HIV Treatment in Sub-Saharan Africa: Now Comes the Hard Part

Amin Khademi, PhD[1]

Denis Saure, PhD[2]

Andrew Schaefer, PhD[3,4]

Kimberly Nucifora, MS[5]

R Scott Braithwaite, MD, MS[5]

Mark S. Roberts, MD, MPP[3,4,6]

[1]Department of Industrial Engineering, Clemson University

[2]Department of Industrial Engineering, University of Chile

[3]Department of Industrial Engineering, University of Pittsburgh

[4]Department of Medicine, University of Pittsburgh

[5]Section of Value and Comparative Effectiveness, NYU School of Medicine

[6]Department of Health Policy and Management, University of Pittsburgh Graduate School of Public Health

Corresponding author:

Mark. S. Roberts

Professor and Chair, Department of Health Policy and Management

A600 Crabtree Hall, University of Pittsburgh, Pittsburgh, PA, 15261

Email: mroberts@pitt.edu

Phone: +1-412-383-7049

Fax: +1-412-624-3146

ABSTRACT

Background: Many countries in Africa are unable to fully treat their HIV-infected population, especially as treatment recommendations expand. International efforts have increased resources available and improved coverage. Patients survive longer with treatment, but are less likely to transmit the disease. The combined impact of these conflicting factors affects the size of the HIV-infected population, and the number of people who will need treatment over time may increase, straining the resources available for treatment.

Methods: We extend a validated simulation model of HIV disease and treatment in Sub-Saharan Africa to represent a dynamic population that includes uninfected and HIV-infected individuals. The model considers the long-term effect of treatment, incorporating both increased life expectancy for treated individuals as well as the impact on transmission through decreased viral load. We estimate the additional resources required to treat the HIV-infected populations in Sub-Saharan Africa under different treatment scenarios, and we propose a new definition of treatment coverage that reflects the dynamic nature of an epidemic.

Findings: In a hypothetical population of 600,000 people of which 7·5% are infected, and eligible for treatment with a CD4 count of <=500 cells/mm^3, assuming a WHO-defined coverage rate of 50% of eligible people, and treating these patients with a single treatment regimen, the HIV population continues to rise over 10 years by 8,572 (a 19·5% increase). Under a test and treat strategy where everyone who is infected is immediately treated, the HIV-infected population at 10 years will remain essentially constant. Prevalence-based estimates of coverage underestimate the resources required to fully treat the current epidemic.

Interpretation: Treatment with antiretroviral therapy increases HIV life expectancy but decreases the likelihood of transmission. Under current treatment effectiveness, the development of resistance and the lower level of transmission for a longer period of time balance out, and even at full coverage, new

infections persist and the HIV-infected population remains large. Increasing coverage increases the size of the HIV-infected population needing treatment and exacerbates the coverage gap. The concept of coverage is dynamic, and a cumulative incidence-based definition of coverage provides a more accurate representation of treatment success.

Funding:

Introduction:

The development of highly active antiretroviral therapy (ART) has revolutionized the treatment of HIV disease, producing dramatic increases in survival.[1-3] However, the benefits of these therapies 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 this problem and increase the resources required to fully treat a population.

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 HIV disease. A measure of the success of these efforts is the increase in "coverage"; the proportion of HIV-infected population 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 a majority of persons in Sub-Saharan Africa live in countries with between 40% and 60% coverage.[4] Although coverage will decline if the current recommendations for treating at CD4<=500 cells/mm^3 are used to determine treatment eligible population.[6]

Expanding coverage has potentially conflicting impacts on the epidemic. One direct consequence of expanded access to treatment is a growth in the size of the HIV-infected population as patients on therapy live substantially longer than patients without therapy.[7-10] Expanding treatment will increase the size of the HIV-infected population who qualify for treatment, and therefore increase the resources required to fully treat that population. In terms of impact on the epidemic, patients on treatment have a lower viral load and are less likely to transmit the disease. However, patients on treatment live much longer and

consequently have more time to transmit the disease. Finally, treatment can induce mutations, which may decrease the effectiveness of treatment, and increase the patient's VL. The purpose of this paper is to estimate the impact of these conflicting effects on the resulting size of the HIV-infected population who qualify for treatment, and the resources necessary to "cover" that resultant population. In addition, we propose a more comprehensive definition of "coverage" than the current WHO measure.

Methods:

We adapted a validated individual simulation model of HIV calibrated with data from Sub-Saharan Africa[11] to represent a population of HIV-infected patients under various assumptions regarding the number of doses of ART available. The population is dynamic in that new infections are added from a susceptible population. Each susceptible individual may become infected in a period according to a probability which is calculated based on the partnership pattern and the VL of the partner.

Because our purpose is to evaluate the effect of treatment coverage on eventual HIV-infected population size, for simplicity we assume that only a single ART regimen is available and analyze the relationship between the resources available for HIV treatment and the resulting size of the HIV-infected population. We relax this assumption in a sensitivity analysis.

Definitions of coverage

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 HIV-infected patients will acquire HIV disease, become ill and die without receiving ART. The current UNAIDS definition of coverage does not account for this phenomenon. As defined in the 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 disease.[4] Therefore, we define two "coverage" concepts: (i) *prevalence-based coverage*, consistent with the UNAIDS definition, which refers to the number of people being treated divided by the eligible HIV-

infected population at a given time; and (ii) *cumulative incidence-based coverage*, which is defined as the portion of patients who received treatment at some point during their life. Prevalence-based coverage does not account for expected growth in the HIV-infected population due to longer survival, whereas cumulative incidence-based coverage does. We illustrate the difference in these definitions through a simple example: Assume there are only two HIV-infected individuals, that untreated patients live exactly two years; that treated patients live exactly 14 years; that there are sufficient resources available to treat only one individual at a time, and assume a new case develops every two years. Figure 1 illustrates this scenario: at any given time, prevalence-based coverage is 50% as one half of 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 (which we term prevalence-based coverage), is a "snap shot" measure, and overestimates the number of HIV-infected individuals who receive treatment, as at most levels of coverage, many eligible HIV-infected patients will acquire HIV, live through their disease and die without receiving ART.

Overview of Individual HIV Model

The HIV simulation model is based on an individual microsimulation that replicates the probabilistic progression of the disease in a patient over time. The model tracks the health of a patient on a daily basis: viral load 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.[7,8,11-15] The simulation model computes HIV-mortality rates based on health and age of a patient, and non HIV-mortality rates based on age and the drugs' toxicity and side effects.

The model has demonstrated the ability to predict time to treatment failure,[7] the development of resistant mutations,[13,14] survival, and change in CD4 count and VL over time,[7,15] 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 patients in Sub-Saharan Africa.[11] We extended this version of the model to conduct our dynamic simulations.

Overview of Population HIV Model

We extend the individual HIV model described above by running multiple unique, simultaneous copies of the model to represent a cohort of HIV-infected patients and to simulate the effect 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/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.[16] 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.[17,18] The probability that a susceptible individual establishes a partnership with an infected individual equals the proportion of infected individuals in the entire population. We randomly choose an infected individual from the infected population and calculate the probability of disease transmission based on the VL and presence or absence of antiretroviral therapy of the selected individual.[19] Note that this is the stochastic version of nonlinear deterministic models used in the literature.

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 (ten years). Infected individuals whose CD4 count drops below a specific CD4 count are considered eligible for treatment. When estimating the differences in coverage, we use a CD4 count <=350 cells/mm^3, as that is the treatment threshold in effect when the current coverage data from WHO is reported. However, when estimating the future impacts on the size of the epidemic, we use a threshold of CD4<=500 cells/mm^3, to reflect the current treatment recommendations. We also assume the average CD4 count of a susceptible

individual at the time of infection using a normal distribution with an average 1000 cells/mm^3 and standard deviation of 111 cells/mm^3, truncated at 500 and 1500 consistent with the literature.[20]

The model therefore incorporates the conflicting effects of treatment on the HIV epidemic. Patients who are on treatment have a lower VL and consequently are less likely to transmit the disease, but live much longer and consequently have more time to transmit the disease. The model includes treatment failure in which patients develop resistant mutations, which increases their VL making them more likely to transmit the disease. We identify the effect of treatment on the population size, and estimate the resource required (in the model this is represented by the number of ART doses) to treat the population.

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

We investigate the implications of a test and treat policy on the population and the amount of resources that are needed to implement it. We simulate the system starting from a population with different coverage levels and estimate the characteristics and size of the population over 10 years. We define our base case to be similar to the situation depicted in Figure 1: we assume an initial 50% coverage of eligible patients, and increase 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 taken, it would be 50%. We test several scenarios, across various assumptions about the amount of ART available for treatment, and also estimate the effect of a "perfect" antiretroviral agent on the epidemic, where we define "perfect" as reducing the probability of transmission to zero for the duration of taking the medication.

The underlying progression model has been previously validated and multiple sensitivity analyses have been reported,[7,8,13,22-24] 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, and the availability of more than one treatment regimen, where we assumed that second line therapy was identical in effectiveness to first line therapy (Table 1).

Simulations

We created an initial population of 43,497 infected patients 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 calculate both coverage measures and the size of the overall and infected population yearly for ten years. To provide stable estimates, we repeat each simulation 30 times and report the average of the results. To illustrate the distinction between coverage measures, we ran similar simulations at different baseline 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 patients found to be HIV positive. We also tested a hypothetical strategy where ART is assumed to be 100% effective in reducing the probability of transmission to zero.

Results:

In our base case analysis, where we assume 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 ten year time horizon (Figure 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. This level of treatment has almost no effect on the number of new infections, 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 <= 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 test and treat scenario where we treat a patient upon infection. The number of new infections significantly declines but the number of infected individuals remains roughly constant.

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 underestimates the portion of an HIV-infected population who are treated at some time during their 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 underestimates the cumulative incidence-based measure by the most. The problem is again illustrated by a specific example. In our base case model there were initially 43,497 patients with HIV infection, of which 18,806 had CD4 counts below 500 cells/mm^3 making them eligible for treatment. A 50% coverage rate implies 9403 patients were being treated. After ten years, the number of people who would need to be treated just to maintain 50% coverage would rise to 12,432 patients: to move to a test and treat strategy where every infected individual was treated would require 52,068 patients be treated after ten years, fully 7·6 times the number of people currently being treated. This implies that the resources required to fully cover the infected population in Sub-Saharan Africa are substantially larger than the resources already dedicated to this effort.

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 viral load did. If the virus is much less transmissible than estimated[19] the number of infected individuals at the end of ten 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 population. As expected adding a second line of 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%), data not shown.

Discussion:

Coverage is not static: it varies through time as treatment impacts the stable population size of HIV-infected individuals. The traditional cross-sectional definition of coverage used by the WHO and UNAIDS, which we have termed "prevalence-based coverage" fails to capture the dynamic nature of the epidemic inherent in the substantially longer lives of those on treatment. Consequently, it underestimates the resources required to fully cover a population.

Our analysis indicates that increasing coverage levels in Sub-Saharan Africa (currently about 50%, on average) is likely to require substantially more resources than implied by current prevalence-based coverage levels. Doubling the current resources available will come nowhere near to fully treating the epidemic. We propose that the concept of cumulative incidence-based coverage, the portion of HIV-infected patients who received treatment at some point in their lifetime, is a more accurate and useful measure of the progress made in HIV care.

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.[11] It accurately replicates the progression of the disease in each treatment scenario, and reports prevalence-based and cumulative incidence-based coverage, and the number of doses of ART required to treat a population of a given size. It incorporates both effects of treatment on the potential for transmission: the decrease in VL decreases the likelihood of transmission, but the increased lifespan, and potential for antiretroviral resistance acquisition, increasing the time of potential spread. Our analysis considers only a single ARV regimen, ignoring the effect of the second and third treatment regimens. However, including multiple ART regimens did not change the basic result, and would compound the resource problem: second and third line therapy is much more expensive than first line,[25] and patients in the simulation live

even longer in the presence of multiple treatment options. Therefore, our analysis likely underestimates the gap in resources required to fully cover a population.

We ignored many capabilities of the underlying HIV model in these simulations, and did not fully represent all of the subtleties of HIV care. For example, a portion of patients will discontinue their HIV medication because of side effects and toxicity: we assumed all treated individuals in the model remained on treatment until death. We re-estimated the results of the model allowing adherence to fall to levels seen in Sub-Saharan Africa (data not shown) and 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 assume that a person is detected essentially immediately upon being infected. Similarly, in the scenarios in which eligibility is used to determine treatment (e.g. a CD4 count of less than 500 cells/mm^3), the model assumes that the eligibility is known immediately upon that patient passing the threshold. While this is certainly an unrealistic assumption, we use it 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 produce are underestimates of how difficult the coverage problem is.

The increase in treatment of HIV disease is Sub-Saharan Africa has been a massive international effort, requiring the cooperation and dedication of individual health ministries in Africa, multiple charitable foundations, the WHO, many developed nations and the pharmaceutical industry. The results of this research indicate that current published coverage data suggesting that the HIV epidemic in Africa is nearly half-way to being fully treated does not take into account the dynamic effects of coverage on the size of the infected population. In terms of resources required to fully treat the epidemic, unfortunately now comes the hard part.

References:

1. Freedberg KA, Paltiel AD. Cost effectiveness of prophylaxis for opportunistic infections in AIDS. An overview and methodological discussion. *PharmacoEconomics.* Aug 1998;14(2):165-174.

2. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *The New England journal of medicine.* Mar 15 2001;344(11):824-831.

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.* Nov 4 1998;280(17):1497-1503.

4. UNAIDS. *Global Report. UNAIDDS report on the global AIDS epidemcic, 2012*: Joint United Nations Program on HIV/AIDS (UNAIDS);2010.

5. WHO. *Progress on global access to HIV antiretroviral therapy: a report on "3 by 5" and beyond*: Worl Health Organization;2006.

6. WHO. 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. 2014; http://www.who.int/hiv/pub/guidelines/arv2013/art/statartadolescents/en/. Accessed 05/22/2014.

7. Braithwaite RS, Justice AC, Chang CC, et al. Estimating the proportion of patients infected with HIV who will die of comorbid diseases. The American journal of medicine. Aug 2005;118(8):890-898.

8. Braithwaite RS, Roberts MS, Chang CC, et al. Influence of alternative thresholds for initiating HIV treatment on quality-adjusted life expectancy: a decision model. *Annals of internal medicine.* Feb 5 2008;148(3):178-185.

9. Chigwedere P, Seage GR, 3rd, Gruskin S, Lee TH, Essex M. Estimating the lost benefits of antiretroviral drug use in South Africa. *J Acquir Immune Defic Syndr.* Dec 1 2008;49(4):410-415.

10. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *The New England journal of medicine.* Apr 30 2009;360(18):1815-1826.

11. 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.

12. 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.* Mar 15 2009;48(6):822-826.

13. Braithwaite RS, Shechter S, Chang CC, Schaefer A, Roberts MS. Estimating the rate of accumulating drug resistance mutations in the HIV genome. *Value in Health.* May-Jun 2007;10(3):204-213.

14. Braithwaite RS, Shechter S, Roberts MS, et al. Explaining variability in the relationship between antiretroviral adherence and HIV mutation accumulation. *The Journal of antimicrobial chemotherapy.* Nov 2006;58(5):1036-1043.

15. Roberts MS, Nucifora KA, Braithwaite RS. Using mechanistic models to simulate comparative effectiveness trials of therapy and to estimate long-term outcomes in HIV care. *Medical care.* Jun;48(6 Suppl):S90-95.

16. Life expectancy at birth, total (years). 2011. http://data.worldbank.org/indicator/SP.DYN.LE00.IN/countries/ZF?display=graph. Accessed 1/13/2014.

17. Garnett GP, Anderson RM. Sexually transmitted diseases and sexual behavior: insights from mathematical models. *The Journal of infectious diseases.* Oct 1996;174 Suppl 2:S150-161.

18. Garnett GP, Hughes JP, Anderson RM, et al. Sexual mixing patterns of patients attending sexually transmitted diseases clinics. *Sex Transm Dis.* May-Jun 1996;23(3):248-257.

19. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS (London, England).* Jul 17 2009;23(11):1397-1404.

20. Reichert T, DeBruyere M, Deneys V, et al. Lymphocyte subset reference ranges in adult Caucasians. *Clin Immunol Immunopathol.* Aug 1991;60(2):190-208.

21. WHO. Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach. . 2010; http://www.who.int/hiv/pub/arv/adult2010/en/index.html. Accessed Accessed August 2010.

22. Braithwaite RS, Conigliaro J, Roberts MS, et al. Estimating the impact of alcohol consumption on survival for HIV+ individuals. *AIDS care.* Apr 2007;19(4):459-466.

23. Braithwaite RS, Kozal MJ, Chang CC, et al. Adherence, virological and immunological outcomes for HIV-infected veterans starting combination antiretroviral therapies. *AIDS (London, England).* Jul 31 2007;21(12):1579-1589.

24. Braithwaite RS, Tsevat J. Is antiretroviral therapy cost-effective in South Africa? *PLoS medicine.* Jan 2006;3(1):e60.

25. Shelton JD, Cohen M, Barnhart M, Hallett T. Is antiretroviral therapy modifying the HIV epidemic? *Lancet.* Nov 27 2010;376(9755):1824-1825; author reply 1825.

Figure legends:

Figure 1: Prevalence-based and cumulative incidence-based Coverage. As an illustrative, simple example, assume that there is only one dose of antiretroviral therapy, that patients without treatment live two years, those on treatment live 14 years, and that there is a new case of HIV about once every two years. During the lifetime of the treated individual seven other patients develop HIV disease and die without treatment. Overall, one of eight patients were 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)

Figure 2 (HIV-infected population): Number of patients living with HIV, eligible for treatment and being treated under different treatment and coverage scenarios. In the base case (Panel A), assuming the ability to treat of 50% of eligible patients, after ten years the number of HIV-infected patients continues to rise, and there is almost no impact on the number of new cases. By increasing coverage to 100% (any with a CD4 count of <=500/mm^3 is treated), the incidence initially declines, but the number of patient living with HIV increases by nearly 8,700 (a 20% increase) as HIV patients 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, where any HIV positive patient is treated (panel C) still results in slowing increasing numbers of patients 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 ten years due to decreased transmission.

Figure 3: Cumulative incidence-based coverage compared to prevalence-based coverage. 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 degree 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 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 percent of people living at that level of prevalence-based coverage in Sub-Saharan Africa. The majority of people are living in countries at or below 50% prevalence-based coverage, which highly underestimate the portion of the population who receives treatment at some time during their life. For this graph, eligibility is defined as treatment if CD4 count is <= 350 cells/mm^3, as that is the definition used for the WHO coverage rates displayed.

Figure 1.

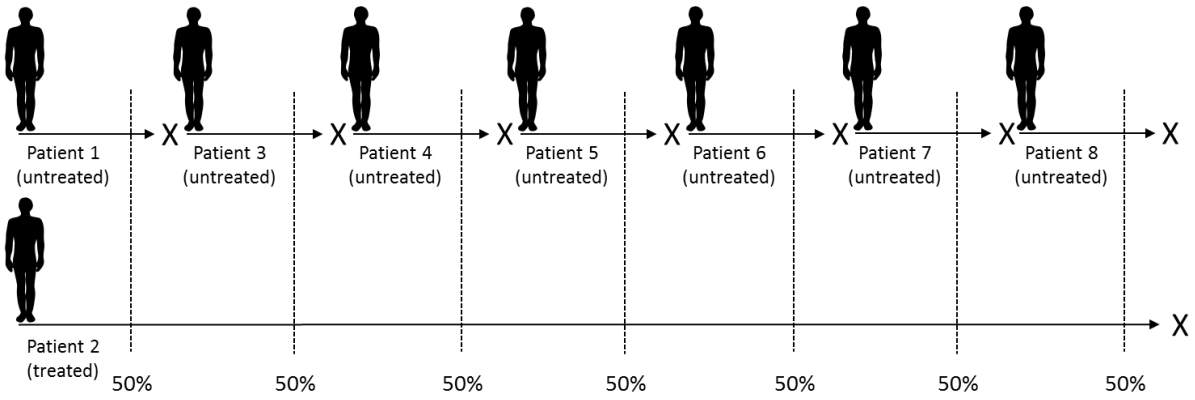
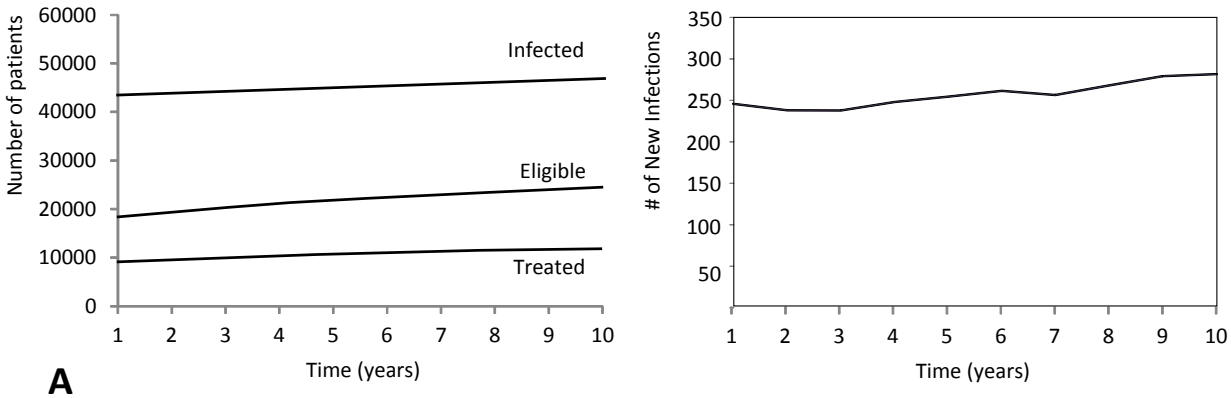
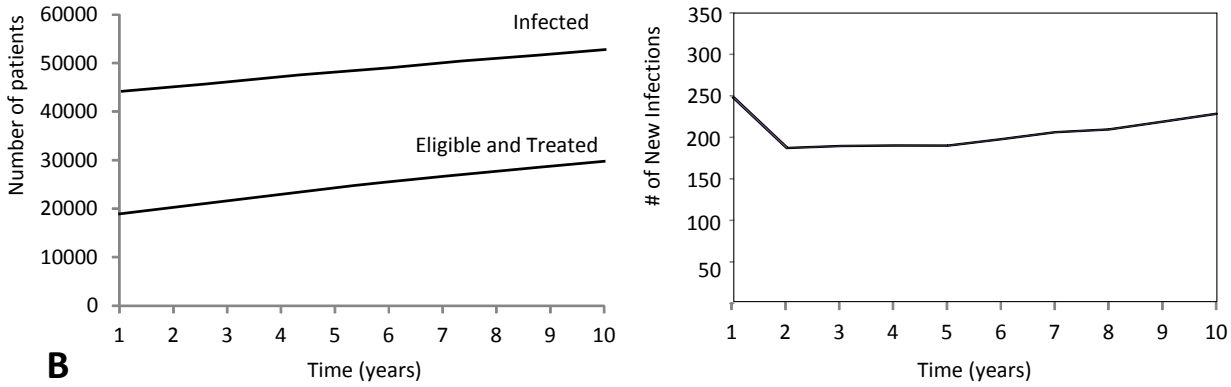

Patient 1
(untreated)
Patient 3
(untreated)
Patient 4
(untreated)
Patient 5
(untreated)
Patient 6
(untreated)
Patient 7
(untreated)
Patient 8
(untreated)
Patient 2
(treated)
50%
50%
50%
50%
50%
50%
50%

Figure 2.



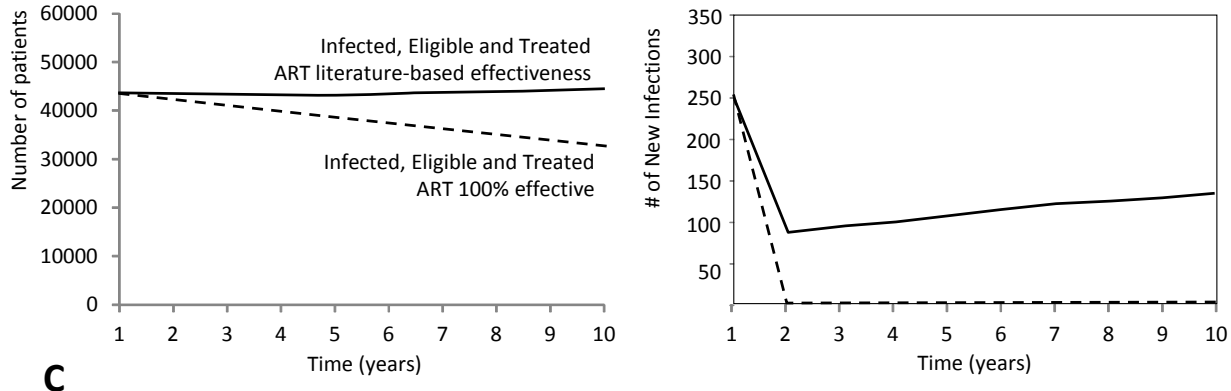
A

50% Coverage – treat @ CD4 < 500 cells/ml



B

100% Coverage – treat @ CD4 < 500 cells/ml



C

100% Coverage – test and treat (no resource constraint)

Figure 3.

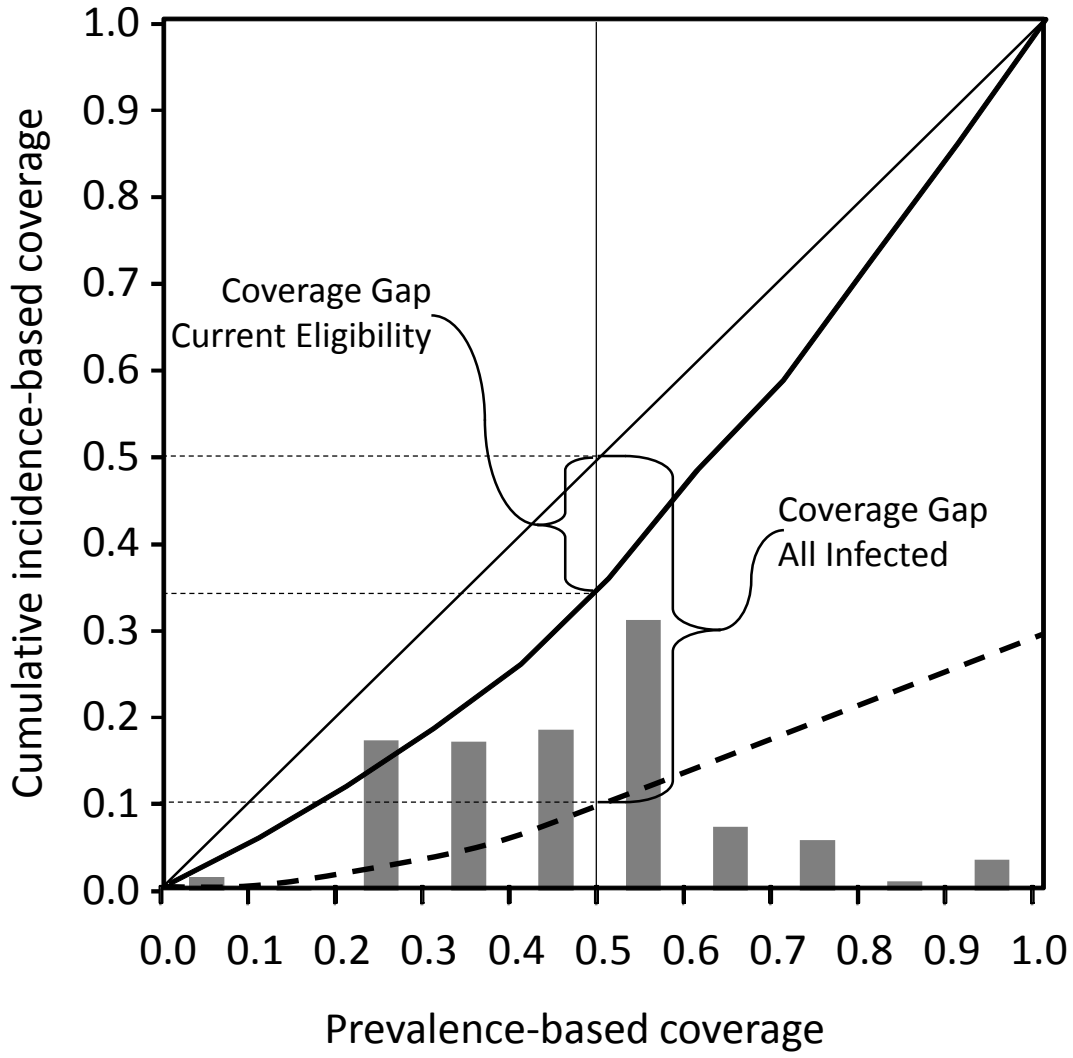

Cumulative incidence-based coverage
Prevalence-based coverage
Coverage Gap
Current Eligibility
Coverage Gap
All Infected
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

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
≥50,000	3.87	9.03	21.09

§ Infection rates are based on 95% confidence intervals from reference 19.