VALUE IN HEALTH 18 (2015) 1113–1119

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

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

Amin Khademi, PhD[1,], Denis Saure, PhD[5], Andrew Schaefer, PhD[3], Kimberly Nucifora, MSc[6], R. Scott Braithwaite, MD, MSc, FACP[6], Mark S. Roberts, MD, MPP[2,3,4]*

[1]*Department of Industrial Engineering, Clemson University, Clemson, SC, USA;* [2]*Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA;* [3]*Department of Industrial Engineering, University of Pittsburgh, Pittsburgh, PA, USA;* [4]*Department of Health Policy and Management, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA;* [5]*Department of Industrial Engineering, University of Chile, Santiago, Chile;* [6]*Section of Value and Comparative Effectiveness, NYU School of Medicine, New York, NY, USA*

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,

* Corresponding author: Amin Khademi, 130-D Freeman Hall, Clemson University, Clemson, SC 29634.
E-mail: Khademi@clemson.edu.

1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2015.10.003

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]

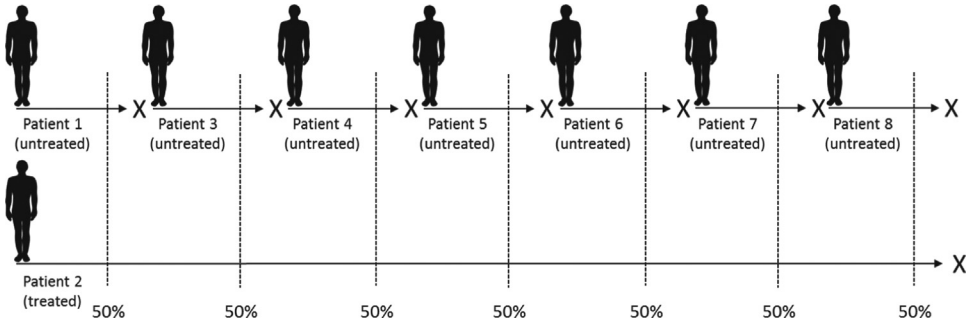

Fig. 1 – Prevalence-based and cumulative incidence–based coverage. *Notes.* **As an illustrative, simple example, assume that there is only one dose of antiretroviral therapy, that infected individuals without treatment live 2 years, those on treatment live 14 years, and that there is a new case of HIV about once every 2 years. During the lifetime of the treated individual, seven other individuals develop HIV disease and die without treatment. Overall, one of eight infected individuals was treated, for a coverage of 12.5% (the *cumulative incidence–based* coverage), but at any instant in time, it appears that 50% of the HIV-infected population is being treated (*prevalence-based* coverage). We also report the enrolment ratio in this example. Assuming that the individuals become eligible after infection, the enrolment ratio at the beginning of the horizon is 50% because two individuals become infected and one started therapy. However, the enrolment ratio is 0% in the next periods. Therefore, cumulative incidence–based coverage more accurately measures the long-run performance and the enrolment ratio more accurately measures the short-time performance of antiretroviral treatment programs.**

both with and without treatment. Recently, a version of the model calibrated with data from western Kenya has been used to test alternative thresholds for treatment initiation and the effect of adherence on the quality-adjusted life-years for HIV-infected individuals in sub-Saharan Africa [14]. We extended this version of the model to conduct our dynamic simulations.

Overview of Population HIV Model

We extended the individual HIV model described above by considering a population of HIV-infected individuals, in which the progression of each individual is governed by the microsimulation model, to simulate the effects of different levels of ART doses. The model also contains a population of susceptible individuals. The birth rate (for infected and uninfected individuals) was set to a constant 0.025 per year, which when coupled with our transmission rates produced a constant prevalence. The probability of death for uninfected individuals is such that their life expectancy is 55 years, representing much of sub-Saharan Africa [15]. Transmission is modeled with the development of a partnership of a susceptible individual with an infected individual, and the model assumes a homogeneous mixing pattern [16,17]. The probability that a susceptible individual establishes a partnership with an infected individual equals the proportion of infected individuals in the entire population. The model randomly chooses an infected individual from the infected population and calculates the probability of disease transmission on the basis of VL and the presence or absence of ART of the selected individual [18].

We constructed the initial population such that at 50% coverage (the current HIV coverage in sub-Saharan Africa), the prevalence remains roughly constant over the simulation horizon (10 years). Infected individuals whose CD4 count drops below a specific CD4 count are considered eligible for treatment initiation. Because the WHO reports on ART coverage are based on the less than 350 cells/mm^3 CD4 count eligibility criterion, we used this threshold to create the initial population. For simulating the epidemic in the future, however, we used a less than 500 cells/mm^3 CD4 count ART eligibility threshold to reflect the current treatment recommendations. We also assumed that the average CD4 count of a susceptible individual at the time of infection follows a normal distribution, with an average of 1000 cells/mm^3 and an SD of 111 cells/mm^3, truncated at 500 and 1500, consistent with the literature [19].

The model, therefore, incorporates the complex effects of treatment on the HIV epidemic: HIV-infected individuals who are on treatment have a lower VL and consequently are less likely to transmit the disease, but they live much longer and consequently have more time to transmit the disease. The model also includes treatment failure: HIV-infected individuals develop resistant mutations, which increases their VL, making them more likely to transmit the disease. We assumed that the probability of transmission depends only on the VL of the infected individual and in particular does not depend on its resistance profile. We relaxed this assumption, however, in our sensitivity analysis, in which we set the probability of transmission for resistant type to be half of the wild type for the same VL category [20]. We identified the effect of treatment on the population size and estimated the resources required (in the model, this is represented by the number of ART doses) for different coverage and ART eligibility criteria.

With insufficient doses to treat all eligible infected individuals, the model chooses which one to start the therapy using the WHO recommendations for resource-limited settings, which prioritizes therapy initiation for the sickest infected individuals (those with the lowest CD4 count) and keeps them on treatment until they die [21].

Researchers have developed models to explore the consequences of ART scale-up and specifically evaluate the test-and-treat strategy on the HIV-infected population [20,22–27]. Granich et al. [22] developed a mathematical model that predicted that HIV can be eliminated in South Africa by implementing the test-and-treat strategy in 40 years with approximately $10 billion less cost than with the Universal Access to Treatment (defined as coverage of at least 80% of the population in need). We investigated the implications of a test-and-treat policy on the population and the amount of resources that are needed to implement it. We simulated the system starting from a population with different coverage levels and estimated the characteristics and size of the population over 10 years. We defined our base case to be similar to the situation depicted in Figure 1: we assumed an initial 50% coverage of eligible HIV-infected individuals, and we increased the amount of medication available over time to exactly treat 50% of the eligible HIV-infected individuals, so at any time the WHO (prevalence-based) measure of coverage is

50%. We tested several scenarios, across various assumptions about the amount of ART available for treatment, and ART eligibility criteria, and we also estimated the effect of a "perfect" antiretroviral agent on the epidemic, where we defined "perfect" as reducing the probability of transmission to zero for the duration of taking the medication. It is important to note that we specifically have chosen not to model a specific resource-limited country; rather, we have made several simplifying assumptions for the purpose of illustrating important concepts concerning the interpretation of coverage.

The underlying progression model has been previously validated and multiple sensitivity analyses have been reported [8,9,11,13,28,29] and we did not repeat those here. We conducted sensitivity analyses related to the population and transmission components of the model including varying the probability of infection given a contact, the birth rate, the infectivity of resistant strains, and the availability of more than one treatment regimen, where we assumed that second-line therapy was identical in effectiveness to first-line therapy.

Simulations

We created an initial population of 43,497 infected individuals and 533,093 susceptible individuals. This size and prevalence was chosen through calculation so that with 50% of the eligible population, and our base assumptions about transmission, the prevalence of HIV remains roughly constant at 7.5%. For each scenario, we calculated both coverage measures and the size of the overall and infected population yearly for 10 years. To provide stable estimates, we repeated each simulation 30 times and reported the average of the results. To illustrate the distinction between coverage measures, we ran similar simulations at different baseline prevalence-based coverage levels, from no (0%) coverage to full (100%) coverage. We also evaluated the 10-year impact on the disease for various proposed treatment strategies including the current WHO treatment strategy (initiate ART at a CD4 count of 500 cells/mm^3) and the proposed strategy to test-and-treat all individuals found to be HIV positive. We also tested a hypothetical strategy in which ART is assumed to be 100% effective in reducing the probability of transmission to zero.

Results

In our base-case analysis, in which we assumed resources sufficient only to treat a prevalence-based coverage of 50%, a CD4 count treatment threshold of 500 cells/mm^3, and effectiveness of therapy as found in the literature, the prevalence of HIV disease remains nearly constant over a 10-year time horizon (Fig. 2). Panel A depicts the number of infected, eligible, and treated individuals under the base assumption that there are always sufficient resources to treat 50% of the eligible population. At this level of treatment, the number of new infections remains roughly unchanged and the size of the HIV-infected population continues to rise. Panel B increases the amount of resources available to allow treatment of all HIV-infected individuals with CD4 counts below 500 cells/mm^3. Although there is some impact on the number of new infections, the size of the infected population continues to rise from a combination of new infections and the increased life expectancy of the HIV-infected population. Panel C depicts the result of the test-and-treat scenario in which we treated an individual upon infection. The number of new infections significantly declines, but the number of infected individuals remains roughly constant.

Our results highlight a nonlinear relationship between the resources needed (in terms of ART doses) and prevalence-based coverage levels as well as ART eligibility criteria. In our base-case model, there were initially 43,497 individuals with HIV infection, of which 18,806 had CD4 counts of less than 500 cells/mm^3, making them eligible for treatment. A 50% prevalence-based coverage rate implies that 9403 patients were being treated. After 10 years, the number of people who would need to be treated just to maintain 50% coverage would rise to 12,432: to move to a test-and-treat strategy, in which every infected individual was treated, would require that 52,068 individuals be treated after 10 years, fully 7.6 times the number of people currently being treated. Note that the purpose of this numerical study was not to predict HIV trends in sub-Saharan Africa, but rather to show that the current recommendations may underestimate the resources needed to increase the coverage. For example, in a country that currently has a WHO-defined coverage of 50%, doubling the resources spent on HIV treatment will provide nowhere near 100% coverage.

Figure 3 illustrates more directly the relationship between the two different coverage measures, and the current context of prevalence-based coverage rates in sub-Saharan Africa. The prevalence-based coverage measure always overestimates the portion of an HIV-infected population treated at some time during the disease by as much as 16%. In sub-Saharan Africa, nearly 85% of the HIV-infected population lives in areas with a prevalence-based coverage below 60%, the range in which the prevalence-based measure overestimates the cumulative incidence–based measure by the most. This shows that the prevalence-based coverage may overestimate the long-run performance of ART programs.

Sensitivity Analyses

Varying the birth rate across the ranges in Table 1 did not change the results over 10 years (data not shown), but varying the infectivity given VL did. If the virus is much less transmissible than estimated [18], the number of infected individuals at the end of 10 years declines by an additional 2500 individuals (a 26.5% reduction); however, if the infectivity of the virus is at the upper 95% confidence limit, the total infected population would grow by as many as 10,000, nearly doubling the HIV-infected population. Our results show that by decreasing the infectivity rate, the prevalence decreases in the base scenario to 5% after 10 years and the test-and-treat strategy with current treatment efficacy could eliminate HIV in 80 years (incidence $<0.1\%$). If the resistant type is less transmissible than the wild type by 50%, the number of infected individuals at the end of 10 years declines by an additional 126 individuals (a negligible reduction). As expected, adding a second-line therapy (assumed equal in efficacy to first-line therapy) exacerbates the coverage problem slightly: By the end of 10 years, the presence of second-line therapy increases the number of HIV-infected individuals by about 415 (4.5%).

Discussion

Policymakers have unanimously used the UNAIDS prevalence-based coverage to measure the success of ART programs especially in resource-limited settings. Like any measure, however, the prevalence-based coverage is not flawless and the implications of its use in decision making should be thoroughly analyzed. The two major disadvantages of the prevalence-based coverage measure highlighted in the literature are as follows: 1) it is less sensitive to annual changes in ART enrolment when ART programs mature, and 2) it is very sensitive to ART eligibility criteria. We emphasize another deficiency of the prevalence-based coverage based on the fact that deaths of untreated (and eligible) individuals improve the measure. We show that the prevalence-based coverage does not capture the phenomenon

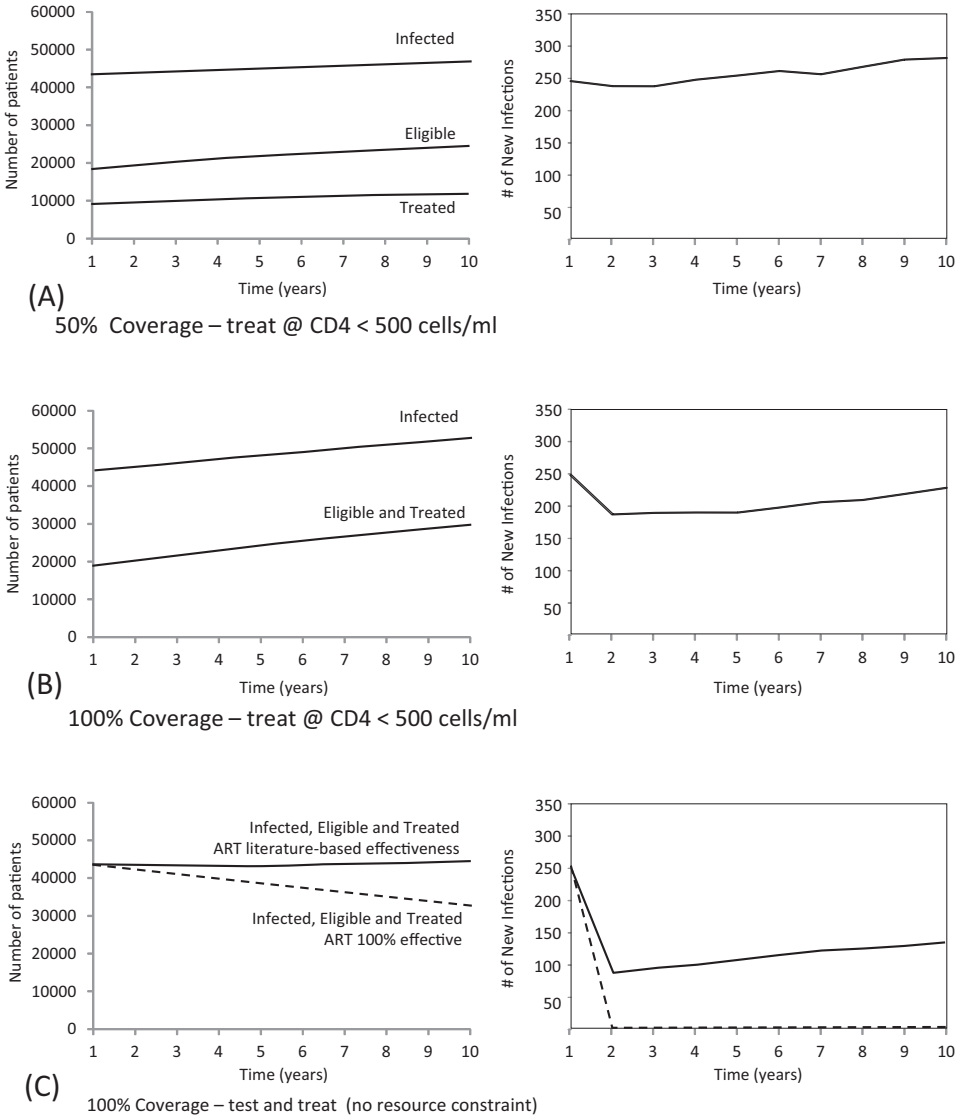

Fig. 2 – HIV-infected population and incidence. *Notes.* **Number of individuals living with HIV eligible for treatment and being treated under different treatment and coverage scenarios. In the base case (A), assuming the ability to treat 50% of the eligible patients, after 10 years the number of HIV-infected patients continues to rise, and there is almost no impact on the number of new cases. By increasing the coverage to 100% (anyone with a CD4 count of $<$500/mm^3 is treated), the incidence initially declines, but the number of individuals living with HIV increases by nearly 8700 (a 20% increase) as HIV-infected individuals live longer, and as new infections continue to occur, even accounting for decrease in their infectivity by VL suppression. Even 100% coverage of a "test-and-treat" strategy, in which any HIV-infected individual is treated (C) still results in slowly increasing the number of individuals living with HIV disease. Only under conditions of 100% coverage, and 100% efficacy (treatment reduces transmission to zero), the number of HIV-infected individuals drops by nearly 11,000 over 10 years because of decreased transmission. ART, antiretroviral treatment.**

that some individuals become infected and die without receiving ART. Therefore, it may overestimate the long-run performance of ART programs.

We introduce a novel definition for coverage, cumulative incidence–based coverage, and show that it is a better measure for estimating the long-run performance of ART performance. We also show that it is less sensitive to ART eligibility criteria and assumptions about rates of mortality and CD4 decline in untreated individuals. Because the cumulative incidence–based coverage tends to measure the long-run performance, it is less sensitive to recent ART enrolment. We propose that the combination of cumulative incidence–based coverage for long-run performance and the enrolment ratio for recent performance may provide a better insight into the progress made in HIV care than would the conventional prevalence-based coverage. Moreover, our analysis indicates that the amount of resources required (in terms of ART doses) increases in a nonlinear fashion by increasing coverage levels and treatment eligibility criteria. In particular, doubling the current resources available will come nowhere near to fully treating all infected individuals.

This work has several strengths and weaknesses. Our simulation model is calibrated using data from east Africa, and the model has demonstrated its ability to predict outcomes in sub-Saharan Africa, a resource-limited setting [14]. It accurately replicates the progression of the disease in each treatment scenario, and it reports prevalence-based and cumulative

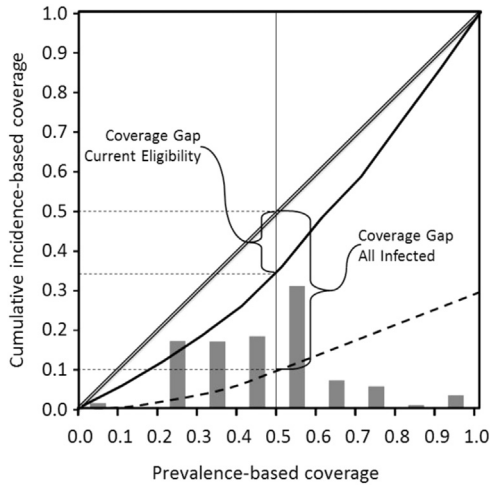

Fig. 3 – Coverage gap. *Notes.* **The relationship between prevalence-based coverage, cumulative incidence–based coverage, and current published prevalence-based coverage rates in sub-Saharan Africa. The solid line represents the relationship between the two coverage measures; the difference between it and the 45° line (compound line) describes the amount by which prevalence-based coverage measures underestimate the portion of the HIV-infected population that is treated. For example, when the observed prevalence-based coverage is 50%, only 34% of the patients who develop HIV will be treated during some portion of their life, producing a "coverage gap" of 16%. The dotted line represents the proportion of the total infected population who are treated at various measures of coverage of the eligible population. The vertical bars represent the percentage of people living at that level of prevalence-based coverage in sub-Saharan Africa. Most of the people are living in countries at or below 50% prevalence-based coverage, which highly overestimates the portion of the population who receives treatment at some time during their life. For this graph, eligibility is defined as treatment if the CD4 count is less than 350 cells/mm^3, as that is the definition used for the World Health Organization coverage rates displayed.**

incidence–based coverage and the number of ART doses required to treat a population of a given size. It incorporates both effects of treatment on transmission: the decrease in VL decreases the likelihood of transmission, but the increased lifespan, and potential for antiretroviral resistance acquisition, increases the time of potential spread. Our analysis considers only a single ART regimen, ignoring the effect of the second and third treatment regimens. Including multiple ART regimens, however, did not change the basic result and would compound the resource problem: second- and third-line therapy are much more expensive than first-line therapy [30], and HIV-infected individuals in the simulation live even longer in the presence of multiple treatment options. Therefore, our analysis likely underestimates the gap between prevalence-based and cumulative incidence–based coverage.

We ignored many capabilities of the underlying HIV model in these simulations, and did not fully represent all the subtleties of HIV care. For example, a portion of HIV-infected individuals will discontinue their HIV medication because of adverse effects and toxicity: we assumed that all treated individuals in the model remain on treatment until death. We re-estimated the results of the model allowing adherence to fall to levels observed in sub-Saharan Africa (data not shown) and found that prevalence-based and incidence-based coverage are slightly less discordant but the overall effect persists. Finally, our model assumes perfect information in the testing of alternative strategies. For example, in the "test-and-treat" strategy, we assumed that a person is detected essentially immediately after being infected. Similarly, in the scenarios in which eligibility is used to determine treatment (e.g., a CD4 count of $<$500 cells/mm^3), the model assumes that the eligibility is known immediately after that HIV-infected individual passes the threshold. Although this is certainly an unrealistic assumption, we used it not only for modeling simplicity but also because it provides the best-case scenario regarding the impact of treatment on the epidemic, and therefore whatever estimates we produced may underestimate how difficult the coverage problem could be.

The increase in the treatment of HIV disease in resource-limited settings has been a massive international effort, requiring the cooperation and dedication of individual health ministries, multiple charitable foundations, the WHO, many developed nations, and the pharmaceutical industry. The results of this research indicate that current published UNAIDS coverage data do not fully take into account the dynamic effects of ART scale-up on the size of the infected population.

Source of financial support: This work was partially supported by National Institutes of Health (NIH) R01AA017385-01 "A computer simulation of the Sub-Saharan HIV pandemic that can estimate benefit and value from alcohol interventions"—PI: Braithwaite (http://www.niaaa.nih.gov/) and U24AA022007-01 "The Operations Research Collaboration for Alcohol Abuse and AIDS – ORCAAA"—PI: Braithwaite (http://www.niaaa.nih.gov/) and by the NSF (NSF CMMI-0546960). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Table 1 – Input parameters for sensitivity analysis.

Input variable	Low	Base	High
Birth rate (per person per year)	0.02	0.025	0.03
Infection rate based on HIV-1 RNA (copies/ml)			
$<$400	0.02	0.16	1.13
400–3499	0.57	2.06	4.17
3,500–9,999	0.84	4.17	20.65
10,000–49,999	2.78	8.12	23.77
$\geq$50,000	3.87	9.03	21.09

Notes. This table reports the base, lower bound, and upper bound on birth rate and infection rates in the sensitivity analysis. Infection rates are based on 95% confidence intervals from Attia et al. [18].

REFERENCES

[1] Freedberg KA, Paltiel AD. Cost effectiveness of prophylaxis for opportunistic infections in AIDS: an overview and methodological discussion. Pharmacoeconomics 1998;14:165–74.

[2] Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. N Engl J Med 2001;344:824–31.

[3] Detels R, Munoz A, McFarlane G, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. JAMA 1998;280:1497–503.

[4] Joint United Nations Programme on HIV and AIDS. Global Report. UNAIDS Report on the Global AIDS Epidemic, 2012. Joint United Nations Program on HIV/AIDS, 2010. Available from: http://www.unaids.org/en/resources/campaigns/20121120_globalreport2012/globalreport. [Accessed September 2014].

[5] World Health Organization. Progress on Global Access to HIV Antiretroviral Therapy: A Report on "3 by 5" and Beyond. Geneva: World Health Organization, 2006.

[6] Johnson LF, Boulle A. How should access to antiretroviral treatment be measured? Bull World Health Organ 2011;89:157–60.

[7] World Health Organization. March 2014 Supplement to the 2013 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. Geneva: World Health Organization, 2014.

[8] Braithwaite RS, Justice AC, Chang CC, et al. Estimating the proportion of patients infected with HIV who will die of comorbid diseases. Am J Med 2005;118:890–8.

[9] Braithwaite RS, Roberts MS, Chang CC, et al. Influence of alternative thresholds for initiating HIV treatment on quality-adjusted life expectancy: a decision model. Ann Intern Med 2008;148:178–85.

[10] Braithwaite RS, Roberts MS, Goetz MB, et al. Do benefits of earlier antiretroviral treatment initiation outweigh harms for individuals at risk for poor adherence? Clin Infect Dis 2009;48:822–6.

[11] Braithwaite RS, Shechter S, Chang CC, et al. Estimating the rate of accumulating drug resistance mutations in the HIV genome. Value Health 2007;10:204–13.

[12] Braithwaite RS, Shechter S, Roberts MS, et al. Explaining variability in the relationship between antiretroviral adherence and HIV mutation accumulation. J Antimicrob Chemother 2006;58:1036–43.

[13] Braithwaite RS, Conigliaro J, Roberts MS, et al. Estimating the impact of alcohol consumption on survival for HIV+ individuals. AIDS Care 2007;19:459–66.

[14] Braithwaite RS, Nucifora KA, Yiannoutsos CT, et al. Alternative antiretroviral monitoring strategies for HIV-infected patients in east Africa: opportunities to save more lives? J Int AIDS Soc 2011;14:38.

[15] Life expectancy at birth, total (years). 2011. Available from: http://data.worldbank.org/indicator/SP.DYN.LE00.IN. [Accessed: September 2014].

[16] Garnett GP, Anderson RM. Sexually transmitted diseases and sexual behavior: insights from mathematical models. J Infect Dis 1996;174 (Suppl. 2):S150–61.

[17] Garnett GP, Hughes JP, Anderson RM, et al. Sexual mixing patterns of patients attending sexually transmitted diseases clinics. Sex Transm Dis 1996;23:248–57.

[18] Attia S, Egger M, Muller M, et al. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS 2009;23:1397–404.

[19] Reichert T, DeBruyere M, Deneys V, et al. Lymphocyte subset reference ranges in adult Caucasians. Clin Immunol Immunopathol 1991;60:190–208.

[20] Wagner BG, Blower S. Universal access to HIV treatment versus universal 'test and treat': transmission, drug resistance & treatment costs. PLoS One 2012;7:e41212.

[21] World Health Organization. Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach. Geneva: World Health Organization, 2010.

[22] Granich RM, Gilks CF, Dye C, et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet 2009;373:48–57.

[23] Blower S, Gershengorn HB, Grant R. A tale of two futures: HIV and antiretroviral therapy in San Francisco. Science 2000;287:650–4.

[24] Dodd PJ, Garnett GP, Hallett TB. Examining the promise of HIV elimination by 'test and treat' in hyper-endemic settings. AIDS (London, England) 2010;24:729.

[25] Velasco-Hernandez J, Gershengorn H, Blower S. Could widespread use of combination antiretroviral therapy eradicate HIV epidemics? Lancet Infect Dis 2002;2:487–93.

[26] Sorensen SW, Sansom SL, Brooks JT, et al. A mathematical model of comprehensive test-and-treat services and HIV incidence among men who have sex with men in the United States. PLoS One 2012;7:e29098.

[27] Khademi A, Saure DR, Schaefer AJ, et al. The price of nonabandonment: HIV in resource-limited settings. Manufact Serv Oper Manage 2015;17(4):554–70.

[28] Braithwaite RS, Kozal MJ, Chang CC, et al. Adherence, virological and immunological outcomes for HIV-infected veterans starting combination antiretroviral therapies. AIDS 2007;21:1579–89.

[29] Braithwaite RS, Tsevat J. Is antiretroviral therapy cost-effective in South Africa? PLoS Med 2006;3:e60.

[30] Shelton JD, Cohen M, Barnhart M, et al. Is antiretroviral therapy modifying the HIV epidemic? Lancet 2010;376:1824–5.