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Determining the Cost-Savings Threshold for HIV Adherence Intervention Studies for Persons with Serious Mental Illness and HIV

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Abstract

Persons with serious mental illnesses are at increased risk for contracting and transmitting HIV and often have poor adherence to medication regimens. Determining the economic feasibility of different HIV adherence interventions among individuals with HIV and serious mental illness is important for program planners who must make resource allocation decisions. The goal of this study was to provide a methodology to estimate potential cost savings from an HIV medication adherence intervention program for a new study population, using data from prior published studies. The novelty of this approach is the way CD4 count data was used as a biological marker to estimate costs averted by greater adherence to anti-retroviral treatment. Our approach is meant to be used in other adherence intervention studies requiring cost modeling.

Keywords

Health expenditures; HIV/AIDS; serious mental illness

Introduction

The advent of highly active antiretroviral therapy (ART) has dramatically improved the treatment standards for those infected with HIV^{1,2}. Its widespread use has been shown to increase the immune function of patients with highly immunocompromised systems (e.g. <50 cell/mL), as well as keeping persons living with HIV at a stable CD4 count level³. A number of studies have examined the cost-effectiveness of ART therapy due to their savings in non-antiretroviral related expenditures, largely comprised of hospital expenditures^{4,5}. The

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mechanism behind these overall healthcare expenditure reductions is that ART treatment leads to better immune function, resulting in less hospitalizations and acute patient care⁶.

However, inadequate adherence to ART, even after HIV suppression has been successful, can result in viral rebound and may in fact contribute to drug resistant mutation of the virus⁷. There is evidence that nearly perfect adherence to ART is required to maintain undetectable viral load levels and hence, a robust immune system⁸⁻¹¹. Reynolds et al. 2004 reports that successful long-term treatment of HIV/AIDS requires at least 95% adherence to ART in order to prevent emergence of drug-resistant HIV variants that lead to regimen failure¹². Yet, adherence to ART is difficult, even in highly motivated subjects¹³. Non-adherence to ART is also compounded by public health concerns, such as its relationship to sustained reduction in viral load to minimize the transmission of drug-resistant virus from both blood and genital secretions¹⁴. As a result, much research has focused on developing interventions to maximize medication adherence among individuals undergoing ART¹⁵.

A particularly vulnerable population has been individuals with serious mental disorders who are comorbid with HIV/AIDS¹⁶⁻¹⁹. Estimates of the prevalence of HIV among persons with mental illnesses vary widely and range from 4% to 23% compared to .4%–.6% in the general population^{16,17,20}. Furthermore, several cost studies have shown that individuals with co-morbid SMI/HIV had much higher health care expenditures than non-SMI persons with HIV and non-HIV persons with SMI²¹⁻²³. There is concern that HIV positive SMI persons may be a greater risk for poor treatment adherence, increasing risk for poorer outcomes and development of treatment resistant virus, and also placing others at greater risk^{20,24}. Wagner et. al (2003)²⁵ looked at adherence to HIV anti-retrovirals among co-morbid persons with SMI and found that a substantial proportion of the study participants displayed poor adherence, indicating the need for further assess the factors that influence adherence to ARTs in this population.

Because of the interest in the cost effectiveness of treating individuals who have ART adherence problems, it is essential for program planners to estimate the cost-savings threshold of an intervention in order to determine the maximum cost that might be spent on the intervention and still be cost effective. An important consideration in determining the cost-effectiveness of an intervention is whether the improvements in the immune function offset the cost of both the ART medication *and* the intervention itself. Specifically, the direct treatment expenditures associated with those receiving an intervention will generally be greater than the treatment as usual control groups, but these costs may be offset by reductions in emergency room visits, hospitalization, and reduced risk for transmission through high risk behaviors. However, reliable cost data is rarely available on trial participants, due to lack of access to and expense in obtaining it, making it difficult for researchers to evaluate the cost savings associated with an intervention.

The goal of this study was to develop a synthetic method to estimate the potential cost saving threshold associated with medication adherence using, as a case study, co-morbid individuals with HIV and serious mental illness who participated in a University of Pennsylvania effectiveness trial known as Preventing AIDS Through Health for Positives (PATH+)^{15,24,26}. This adherence trial collected CD4 and viral load biomarker data at

baseline and follow-up, a common set of data elements in these types of studies. Cost data for the current analysis was used from two sources; 1) a randomized adherence intervention trial of HIV participants at the University of Alabama (UAB) HIV clinic by Chen et al.,²⁷ based on CD4 counts and 2) an administrative claims study of co-morbid HIV/SMI individuals by Rothbard et al.,²² treated in the same public service system as the PATH+ participants. The cost perspective used here was to the healthcare provider and was constructed using reimbursement or expenditure data from insurers.

A full scale cost-effectiveness analysis of PATH+ would include examination of PATH+'s programmatic costs relative to the money saved due to reduced medical costs consumed via improved CD4 cell count. However, we do not know with certainty the cost of PATH+ because it was embedded within a 5 year research grant, and the study nurses had additional research responsibilities beyond their direct care, which limits our ability to account for the cost of intervention. Furthermore, we do not know what cost savings were accrued as a result of changes in adherence behaviors, or over what time period.

Methods

CD4 Count and Cost Savings

We chose to use improvements in CD4 counts to estimate cost savings of the PATH+ adherence intervention because the CD4 count level is a standard indicator for immune function, and among HIV patients, an indicator for severity of disease progression. Patients with low CD4 counts have a higher risk of progression to AIDS and related death²⁸. The stage of severity of the illness, as measured by CD4 levels, is a major determinant of healthcare costs as evidenced by the observed variability in costs associated with patients at different CD4 levels. For instance, Krentz et al.'s study found that the mean costs for late presenters who have CD4 counts <200 cell/mL was more than twice as high as those for early presenters²⁹. Moreover, a study by Freedberg et al. found that the initial CD4 cell count and drug costs were the most important determinants of costs, clinical benefits, and cost effectiveness³⁰. Given evidence of a relationship between CD4 count and stage of HIV progression, we employed CD4 count as a proxy or reasonable biomarker for association with HIV related health expenditures. The use of CD4 count as a determinant of healthcare expenditure is further supported by the Chen et al. study, where they reported a statistically significant association between cost and CD4, but not viral load, which does not appear to be linearly related to cost. Their study followed HIV positive patients for 12 months, and found significant differences in expenditures between patients whose baseline CD4 count was 0-50 cell/mL as compared to those with ≥ 350 cells/mL²⁷. The UAB cost estimates, based on CD4 counts, have been widely used in modelling HIV prevention cost savings because they take a comprehensive approach to HIV care, including costs of treatment, inpatient/outpatient services, and hospice^{31,32}.

The approach we are using here differs substantially from previous studies that simply examined prescription of ART or used viral loads as outcome indicators in calculating cost effectiveness³³⁻³⁵. We think that using CD4 as a direct measure of immune function is a better clinical indicator, since it is more proximal to the development of opportunistic infections. We use this synthetic estimation to develop a cost effectiveness threshold for

PATH+ as an exemplar for other HIV interventions that will increasingly focus on treatment as prevention^{36,37}.

Study Design and Data Sources

Two data sources were used in this analysis: cost data from the UAB HIV intervention study consisting of CD4 count and health expenditure, and CD4 data from the UPENN PATH clinical trial HIV intervention study.

The first data source used the results from a 2006 published study of mean annual healthcare expenditures for HIV positive patients at the University of Alabama at Birmingham (UAB) HIV clinic²⁷. The data consisted of Medicare calculated healthcare expenditures for CD4 counts of patients taken at baseline and stratified into four CD4 groups: 0-50 cells/mL, 50-199 cells/mL, 200-349 cells/mL, and 350 cells/mL. The final UAB study sample consisted of 635 patients, of whom 62 belonged to the <50 cells/mL category, 99 in the 50-199 cells/mL, 143 in the 200-349 cells/mL, and 331 in the 350 cell/mL category. Most of the study patients were white men who had sex with men, and over 80% of the patients were receiving ART at baseline. The healthcare expenditures were determined using reimbursement rates from 2001 Medicare data and the average wholesale prices of drugs for that period. Researchers calculated each patient's healthcare costs for 12 months, breaking down the costs into five categories: hospital costs, ART medications, non-ART medications, physician/clinic fees, and other outpatient expenditures. The UAB's study sample consisted of HIV positive patients receiving primary care at the UAB HIV clinic that had a baseline CD4 cell count on March 1, 2000 and had at least one follow-up clinic visit or hospital admission between June 1 2000 and March 1 2001. The UAB expenditure data was used to estimate the relationship between cost differences and changes in CD4 counts of our PATH+ study sample, based on the assumption that this relationship between CD4 counts and healthcare expenditures is unaffected by race, gender, and other patient demographics.

Our other data source was from the University of Pennsylvania HIV intervention trial PATH+^{15,24,26}. The PATH+ study goal was to improve the immune function of participants living with HIV and a serious mental illness (SMI). The intervention used advanced practice nurses to maintain at least 80% ART therapy adherence for individuals randomized to the intervention group. Inclusion criteria required that participants were age 18 or older, spoke English, lived within city limits of Philadelphia, had a physician diagnosed disorder of serious mental illness (schizophrenia, major affective disorders) and were HIV positive. Overall, the PATH+ clinical trial enrolled 238 HIV-positive participants with SMI of which 128 were randomized to the intervention group while 110 were allotted to the control group. However, only 100 of the intervention and 81 of the control participants had CD4 measurements at baseline and 12 months and as such, only 181 participants were used in our study. There were not statistically significant differences between the intervention and control groups in terms of age, gender, race/ethnicity, education, and employment. The groups were also similar with respect to type of mental disorder and number of years since HIV diagnosis. The data contained CD4 counts of all patients at baseline and throughout the study period.

Part 1: Cost Estimate Analysis

The expenditure data from the UAB HIV clinic patients were used to create an estimate of the relationship between cost and CD4 count. Since the relationship between expenditure and CD4 count differs greatly based on a patient's baseline CD4 category (e.g. highly acute patients may observe greater cost savings with CD4 improvements than healthier patients), we chose to create separate slope estimates (β_i) for each CD4 category. Specifically, the UAB investigators categorized their study participants into the four distinct baseline CD4 strata: 0-50 cells/mL, 50-199 cells/mL, 200-349 cells/mL, and 350 cells/mL, and reported the mean annual expenditure for participants in each stratum. We used the difference in the averages between two adjacent CD4 count categories to create an estimate for cost savings associated with a unit change in CD4 count, given a participant's baseline CD4 category. This calculation can be represented as:

$$\beta_i = \frac{(C_{i+1} - C_i)}{([CD4_{i+1}] - [CD4_i])} \quad (1)$$

where for $i=1,2,3,4$, $[CD4_i]$ is the lower bound (left interval) of baseline CD4 category i and C_i is the total cost for baseline CD4 category i . After obtaining the estimate for cost savings per CD4 count for each of the four CD4 categories, we then used the baseline CD4 data for all PATH+ study participants to categorize them into one of the four distinct baseline CD4 strata: 0-50 cells/mL, 50-199 cells/mL, 200-349 cells/mL, and 350 cells/mL. Separate slopes (betas) were created for each baseline CD4 category, and each participant's total change in CD4 count was multiplied by the CD4-category specific beta to get total change in healthcare expenditure. This method assumes that CD4 declined linearly with expenditure once the CD4 category specific beta was taken into account. For each of the j participants, we calculated their change in CD4 count from baseline to 12 months, given as:

$$\delta_j = CD4_{j,12Months} - CD4_{j,Baseline} \quad (2)$$

Since the PATH+ study was a comparative effectiveness trial, each study participant belonged to either the intervention or control group, based on their randomization into the study. For each of these two groups, we multiplied the slope estimate (β) for cost-CD4 relationship by each participant's difference in CD4 count from baseline to 12 months. By summing these totals, we obtained an estimated cost savings for the control and intervention groups. This can be defined as:

$$Cost\ Savings\ (S) = \sum_{i=1}^4 \sum_{j=1}^{n_i} \beta_i \delta_{ij} \quad (3)$$

where $i=1,2,3,4$ and $j=1,2,3,\dots,n_i$ for the i th CD4 category and j th study participant. All statistical analyses were performed using R Cran (Free Software Foundation, Boston, MA).

Results

Estimating the Relationship between CD4 Count and Total Healthcare Cost

There were four CD4 categories in the UAB study (0-50 cells/mL, 50-199 cells/mL, 200-349 cells/mL, and ≥ 350 cells/mL), and the mean annual expenditure for each of the categories was \$36,532, \$23,864, \$18,274, \$13,885, respectively. The slope estimates for Category 1, 2, 3, and 4 were −253.36, −37.27, −29.26, and 0 dollars/CD4, respectively. Our slope coefficients support the literature that changes in CD4 count are most sensitive to cost differences for highly acute patients (0-50 cell/mL). Based on the finding in Chen et al.²⁷ that cost differences vary little with CD4 changes above the 350 cell/mL threshold, we set the slope of category 4 to zero ($\beta_4 = 0$).

Change in CD4 Count

The next step in our estimation was to calculate each study participant's change in CD4 count over the clinical trial study period. In our example, the 181 PATH+ participants were followed for 12 months. Differences are represented as 12 months minus baseline, such that positive numbers represent improvements in CD4 count, and negative numbers represent declines in CD4 count. The overall average difference in CD4 count from baseline to 12 month for the experimental group was an increase of 92 cells/mL, while the control group had an average increase of 9 cells/mL. The greatest difference by category was found in participants in Category 1 (baseline CD4 count less than 50), where intervention participants averaged an increase of 264 cells/mL and control participants averaged a decrease of 8 cells/mL ($p < 0.01$). The other three categories (50-199, 200-349, ≥ 350) did not see statistically significant differences.

Cost Estimate

We then used the slopes relating costs to change in CD4 count to apply our proposed method for calculating cost savings to the PATH+ participant data. The slope estimates for Category 1, 2, 3, and 4 were −253.36, −37.27, −29.26, and 0 dollars/CD4. The greatest cost savings for the intervention group are attributable to CD4 category 1 (−\$267,802), or the participants with the highest acuity. In the control group, the largest cost savings were found for category 2 (−\$77,291), participants with CD4 counts between 50 and 199 cells/mL.

Discussion

The methods proposed in this paper are intended to provide researchers with an approach for estimating potential cost benefits of HIV treatment as prevention programs for specific subpopulations (i.e. SMI population) when CD4 counts are available and actual cost data is not. This is based on the premise that the use of and adherence to ART results in improvements in immune function as reflected in higher CD4 count, which by extension lowers overall healthcare costs due to reductions in opportunistic infections and associated costs of their treatment³². In our implementation of this method on data from the PATH+ study, we found that the intervention resulted in cost savings equal to \$3,735/participant. This cost saving estimate per participant can be interpreted as the maximum cost of the intervention per year. In our example, the cost of the intervention would need to be less than

\$3,735/participant in order to have any net cost savings. Given the fact that our findings showed that changes in healthcare expenditure were most sensitive for individuals with low CD4 counts, the greatest potential for cost savings in HIV adherence trials may be achieved by targeting the most acute patients.

The use of an adjustment ratio for modifying the UAB costs to more accurately apply to the PATH+ population resulted in UAB cost estimates that were one third lower than the comorbid HIV-SMI population but one third higher than the PA Medicaid HIV population alone. Support for this is based on the Rothbard et al. study²¹ that found that individuals living with HIV/SMI had nearly twice the annual healthcare costs as compared to persons living with HIV only but the increased costs were primarily from additional psychiatric related treatment, not medical care. Furthermore, Himelhoch et al.³⁸ found significantly lower risk for discontinuation of ART among patients with SMI relative to those with no psychiatric disorders, which could result in comorbid patients having less serious HIV related medical problems and thus lower healthcare costs than the average HIV only patient.

Limitations

It should be noted that this estimation approach is not intended to mirror a traditional cost-effectiveness or net cost-benefit analysis as it is focused on estimating healthcare expenditure changes only^{39,40}. Thus, the analysis does not take into consideration the net cost of the intervention itself, which is based on the particular components of the PATH+ program that was implemented.

A methodological issue in this study was our inability to construct confidence intervals for our slope estimates given that individual level data on CD4 counts and costs from the original UAB study dataset was not available to our research team. This limited us from being able to create a more precise estimate of the relationship between change in healthcare expenditure and CD4 count. Future studies may be able to improve on these estimates.

Implications and Future Research

The analysis of cost remains a critical and highly relevant issue in a period where healthcare expenditures continue to escalate. Given that accurate healthcare cost data for most clinical trial participants are either not easily attainable or labor intensive to try to collect, our approach to estimating cost savings synthetically based on published estimates from other studies provides investigators with an efficient means of approximating the cost savings of their intervention using only participants' changes in CD4 count over time, which is generally collected as part of routine care. In addition to the SMI population we intervened with in PATH+, we also believe that our method can be applied to clinical trials associated with reduction in alcohol and substance use among HIV positive patients^{41,42}, or any other complex HIV patient population, since the goal of is to improve immune function through better adherence to ART.

We provide this method with the understanding that refinements can and should be made to improve the accuracy of the estimates. Future research can adjust expenditures by sub population groups, insurance source, geographic site and by validating this approach by comparing the differences in actual and estimated costs in studies where actual cost data is

available. Finally, since cost studies generally require large samples, it is important to pursue this approach with a larger sample size.

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