White Paper

Impact of Pharmaceutical Innovation in HIV/AIDS Treatment during the Highly Active Antiretroviral Therapy (HAART) Era in the US, 1987-2010:
An Epidemiologic and Cost-impact Modeling Case Study

Michael J. Lacey, MsC₁,
George J. Hanna, MD₂,
Jeffrey D. Miller, MS₃,
Talia S. Foster, MS₃,
Mason W. Russell, MAPE₃
₁MJL3 Group LLC, Newton, MA, USA; ₂Princeton, NJ, USA; ₃Truven Health Analytics, Cambridge, MA, USA

December 2014
Tremendous strides have been made over the past 25 years in the prevention and treatment of HIV Infection and AIDS (HIV/AIDS). Since peaking in 1995, death rates have fallen nearly 85%.
Introduction

Tremendous strides have been made over the past three decades in the prevention and treatment of HIV infection and AIDS (HIV/AIDS). The HIV/AIDS pandemic was first recognized in 1981 and it was initially associated with considerable morbidity (opportunistic infections and cancers) and high mortality in a previously young and healthy population [1]. In 1990 HIV/AIDS was ranked 7th among diseases and injuries most likely to cause premature mortality in the U.S. By 2010, HIV/AIDS ranked 23rd on this list[2]. Today with access to treatment, what was once an acutely fatal illness is now largely a manageable chronic condition.

Drug development efforts resulted in the first FDA-approved medicine in 1987, the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, a subset of the broader class of antiretrovirals (Figure 1). However, its use as monotherapy produced modest, short-lived effects. Starting in 1991, additional nucleosides were approved by FDA for HIV infection, allowing the possible use of combination antiretrovirals to treat HIV disease. The first non-nucleoside class antiretroviral, the protease inhibitor saquinavir, was approved by FDA in December 1995, and was followed by approval of additional protease inhibitors as well as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and other classes such as integrase inhibitors. This ushered the era of highly active antiretroviral therapy (HAART), defined as a regimen consisting of multiple antiretroviral drugs in combination. HAART, now often composed of two NRTIs in combination with a third antiretroviral of a different class (commonly a protease inhibitor, a NNRTI or an integrase inhibitor), proved capable of profound and durable suppression of HIV in an infected individual.

Based on compelling data from clinical trials of combination antiretroviral therapy, HIV treatment guidelines in 1996 started recommending combination antiretroviral regimens, which later came to be know as “HAART”.

In parallel, sharp declines in morbidity and mortality among persons living with HIV/AIDS were noted starting between 1993 – 1996 and decreases became dramatic starting in 1996[1]. In the US, age-adjusted death rates due to HIV disease have declined from 16.2 per 100,000 persons in 1995 to 2.6 per 100,000 in 2010. In other words, since the introduction of these revolutionary treatments, the death rate has fallen nearly 85%[3].

Many factors have contributed to the declines in HIV/AIDS death rates. These include public health prevention programs, greater access to medical care for at risk populations, improvements in opportunistic infection prophylaxis and treatment, and greater clinical experience of providers in managing HIV/AIDS.

However, the ability to suppress HIV in infected individuals with antiretroviral combinations, even with early HAART regimens, directly resulted in marked immunologic improvements and decreases in morbidity and mortality[4–6].
In other words, since the introduction of these revolutionary treatments, the death rate has fallen nearly 85%.[3]

The progress that has been made against HIV/AIDS over the past several decades has been incredible. This paper has undertaken to presuppose the existence of an alternative reality: where would we be today had HAART and all the innovations which followed never come into existence? Had innovation stopped prior to the introduction of these medicines, how many more may have died prematurely? What sort of social and economic losses would have been realized as a result of the additional lives that were lost?

In pursuit of these questions this paper has constructed a conceptual framework for analyzing the value brought to patients and society as a result of the deaths that were avoided and the years of life gained in the decades following the introduction of HAART. This exercise focuses specifically on the value gained as a result of reductions in mortality.

**Construction of Analytical Framework**

The enormous social cost of HIV/AIDS is reflected in years of potential life lost (YPLL) due to premature mortality when compared to the risk-adjusted life expectancy in the absence of HIV/AIDS. The U.S. Centers for Disease Control (CDC) estimates that from 1995 to 2010 the YPLL among persons who lived with HIV/AIDS declined from a high number of 593,300 lost life-years due to premature mortality in 1995 to a low of 76,600 lost life-years due to premature mortality in 2010. These improvements closely mirror the observed reduction in mortality rates (Figure 2). Life-expectancy post-HIV infection has improved dramatically since the early 1990’s and in the United States and Canada life expectancy among treated HIV-positive individuals now approaches that of the general population[7,8].
There is also a significant social and economic burden of treating HIV/AIDS. From an economic perspective, the value of prevention is often quantified as the direct medical care costs for HIV infection averted. Recent research has estimated the direct lifetime cost of treating a new HIV infection ranged from $253,000 to $402,000 from time of infection[9].

Cost of treating HIV/AIDS has been estimated to be $19,955 per patient per year (2006 dollars). This includes $10,205 in HAART drug costs, $2,670 in hospitalization costs and $7,080 in other costs[10].

The value of averting HIV infections through prevention strategies has been estimated using a variety of approaches. Using a simulation based model using population level incidence and transmission rates, direct cost savings over the period 1991-2006 due to prevention efforts was estimated to be $129.9 billion in costs savings (1996 dollars) in the base case and ranged from $70.3 billion to $515.3 billion depending on assumed transmission rate[11]. A second study using a different methodology aggregated the direct and indirect cost of an HIV/AIDS diagnosis in the US. Cumulatively the direct costs of new HIV infections were estimated to be $36.4 billion in 2002, including $6.7 billion in direct costs and $29.7 billion in

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**Economic Costs—Direct and Indirect**

**Direct costs** include those associated with pharmaceuticals, hospitalizations, physician and specialist visits and other medical-care that consumes tangible healthcare resources.

**Indirect costs** are those related to lost economic productivity due to illness or premature mortality. For example, lost wages due to work loss for the patient and their caregivers. These costs are called indirect costs since because they are not directly involved in healthcare delivery but are nonetheless still contribute to the total value of health services and interventions.
indirect costs [12]. Reductions in resource utilization related to hospitalization also closely follow improvements in morbidity and mortality (Figure 3). This has occurred despite the fact that the overall prevalence of persons living with HIV has increased from 760 thousand in 1996 to 1.2 million as of 2012 [3].

![Figure 3. Hospitalization Rates per 100,000 for HIV-Related Infections in the US, 1993-2012](image)


**Study Objectives**

Assessing the value of prevention of early mortality requires estimating the added benefit of the expected economic productivity among individuals with increased lifespan minus the added costs of caring for individuals over time. The purpose of this analysis is to estimate the net-economic benefit of prevention and treatment during the early HAART era spanning 1996 through 2010. We use data from a variety of sources and statistical modeling techniques to derive our estimates. A simplified schematic representation of the model is shown below (Figure 4).
The focus of our research is to estimate the value of innovation in the prevention and treatment of HIV/AIDS by developing a statistical model to simulate a world without antiretroviral and HAART innovation (including the many innovations that followed). We have structured our case study around three questions:

1. In the US setting, what are the differences in estimated mortality rates (per 100,000) between actual observed HIV/AIDS population and a hypothetical HIV/AIDS cohort without access to antiretroviral and HAART therapies over the period 1987-2010?

2. What are the differences in number of premature deaths and years of potential life lost (YPLL) between these two cohorts?

3. What was the net economic value and cost effectiveness from averting premature mortality minus cost of treating HIV/AIDS among survivors between these cohorts?
Methods
To estimate the value to patients and society of therapy during the HAART era we developed an epidemiologic and cost-impact model in MS Excel®. We first compare actual death rates among persons with HIV disease observed during the study observation period (1987-2010) to a cohort in a hypothetical scenario in which antiretroviral agents and HAART regimens were not developed. We used actual death rates from the period (1987-1995) defined as the pre-HAART period to develop a statistical model to project expected death rates during the HAART period (1996-2010). Death rates were taken from published CDC data [3]. Projected death rates were estimated using linear regression with exponential smoothing.

Net deaths averted were defined as the net difference in expected versus observed cases in each year of the study period. Life years lost per case due to premature mortality was estimated based on CDC estimates of years of potential life lost (YPLL) from premature mortality [9]. Total YPLL equals YPLL per case multiplied by total number of deaths averted.

Use of Cost-Impact Models in the Evaluation of Health Interventions and Therapies

Cost-impact models help estimate the total financial impact of a public health program or therapy within a population. In this case study we take the perspective of the entire US society. Cost impact is measured by the net difference between the economic value (in US dollars) of benefits realized by a new program or therapy minus the costs of providing the new service or therapy.

Net Economic Benefit (NEB) = Added Economic Benefit - Added Treatment Costs

For example, one of the primary impacts of HAART therapy is the marked reduction in mortality rates among persons living with HIV infection. Our cost impact model accounts for both the dollar value of wages earned by persons who are now alive due to the therapy and compare this to the therapy costs and medical resources (i.e., hospitalizations, specialist visits, drug therapy) used by these individuals. The cost impact (Net Economic Benefit) is the difference between these benefits and costs.

Net Economic Benefit (NEB) was chosen as a suitable measure as it takes into account the economic benefit associated with increased life expectancy balanced against the added cost of treatment for the increased life expectancy due to improved outcomes. Patients who live longer will participate in the labor force and contribute to increased societal productivity. Counterbalancing this effect is the marginal cost of caring for persons living with HIV over the extended life expectancy.

We estimated productivity benefit based on US National Median Wage in 2012 [13] and inflated by 30% [13] to account for the value of employee benefits. This value was further adjusted to account for individuals not participating in the labor force due to a variety of reasons including unemployment, inability to participate in the labor force or retirement [14]. These income estimates were then adjusted to 2010 levels using the National Wage Inflation Index (2012) [15].
Annual costs of HIV treatment per year are based on a recent study of a large sample of persons living with HIV disease from more than 10 participating treatment centers. Average annual costs were estimated to be $19,599 including approximately $10,203 for HAART per year (2006 dollars) [10]. Costs were then inflated to 2010 dollars [15]. Following standard methodology, all cost measures were then discounted by 3% per year to arrive at a net present value for the costs of care in each year. The aggregate cost of treating HIV (including costs of HAART and non-HAART costs such as hospitalizations, specialist visits, and drugs other than HAART) was estimated as the discounted cost per year multiplied by the number of life years saved [16].

The cost impact model compares the dollar value of wages earned by persons who are now alive due to the therapy to the costs of therapy and medical resources (i.e., hospitalizations, specialist visits, drug therapy) used by these individuals. Therefore, the cost impact (Net Economic Benefit) is the difference between these productivity gains and added direct medical costs.
Results

The model illustrates the difference between actual mortality rates and a scenario of what might have happened if innovation had essentially stopped just prior to the advent of HAART therapies beginning during the period 1994 – 1996.

The model found a substantial number of premature deaths averted during the HAART era. The projected mortality curve reflects a continuation of the continuous increase in annual mortality rates observed prior to the HAART era. The model predicts a slowing of the rate of increase to reflect the likely changes public health prevention efforts if HAART therapies were never developed. We adopted this assumption to ensure that we did not overestimate the predicted mortality ratio.

Our primary result is that an estimated 862,396 premature deaths were averted since the beginning of the HAART era. This result is depicted in Figure 5. The white area depicts actual mortality rates (%). The shaded blue area represents the difference between the projected and actual mortality rates over the entire period.

Each premature death represents more than one year of potential life lost based on the methodology described above. For example if a person dies at age 30 and their life expectancy was 70 years then this individual would represent 70 – 30 = 40 years of potential life lost (YPLL). Conversely, if this person were kept alive due to improved treatment the number of years of potential life gained (YPLG) would be 40 YPLG.

Model results show that a cumulative 27,685,660 life years were gained from deaths averted over the period from 1996-2010 in the US (Figure 5). The cumulative value of increased wages earned was $857 billion. Total HIV/AIDS treatment costs (HAART-related and non-HAART related) were $242 billion. Added HAART related costs were $126 billion (52%) and non-HAART related costs were $116 billion (48%) of the total $242 billion in added costs. Net Economic Benefit (NEB) over the period 1996 – 2010 was $615 billion ($857 billion minus $242 billion)(Figure 6).
Figure 5. Age-adjusted death rates for HIV disease in the US 1987-2010, Actual versus Projected


Figure 6. Net Economic Benefit of HAART Therapies, 1996-2010.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Benefit</th>
<th>Cost</th>
</tr>
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<tbody>
<tr>
<td>Cumulative Value of Productivity Increase</td>
<td>$857 B*</td>
<td></td>
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<tr>
<td>Cumulative Value of HAART Costs</td>
<td></td>
<td>$126 B</td>
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<tr>
<td>Cumulative Value of Non-HAART Costs</td>
<td></td>
<td>$116 B</td>
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<tr>
<td>Total HIV/AIDS Treatment Costs</td>
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<td>$242 B</td>
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<tr>
<td>Net Economic Benefit</td>
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*B = billions
Discussion
In this investigation, we focused on the most objective measure of HAART effectiveness, the decrease in mortality (and increase in life expectancy). Several factors have contributed to the decline in HIV/AIDS-related mortality in the US, including public health prevention programs, improvements in opportunistic infection prophylaxis and treatment, greater clinical experience of providers in managing HIV/AIDS, as well as availability of antiretroviral therapy. Disentangling these factors to assess the contribution of only one of them is challenging. Nonetheless, clinical trial data clearly confirm the profound effect of combination antiretroviral regimens on morbidity and mortality, even with early HAART regimens that lacked the tolerability, durability of viral suppression, and ease of administration of modern regimens [4,5]. Furthermore, the early-observed decline in HIV/AIDS mortality was strongest in patients prescribed HAART regimens compared to those on less optimal or no antiretroviral therapy[6].

The potentially synergistic two-way interaction between these factors should be borne in mind. For example, availability of effective treatments may increase desirability and acceptability of testing and counseling programs from a patient perspective, since a positive diagnosis no longer is a hopeless condition, and a patient at risk is less afraid of a potential positive test result. This may lead to increased testing and counseling with larger impact on preventing infection of HIV-negative individuals. From a public health perspective, availability of testing and counseling programs not only serves as a prevention program for those who are HIV-negative, but also enables connection of newly diagnosed HIV-positive individuals into earlier and more effective care, with downstream improvements in morbidity and mortality. Such synergistic interactions between factors are difficult to control in a model and may underestimate the effect of a single factor.

Additionally, ongoing innovation in antiretroviral drug development has resulted in the availability of more convenient, better tolerated, durable and safer HAART regimens, some of which are now available as single-tablet regimens taken once daily. This, along with the recognition that immunological damage from HIV can occur early during the time course of the infection, has also influenced clinical practice and timing of initiation of treatment. US guidelines recommend starting treatment earlier in the disease course in order to optimize long term morbidity and mortality benefits[17]. The actual progressive decreases in mortality over time likely reflect in part these two additional factors. Therefore projected estimates of mortality and economic benefits may increase with time since the early HAART years.

HAART has been successful not only in preventing AIDS and death in HIV-infected individuals, but also markedly reducing the transmission rate of HIV from infected individuals on therapy to their partners[18]. Treatment therefore may also serve as prevention of transmission, and our model does not directly assess this beneficial effect of HAART.

Similarly, it is worthwhile to note in the absence of the availability of HAART regimens, a number of other interventions may have sought to ameliorate the impact of this public health crisis. For instance, in the absence of effective treatment options there may have been a scale up in public health and behavioral interventions as well as shifts in non-pharmaceutical based provision of healthcare services that may have influenced the trajectory of the disease. The many unknowns of a world in which effective HIV/AIDS therapy had not emerged represent the inherent challenges in projecting the epidemiology of disease. Nonetheless, the impact of HAART is widely recognized to have provided tremendous value to patients and society. This analytic framework is intended to demonstrate in objective terms the benefit of innovation and the important role that medicines play in transforming the treatment of disease.
Antiretroviral drug development has been an example of historical success of rapid and highly targeted drug development, with only 6 years between recognition of the disease and the first antiretroviral approval, and with over 25 unique antiretrovirals approved in subsequent years \[19\]. The striking improvements in morbidity and mortality of HIV/AIDS have been largely due to pharmaceutical innovation that produced effective antiretroviral therapy and HAART, with significant social net economic benefit.

The results of this analysis suggest that as a result of HAART and the subsequent innovations that followed, **an estimated 862 thousand premature deaths were avoided, 27 million life-years were saved, and $615 billion in economic value was gained in the United States alone**. This example of antiretroviral drug development makes a strong case for continued investment and innovation in pharmaceutical research and development aiming to address serious unmet medical needs.
References


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