility reported for individuals infected with HIV [30]. Choosing the lowest plausible utility value for susceptible individuals biases results against a prevention program. In addition, for all parameters related to primary infection, we assumed values on the upper end of the plausible range. We assumed that the phase would last 60 days, that viral load would remain at 6 log-copies/ml throughout the phase, and that there would be no decrease in risk behavior. Transmission during the primary phase was assumed to be unaffected by the program to increase uptake of HAART.

The incremental net benefit we calculated was based on a payer perspective. Taking a societal perspective and including indirect costs, although outside the scope of this study, would likely yield a higher incremental net benefit associated with HAART expansion. Indirect costs are those borne to society when individuals who would otherwise be able to work cannot due to illness or death. In the United States, the indirect costs associated with HIV have been estimated to be substantially higher than the direct costs [42]. The HAART expansion scenario was associated with improved health among individuals currently infected with HIV as well as reduced transmission of new infections, both of which would reduce the burden of indirect costs and increase the incremental net benefit.

In this study, we described a methodology for evaluating a preventive intervention for an infectious disease with a lengthy clinical course, providing a framework that could potentially be used in other similar applications. On the basis of this methodology, an intervention to increase the HAART treatment rate from 50 to 75% of HIV-infected individuals with CD4 cell count below 350 cells/μl in British Columbia was demonstrated to be a cost-effective strategy. This result was obtained under several conservative assumptions that were chosen to bias results against the intervention. Due to these assumptions, it is plausible that the actual net benefit associated with the intervention is even higher than that reported here. These cost-effectiveness results are consistent with public health objectives: all individuals who are eligible for an established life-saving treatment should receive it.

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