Published in final edited form as:
Health Aff (Millwood). 2014 March ; 33(3): 362–369. doi:10.1377/hlthaff.2013.0830.

Early HIV Treatment In The United States Prevented Nearly 13,500 Infections Per Year

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Abstract

In recent years, guidelines for HIV treatment have recommended initiation of combination antiretroviral therapy (cART) earlier in the course of the disease than was previously the case. These recommendations stem in part from growing evidence that treatment reduces the risk of sexual transmission. We used an epidemiological model of disease transmission and progression to assess HIV prevention through early treatment—that is, initiation of cART when CD4 white blood cell counts are in excess of 350 cells/mm^3.(CD4 cells are involved in the immune system's defense against tumors and infection; the number of CD4 cells in a cubic millimeter of blood is a standard measure of immune response to antiretroviral therapy.) We estimated that the actual timing of treatment initiation in the United States prevented 188,000 HIV cases in the period 1996-2009. "Very early" treatment (at CD4 counts greater than 500 cells/mm^3) accounted for one-fifth of the prevented cases. For all of the prevented cases, the losses in life expectancy that were avoided were worth $128 billion, assuming that a life-year has a value of $150,000. These findings underscore the cost-effectiveness of early HIV treatment.

Recent guidelines for HIV treatment have recommended the use of combination antiretroviral therapy (cART) earlier in the course of the disease than had previously been the case. The 2009 update to the official US guidelines recommended cART initiation for people with CD4 counts of 350-500 cells/mm^3.(1) (CD4 cells are involved in the immune system's defense against tumors and infection; the number of CD4 cells in a cubic millimeter of blood is a standard measure of immune response to antiretroviral therapy.) The latest US guidelines, issued in February, 2013 recommend initiation with CD4 counts in excess of 500 cells/mm^3.(2) In June 2013 the World Health Organization revised its guidelines to recommend cART initiation for patients with CD4 counts of 350-500

cells/mm^3 but stopped short of recommending cART with CD4 counts above 500 cells/mm^3.(3)

These changes in treatment paradigms resulted from increasingly strong evidence that early cART use ameliorates HIV-related morbidity and mortality. For example, a group of collaborative North American cohort studies concluded that people who deferred cART initiation until their CD4 counts fell below 350 cells/mm^3 experienced a 69 percent higher risk of death than people who initiated cART with counts of 350-500 cells/mm^3.(4)

The finding that early cART use provides important clinical benefits to people living with HIV/AIDS has also been demonstrated in a number of other studies.(5-9) Another article in this issue of *Health Affairs* assesses the clinical and economic value to HIV-positive people of early cART use (in accordance with US treatment guidelines).

Another rationale for early treatment is the growing evidence that cART use reduces the risk of sexual transmission of HIV to uninfected people. For example, a multicontinental randomized trial enrolled 1,763 serodiscordant couples in which the HIV-positive partner had a CD4 count of 350-550 cells/mm^3. The researchers found that the risk of transmission was 96 percent lower when couples initiated cART before the CD4 count fell below 250 cells/mm^3 or an AIDS-related illness occurred.(10) Another randomized trial in which the HIV-positive partner had a CD count 250 cells/mm^3 found a 92% reduction in risk among those who initiated cART. These focused on heterosexual transmission(10,11); other research points to a substantial decrease in transmission risk among homosexuals due to cART use.(12)

We analyzed the effects of early cART initiation on HIV incidence in the United States in the period 1996-2009. To do so, we adapted an epidemiological model of HIV transmission and progression and used published data to specify model inputs appropriate to the US context, for example, the number of people living with HIV/AIDS when cART became available.

In related research, Elisa Long and colleagues investigated a “test and treat” strategy—that is, [please provide]. They found that such a strategy could cost-effectively prevent a substantial number of HIV cases in the United States.(13) Neeraj Sood and colleagues and Rochelle Walensky and colleagues modeled the effects of test-and-treat approaches in Los Angeles and Washington, D.C., respectively, and found [please briefly explain their findings].(14,15)

Although these studies offer valuable insights, ours focused squarely on the important issue of when to begin treatment, specifically, whether to initiate cART in patients with CD4 counts of 350-500 cells/mm^3 and in patients with counts above 500 cells/mm^3. As noted above, current US and World Health Organization guidelines disagree about when cART should be initiated. In addition, we quantified the economic value, or benefit in dollar terms, of the losses in life expectancy that were avoided because of the prevented cases of HIV. We were able to contrast the benefits of early cART use to people who were HIV-negative with the benefits to people living with HIV/AIDS.

Study Data And Methods

To assess HIV prevention associated with early cART use, we used a model of HIV transmission and progression to predict incidence based on the timing of cART initiation. We then quantified the losses in life expectancy that were avoided because of the cases that were prevented. Finally, we estimated the value of the life-years that were saved through early treatment.

Disease Model

We adapted to the US setting an epidemiological model from a well-known study of the HIV epidemic in South Africa by Reuben Granich and colleagues.(16) Lisa Eaton and coauthors provide a useful comparison and review of a variety of models of the South African epidemic.(17) We next describe the model of Granich and colleagues and its adaptation to our setting (technical details are provided in the online Appendix).(18)

In the model, HIV-negative individuals can be infected through sexual contact with people living with HIV/AIDS. Once infected, individuals progress in their disease and ultimately die from AIDS (or another cause.) The use of cART slows the rate of disease progression. (16)

The rate of new infections depends on viral load and sexual activity among people living with HIV/AIDS. Viral load and shedding of HIV in semen decrease with cART use,(19-22) and treatment makes individuals less infectious.(10,23) We generalized the Granich model(18) to allow infectivity to depend on disease stage. This change is consistent with evidence that viral load and sexual activity vary with disease stage.(24,25)

In another extension of the model, we allowed for a time trend in infectivity to capture factors such as safer-sex practices, which might be motivated by considerations such as altruism. These factors might have altered incidence rates over the analysis period.

We used the resulting model to analyze HIV incidence in the United States between 1996, when cART was introduced, and 2009, when US guidelines were revised to recommend earlier treatment. Disease stage was defined by CD4 counts, and early treatment was defined by initiation of cART with a CD4 count above 350 cells/mm^3.

Specifically, we compared incidence of HIV based on the actual timing of cART initiation over the study period to what incidence would have been in the absence of any early treatment. We also investigated the effects of “very early” treatment, based on a scenario in which treatment was unavailable for patients with CD4 counts above 500 cells/mm^3. In this scenario, the probability of initiating treatment at CD4 counts above 500 cells/mm^3 was set to zero, and the actual probability was added to the probability of initiating treatment at CD4 counts of 350-500 cells/mm^3.

Published data were used to specify model inputs whenever possible. For example, Mari Kitahata and colleagues documented rates of cART initiation by CD4 count,(4) and Ira Longini and coauthors reported rates of disease progression among HIV-positive members of the US Army in the pre-cART era.(26)

HIV prevalence in 1995 was taken from the HIV/AIDS Annual Surveillance Report of the Centers for Disease Control and Prevention (CDC).(27) The distribution of cases by disease stage was obtained from the HIV Cost and Services Utilization Study.(28) We investigated the robustness of our results by varying model input values using sensitivity analyses.(18)

Where published data were unavailable, we specified model inputs by calibrating predicted incidence of HIV under the baseline specification of the model to published estimates of incidence over the study period.(29,30)

The key assumption in the analysis was that a person treated with cART was 90 percent less infectious than an untreated person early in the course of the disease. This assumption is conservative, provided that the prevention rate is similar for all modes of transmission.(10,11) In the analysis, we allowed the use of cART to "ramp up" over time, in line with the trajectory of HIV prescription fills in the United States.(31)

The model used here was developed for a generalized HIV epidemic, although the United States has experienced multiple focused epidemics instead. For this reason, we considered a wide range of values for the number of people who were susceptible to HIV infection.

Life Expectancy And Its Value

To quantify the losses in life expectancy that were avoided for prevented cases, we compared life expectancy for people with HIV to that for people without HIV. Life expectancy for people living with HIV/AIDS was determined according to the disease model, under the scenario in which there was no early treatment (that is, no cART initiation at CD4 counts above 350 cells/mm^3). For life expectancy without HIV, we used life tables from the CDC for the year 2000.(32) We assumed that, in the absence of early cART use, HIV infection would occur at the average age at infection in 2000, which we calculated from the CDC's *HIV/AIDS Surveillance Report* for that year.(33)

To determine the value of the life-years that were saved through early cART initiation, we relied on the literature on willingness to pay for reductions in mortality risk in the workplace and other settings.(34,35) This literature suggests that a range of $50,000 to $300,000 is plausible (and even arguably somewhat conservative) for the value of a life-year. In valuing life expectancy, we discounted the differences in annual survival probabilities, by HIV status, over the course of individuals' lives at a rate of 3 percent, consistent with the recommendation of the US Public Health Service's Panel on Cost-Effectiveness in Health and Medicine.(36)

Limitations

Our HIV model had a number of limitations. We focused exclusively on sexual transmission, and we assumed that sexual partners were chosen at random. In addition, the quality of life was not analyzed. We address these limitations below.

Study Results

Published estimates of HIV incidence in the United States in the period 1996-2009 total 772,500 cases (Exhibit 1). Based on the actual timing of cART initiation, our model of disease transmission and progression predicted an incidence of 773,200 cases. Both the estimated and the predicted incidence had a brief uptick and then decreased slowly.

If early treatment had not been available in 1996-2009, HIV incidence would have been substantially higher early in the period (Exhibit 2). This is because people in the relatively early stage of HIV would have been more likely to infect their sex partners. Incidence would have decreased dramatically, however, as people with advanced disease gained access to cART. With the passage of time, the gap between incidence with and without early treatment widens, since transmission through cases at the relatively early stage would have compounded.

Without any early treatment, predicted HIV incidence in 1996-2009 would have totaled 962,000 cases. That is nearly 25 percent higher than the predicted incidence based on the actual treatment. Thus, the model suggests that early treatment prevented 188,000 HIV cases over the period, or about 13,500 cases per year.

The gap between incidence treatment at CD4 counts below 500 cells/mm^3 but not above that point and the predicted incidence for the actual treatment is somewhat narrower than the gap between the actual treatment and no early treatment (Exhibit 2). Four-fifths of the 188,000 HIV cases prevented through early treatment resulted from cART initiation at CD4 counts of 350-500 cells/mm^3, and one-fifth from “very early” initiation, at CD4 counts above 500 cells/mm^3.

Prevention through early treatment avoided substantial losses in life expectancy. The model predicted that a person at the mean age of infection (thirty-five years in 2000) could expect to live 32.3 years after HIV infection in a scenario with cART initiation at CD4 counts below 350 cells/mm^3. In contrast, a thirty-five-year-old could expect to live 44.0 years—an additional 11.7 years—by avoiding HIV infection.

The value, or benefit in dollar terms, of a prevented case of HIV is $678,000, assuming that each of the life-years saved (about 4.5 years, after discounting the 11.7 future years of life to their present value, as explained previously) is worth $150,000. Exhibit 3 shows the value of a prevented case assuming that each life-year saved is worth various amounts.

The total value of all prevented cases ranges from $43 billion to $256 billion (Exhibit 4). Using the midrange figure of $150,000 per life-year saved, the total value of early cART treatment as HIV prevention in the period 1996-2009 is $128 billion.

Discussion

The model of HIV disease transmission and progression in this study suggests that early treatment (cART initiation at CD4 counts above 350 cells/mm^3) prevented 188,000 new infections in the United States between 1996 and 2009, or about 13,500 cases per year.

Disease models represent complex phenomena, potentially raising concerns about the validity of these findings. To specify model inputs appropriate to the US context, we used published data whenever possible. Otherwise, we calibrated the model to published estimates of incidence over the study period.

The results were not particularly sensitive to changes in model inputs. It is also noteworthy that we generalized an established model to capture factors—such as safer-sex practices—that might have altered incidence rates over the analysis period. In our calibrated model, the risk of infection associated with unmodeled factors decreased by 4.3 percent per year.

The HIV epidemic in the United States has been concentrated in a number of relatively high-risk populations. Therefore, we considered a range of values for the number of people at risk of HIV infection. We found that the number of infections prevented varied little with the size of the susceptible population. This focus on relatively high-risk individuals helps mitigate concerns about heterogeneity in the sources of disease transmission.

Our model focused on sexual infection, however, and did not distinguish between homosexual and heterosexual contact. As of 2009 injection drug use (without male-to-male sexual contact) accounted for 5 percent of reported HIV cases, and heterosexual contact accounted for another 17 percent—for a total of 22 percent, compared to a 35 percent of reported cases for 1996.(37,38)

Other limitations of the disease model may be more consequential. In particular, sexual partners were assumed to be chosen at random. However, there is evidence that partners are selected based in part on their HIV status.(39) A simulation analysis has suggested that such “serosorting” could reduce HIV prevalence by as much as one-third.(40) Another study found that HIV-negative men who engaged in serosorting were about 10 percent less likely to become infected, compared to those who did not serosort.(41)

Yet the effects of serosorting are not fully understood.(17) Serosorting may taper off after HIV infection,(42) and uncertainty about a partner’s HIV status may even serve to increase the risk of infection.(43,44)

In any event, the infections avoided through early treatment prevented substantial losses in life expectancy. According to the inputs to the disease model, HIV infection reduced longevity by 11.7 years. Assuming that a life-year is worth $150,000 in today’s dollars, the value of each prevented case was $678,000, after discounting future survival probabilities as recommended by the Public Health Service’s Panel on Cost-Effectiveness in Health and Medicine.(36) As a basis of comparison, the value of prevention has been estimated at $69,000 for each case of obesity and $158,000 for each case of smoking (both measured in 2012 dollars).(45)

The value of a life-year has long been of interest, and it remains a matter of some debate.(46,47) Richard Hirth and colleagues analyzed forty-two estimates of the value of life from the literature.(34) They found that studies of risk avoidance behavior yield a median estimate of the value of a life-year of $505,400 in the context of workplace safety and $110,200 in other contexts, such as automobile purchases (both in 2004 dollars). In another

prominent review, Kip Viscusi and Joseph Aldy found that the value of a statistical life ranges from $5 million to $12 million, with a median of $7 million.(35) These numbers are compatible with a range of $150,000-$360,000 for the value of a life-year. Based on this evidence, we considered $50,000 to $300,000 to be a plausible and somewhat conservative range.

For all of the HIV cases prevented through early treatment during the period 1996-2009, the value of avoided life expectancy losses totaled $128 billion. Each prevented case entailed an extra 2.8 person-years of cART use (Jeffrey Eaton and colleagues have estimated a range of 5-20 person-years of therapy per averted infection in South Africa).(48)

Spending on cART was on the order of $5 billion higher as a result of early treatment, given the cost of therapy in 2009.(49) This figure does not include the cost of medical treatment resulting from longer life expectancy. However, early cART treatment has been found to be cost-effective even when lifetime medical costs were accounted for.(50)

Our results have important implications for policy makers and medical practitioners alike. The World Health Organization recently revised its guidelines to recommend cART use at CD4 counts of 350-500 cells/mm^3. Our results are not necessarily generalizable beyond the United States. However, our findings suggest that treatment at CD4 counts above 500 cells/mm^3 merits careful consideration, particularly in light of recent evidence.(4,51) Of course, the preventive benefits of relatively early initiation of treatment must be weighed against the risk of breeding new strains of HIV that are resistant to current treatment regimens.(52)

Whatever the threshold, ensuing that treatment is initiated at the appropriate time is a critical challenge. Another article in this issue of *Health Affairs* considers public health services that might help promote initiation and adherence, including outreach case management, peer navigators, and language services.(53) The authors conclude that such services could be effective in helping the county of Los Angeles meet its goals of increased viral load suppression, decreased HIV incidence, and increased knowledge of HIV status.

Reducing the future incidence of HIV requires access not only to cART, but also to testing for HIV. Long and colleagues analyzed a test-and-treat strategy and concluded that screening low-risk individuals once and high-risk individuals annually would increase the number of HIV cases that could be prevented in the United States by nearly 70 percent, compared to expanding access to treatment alone.(13)

As treatment lengthens the time that people living with HIV/AIDS remain healthy and sexually active, health care practitioners and the public health community must continue and even strengthen their efforts to raise awareness about the risks of sexual activity and methods for avoiding these risks. Although serosorting helps reduce the risk of HIV transmission, condom use remains an essential tool for disease prevention.(17)

Conclusion

Our study underscores the case for the early initiation of HIV treatment. Although we have not addressed the quality of life here, cART use is likely to improve it.(54) Thus, our findings probably understate the economic value of early initiation. Another article in this issue of *Health Affairs*(53) analyzed the benefits of early cART initiation (consistent with recent treatment guidelines) for HIV-infected individuals in the United States. The authors found that the value of early treatment to people living with HIV/AIDS was, if anything, smaller than the value to individuals who were HIV-negative but would otherwise become infected. The benefits of early cART use in terms of prevention significantly enhance the cost-effectiveness of early HIV treatment.

Acknowledgments

This research was supported by the National Institutes of Health through its support of the Economics of Treating Viral STIs (Grant No. 5R01HD054877) and Bristol-Myers Squibb. The authors are grateful to Ron Brookmeyer for helpful comments.

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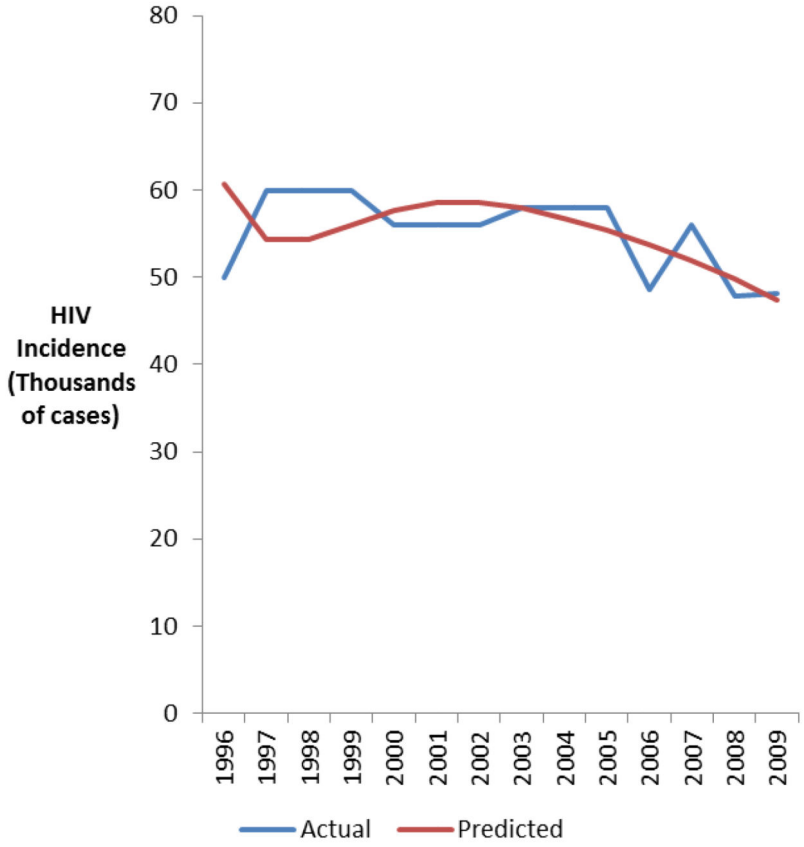

Exhibit 1. Actual And Predicted HIV Incidence In The United States, 1996-2009
SOURCE Authors' calculations.
NOTES Actual HIV incidence is based on published estimates of incidence. Predicted incidence is the incidence predicted by the authors' model, described in the text.

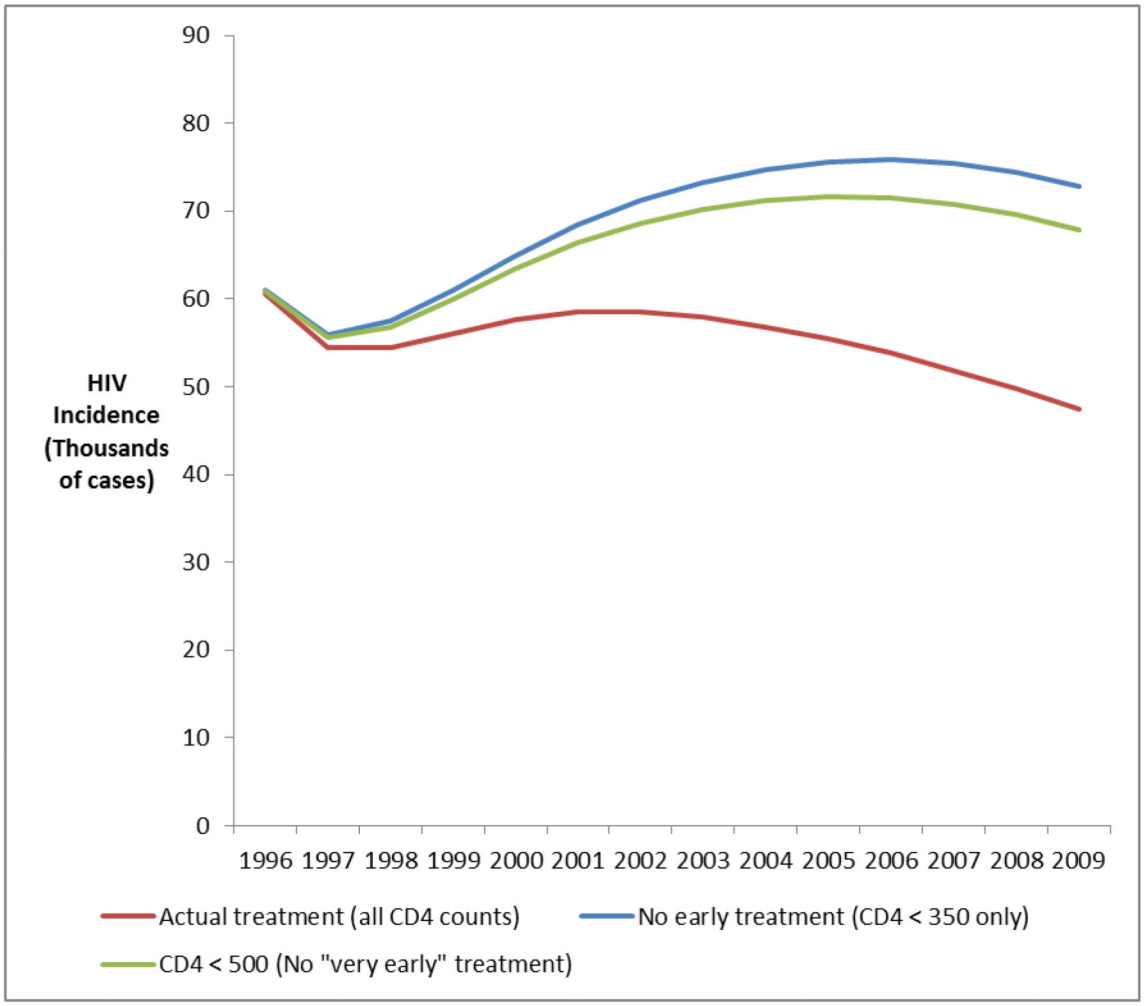

Exhibit 2. Predicted HIV Incidence In The United States, 1996-2009, With And Without Early Treatment

SOURCE Authors' calculations.

NOTES Actual treatment is the estimated rate of treatment with combination antiretroviral therapy (cART), according to CD4 count over 1996-2009. No early treatment is treatment at CD4 counts of less than 350 cells/mm^3 only. No very early treatment is treatment at CD4 counts of less than 500 cells/mm^3 only.

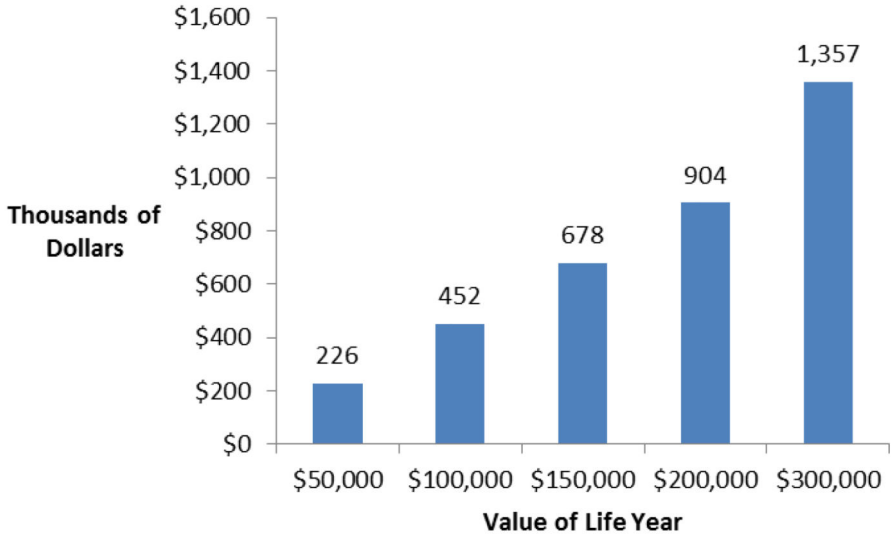

Exhibit 3. Value Of A Case Of HIV In The United States Prevented Through Early

SOURCE Authors' calculations.

NOTE Assuming treatment with combination antiretroviral therapy (cART) at CD4 counts of less than 350 cells/mm^3 only.

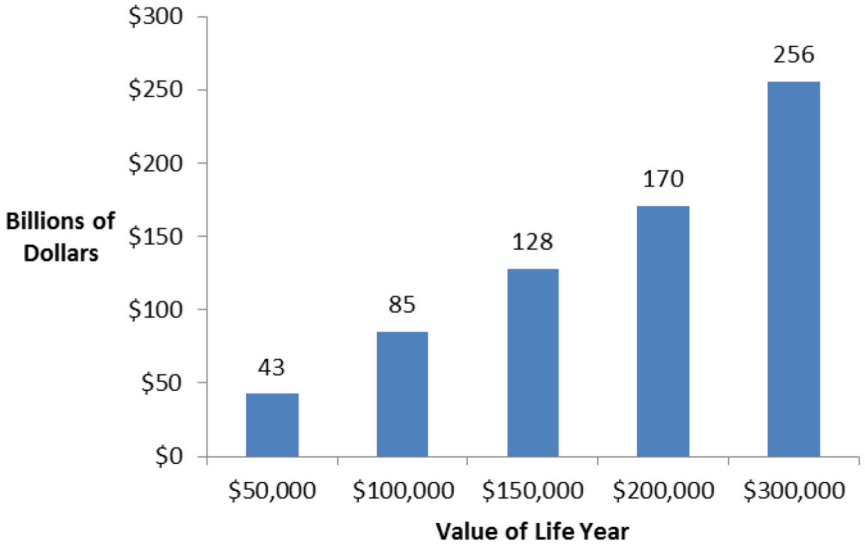

Exhibit 4. Total Value Of All Cases Of HIV In The United States Prevented Through Early Treatment, 1996-2009

SOURCE Authors' calculations.

NOTE Assuming treatment with combination antiretroviral therapy (cART) at CD4 counts of less than 350 cells/mm^3 only.