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HIV Treatment in Resource-Limited Environments: Treatment Coverage and Insights

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ABSTRACT

Background: The effects of antiretroviral treatment on the HIV epidemic are complex. HIV-infected individuals survive longer with treatment, but are less likely to transmit the disease. The standard coverage measure improves with the deaths of untreated individuals and does not consider the fact that some individuals may acquire the disease and die before receiving treatment, making it susceptible to overestimating the long-run performance of antiretroviral treatment programs. **Objective:** The objective was to propose an alternative coverage definition to better measure the long-run performance of HIV treatment programs. **Methods:** We introduced cumulative incidence–based coverage as an alternative to measure an HIV treatment program's success. To numerically compare the definitions, we extended a simulation model of HIV disease and treatment to represent a dynamic population that includes uninfected and HIV-infected individuals. Also, we estimated the additional resources required to implement various treatment policies in a resource-limited setting. **Results:** In a synthetic population of 600,000 people of which 44,000 (7.6%) are infected, and eligible for treatment with a CD4 count of less than 500 cells/mm^3, assuming a World Health Organization (WHO)-defined coverage rate of 50% of eligible people, and treating these individuals with a single treatment regimen, the gap between the current WHO coverage definition and our proposed one is as much as 16% over a 10-year planning horizon. **Conclusions:** Cumulative incidence–based definition of coverage yields a more accurate representation of the long-run treatment success and along with the WHO and other definitions of coverage provides a better understanding of the HIV treatment progress.

Keywords: antiretroviral therapy, coverage, HIV treatment, resource-limited, simulation.

Introduction

The development of highly active antiretroviral therapy (ART) has revolutionized the treatment of HIV disease, producing dramatic increases in survival [1–3]. The benefits of these therapies, however, have not been fully realized in many resource-limited environments. The lack of sufficient treatment has been especially severe in sub-Saharan Africa, where many countries are able to provide treatment to only a small portion of the HIV-infected population [4]. Recent recommendations that support a "test-and-treat" strategy, with treatment being recommended for all HIV-infected individuals regardless of CD4 count, will exacerbate the problem of insufficient treatment resources.

Over the past decade, many sub-Saharan African nations, in cooperation with developed nations, the pharmaceutical industry, the World Health Organization (WHO), and many private charities have increased the resources available to treat the HIV epidemic. A measure of the success of these efforts is the increase in "coverage": the proportion of HIV-infected people meeting criteria for treatment who are being treated. In 2003, the average coverage levels in sub-Saharan Africa were only 3%, which had increased to 17% by 2005 [5], which still left large portions of the population untreated. In just a few years, international efforts have increased coverage rates substantially, and now most of the persons in sub-Saharan Africa live in countries with between 40% and 60% coverage [4]. The effects of increasing treatment resources on the epidemic are complex: on the one hand, HIV-infected individuals on treatment live substantially longer than do those not on therapy; on the other hand, HIV-infected individuals on treatment have a lower viral load (VL) and are less likely to transmit the disease. Also, treatment can induce mutations, which may decrease the effectiveness of treatment,

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and increase the HIV-infected individuals' VL. Therefore, the standard Joint United Nations Programme on HIV and AIDS (UNAIDS) "snapshot" definition of coverage, which we name *prevalence-based coverage*, may fall short in measuring the performance of ART programs. For example, Johnson and Boulle [6] note that as ART programs mature, the prevalence-based coverage becomes less sensitive to annual changes in ART enrolment and consequently it says relatively little about the recent performance. Moreover, the prevalence-based coverage is very sensitive to the treatment eligibility criteria and it will decline if the current recommendations for treating at a CD4 count of less than 500 cells/mm^3 are used to determine the treatment-eligible population [7]. Johnson and Boulle [6] also propose the "enrolment ratio," the fraction of ART initiation to HIV disease progression, as an alternative measure to complement the prevalence-based coverage.

In this study, we propose a new definition for coverage, which we name *cumulative incidence–based coverage*, and show that it may be a better representation of the long-run performance of ART programs than is the conventional prevalence-based coverage. In particular, unlike the prevalence-based coverage, which improves by deaths among HIV-infected individuals not on treatment, the cumulative incidence–based coverage is less sensitive to the rates of mortality, CD4 count decline in untreated individuals, and ART eligibility criteria. To compare the estimates of the prevalence-based and cumulative incidence–based coverage in a resource-limited setting, in which the effects of ART expansion on the size of the HIV-infected population who qualify for treatment are complex, we extend an individual HIV progression model and incorporate viral transmission. We also investigate the effects of various coverage and eligibility decisions on the HIV-infected population and required ART resources.

Methods

First, we review the current coverage metrics, discuss their shortcomings, introduce a new metric, discuss its strengths and weaknesses, and show how this new metric alongside other metrics provides a better understanding of the overall performance of ART programs. Second, we describe the population simulation model and use it to test how different coverage and ART eligibility criteria affect HIV-infected population size and treatment volume over time.

Definitions of Coverage

As defined in the UNAIDS 2010 report, coverage is "based on the estimated unrounded numbers of adults receiving antiretroviral therapy and the estimated unrounded need for antiretroviral therapy," which describes a measurement based on the prevalence of the disease [4]. This prevalence-based coverage has several deficiencies previously discussed in the literature. For example, it is less sensitive to recent changes in ART enrolment for mature ART programs, and is very sensitive to changes in ART eligibility criteria [6]. Therefore, Johnson and Boulle [6] provide the enrolment ratio as another definition; its numerator is the number of individuals starting ART in a given year, and the denominator is the number of individuals becoming eligible for ART in the same year. They show that the enrolment ratio may be more accurate in measuring the recent performance of ART programs.

We emphasize another deficiency that is based on the fact that deaths among those not on treatment improve the current metric. In particular, the size of the HIV-infected population will change over time depending on the amount of ART available. When not everyone in the population can be treated, some individuals will acquire the disease, become ill, and die without receiving ART. The current UNAIDS definition of coverage does not account for this phenomenon. Therefore, we define cumulative incidence–based coverage as the portion of HIV-infected individuals who received treatment at some point during their life. The cumulative incidence–based coverage is defined over a horizon rather than a specific point in time. Its numerator is the number of individuals who became infected and received treatment (at some point) in a horizon, and its denominator is the total number of individuals who became infected in that horizon. Note that this definition is flexible and one may adopt its numerator and/or denominator to measure the "favorite" outcome. For example, in our numerical study, we consider another version of the cumulative incidence–based coverage in which the denominator represents the total number of individuals who become infected and eligible in the horizon.

We illustrate the difference in these definitions through a simple example: Assume that there are only two HIV-infected individuals, that untreated individuals live exactly 2 years, that treated individuals live exactly 14 years, that there are sufficient resources available to treat only one individual at a time, and that a new case develops every 2 years. Figure 1 illustrates this scenario: at any given time, prevalence-based coverage is 50% as one half of the current HIV-infected population is being treated, but over a 14-year period, only one of a total of eight HIV-infected individuals received treatment, for a cumulative incidence–based coverage of 12.5%. The common interpretation of coverage overestimates the number of HIV-infected individuals who receive treatment because at most levels of coverage, many individuals will acquire HIV, live through their disease, and die without receiving ART. Therefore, the standard coverage metric may overestimate the long-run performance of ART programs especially in resource-limited settings.

Like any metric, the cumulative incidence–based coverage has some potential weaknesses. Although it captures the long-run performance of an ART program better than does the prevalence-based coverage, it is less sensitive to recent advances in treatment trends, similar to the prevalence-based coverage. In addition, because its numerator is the number of infected individuals who received treatment at some point in their life, it does not take into account the compliance of individuals to ART; that is, an individual who is alive and no longer on ART is considered in its numerator. Finally, calculating the cumulative incidence–based coverage might be harder than calculating the WHO one because it requires data on how many infected individuals have died over the past years in addition to the number of individuals who have become infected.

Overview of Individual HIV Model

The HIV simulation model is based on an individual microsimulation that replicates the probabilistic progression of the disease in an HIV-infected individual over time. The model tracks the health of an HIV-infected individual on a daily basis: VL updates consider the history of resistant mutation and compliance, and CD4 count updates consider several factors such as VL, treatment status, and age; it also replicates the progression of resistant mutations. The development, mechanics, and validation of this model have been previously described [8–14]. The simulation model computes HIV mortality rates on the basis of health and age of an infected individual and non-HIV mortality rates on the basis of age and the drugs' toxicity and adverse effects.

The model has demonstrated the ability to predict time to treatment failure [8], the development of resistant mutations [11,12], survival, and change in CD4 count and VL over time [8,13]