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Performance of a Mathematical Model to Forecast Lives Saved from HIV Treatment Expansion in Resource-Limited Settings

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Abstract

Background—International guidelines recommend HIV treatment expansion in resource-limited settings, but funding availability is uncertain. We evaluated performance of a model that forecasts lives saved through continued HIV treatment expansion in Haiti.

Methods—We developed a computer-based, mathematical model of HIV disease and used incidence density analysis of patient-level Haitian data to derive model parameters for HIV disease progression. We assessed internal validity of model predictions and internally calibrated model inputs when model predictions did not fit the patient-level data. We then derived uncertain model inputs related to diagnosis and linkage to care, pre-treatment retention, and enrollment on HIV treatment through an external calibration process that selected input values by comparing model predictions to Haitian population-level data. Model performance was measured by fit to event-free survival (patient-level) and number receiving HIV treatment over time (population-level).

Results—For a cohort of newly HIV-infected individuals with no access to HIV treatment, the model predicts median AIDS-free survival of 9.0 years pre-calibration and 6.6 years post-calibration versus 5.8 years (95% CI 5.1, 7.0) from the patient-level data. After internal validation and calibration, 16 of 17 event-free survival measures (94%) had a mean percentage deviation between model predictions and the empiric data of <6%. After external calibration, the percentage deviation between model predictions and population-level data on the number on HIV treatment was <1% over time.

Conclusions—Validation and calibration resulted in a good-fitting model appropriate for health policy decision making. Using local data in a policy model-building process is feasible in resource-limited settings.

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Keywords

HIV/AIDS; antiretroviral therapy; mortality; resource-limited settings; simulation; model performance; calibration; validation

BACKGROUND

Antiretroviral therapy (ART) for the treatment of HIV has increased survival,¹ transforming HIV disease into a manageable chronic disease. In resource-limited settings, substantial donor disbursements and decreasing ART drug prices have facilitated large increases in the number initiating ART.² Increasing demand for ART against a backdrop of funding gaps and capacity constraints suggest efficient use of existing resources and more effective programmatic planning is required.^{2–8}

Clinical and policy decisions at all points along the continuum of HIV treatment and care — ranging from implementing effective interventions to improve case identification to using efficient strategies to improve patient retention on ART — have an impact on country-level planning efforts. Some empirical evidence of the effectiveness of interventions applied along this continuum exists, but trial and observational data are limited by short length of follow-up, inability to identify all of the clinical and epidemiologic factors that may influence outcomes, and logistical and ethical barriers to comparing all possible combinations of strategies.⁹

Mathematical policy models can be used to address these limitations by synthesizing available data and forecasting the course of disease in individual patients or populations after implementing different policies. Mathematical models increasingly inform the HIV clinical and policy debate,¹⁰ but complex HIV disease models may be less accessible to decision makers, especially in resource-poor settings.¹¹ Systematic and transparent assessment of model structure and performance can improve acceptance of model predictions by the intended consumers of model results.^{11,12}

Motivated by a need to forecast demand for HIV treatment in Haiti,¹³ we developed a country-specific mathematical model of the natural history and treatment of HIV disease. Designed for clinical and policy decision makers, the multi-cohort state-transition model uses local data and has a simplified structure reflecting key points of engagement along the continuum of HIV clinical care. Distinct from compartmental models that can explicitly address the dynamic prevention effects of ART,^{6,7} this model leverages locally available data to address broader programmatic questions about the impact of clinical care engagement on population-level survival and other clinical care targets (e.g., number tested and linked to care, number lost to follow-up, numbers receiving ART by regimen, and ART coverage). Both the model's relatively simple structure and implementation in widely available Microsoft Excel (Redmond, Washington, USA) are by design. These features facilitate transparency and accessibility of policy results to consumers (e.g., implementing partners of key funders, country-level stakeholders representing major donors, technical staff at the Ministry of Health) and future trained users (e.g., local representatives of multilateral agencies such as Global Fund) of the model.

In this paper, we describe a practical approach to developing a mathematical model designed for clinical and policy audiences in a resource-limited setting. Using a reproducible validation and calibration process, we assess the model's performance against Haitian patient-level and population-level data.

METHODS

Analytic overview

We developed and assessed the performance of a multi-cohort, state-transition model of HIV disease in Haiti using local data for model input parameters. An underlying motivation in developing the model was to maintain transparency and accessibility for policy makers. To that end, we adopted a simplified model structure, implemented the model in widely available Microsoft Excel (Redmond, Washington, USA), used reproducible methods to derive model input parameters, and assessed model performance against available local patient-level and population-level data.

The process involved several iterative steps (Figure 1). First, patient-level data from Haitian observational cohorts and a randomized trial of early versus delayed HIV treatment were used to develop model health states.^{14–20} Incidence density analysis was conducted to derive model transitions — in the form of probabilities — between health states for treated and untreated disease progression.^{13,21–23} Second, we compared model predictions of untreated and treated HIV disease progression to the patient-level data using multiple measures of fit (i.e., internal validation process).^{24–27} Third, when model predictions did not exhibit a good fit due to model structure simplifications, we applied an algorithm to improve goodness of fit between predicted and observed outcomes (i.e., internal calibration process).^{24,25} Finally, to derive unknown model inputs for rates of diagnosis and linkage to care, pre-treatment loss to follow-up, and ART enrollment, we simultaneously varied multiple model parameters across multiple simulated cohorts and selected model inputs based on the fit of model predictions to population-level data from Haiti (i.e., external calibration process).^{24,27} Measures of model performance were determined by model fit to patient-level data on event-free survival and to population-level data on the number on ART over time.

Model

The multi-cohort, state-transition model is a deterministic model consisting of 12 main health states defined by disease progression and engagement with clinical care (Figure 2). Hypothetical cohorts progress through three mutually exclusive stages of untreated disease: Asymptomatic disease (corresponding to CD4 count >350 cells/ μL), Intermediate HIV disease (CD4 count 200–350 cells/ μL), and AIDS (CD4 count <200 cells/ μL). Within each annual model cycle, fractions of each cohort can remain out of care, enter pre-treatment care, initiate ART, become lost, or die. Death, an absorbing state, may occur from AIDS- or non-AIDS-related causes; mortality risk varies based on both disease stage and clinical engagement. Additional model details are available in the supplementary content published elsewhere (see online supplementary content).¹³

We evaluated the model's performance for hypothetical HIV-infected cohorts during the antiretroviral scale-up period in Haiti, between 2004 and 2009. A hypothetical prevalent cohort (2004) was assigned to different health states, and newly HIV-infected cohorts successively entered the model in each subsequent year (2005–2009). Transition probabilities govern the movement of fractions of each cohort among health states. Model outcomes are estimated for each year between 2004 and 2009 by summing across cohorts. Main outcomes include the number of individuals on ART, total number of adult individuals living with HIV, and ART coverage, defined as the fraction of the treatment-eligible HIV-infected population that receives ART.

The model makes several assumptions that reflect current clinical practice in Haiti and in other resource-limited settings. A maximum of two sequential ART regimens are assumed available and treatment monitoring consists of semiannual CD4 tests and quarterly clinic visits.⁵ ART initiation earlier in the course of disease (e.g., at CD4 count 200 – 350 cells/ μ L) is associated with less rapid disease progression and improved health outcomes compared to ART initiation later in the course of disease (e.g., CD4 count <200 cells/ μ L).¹⁸ Detection of ART failure and switching to a second-line regimen occurs as a result of clinical events and CD4 count monitoring of treatment response.⁵ Individuals in care but not receiving ART have decreased mortality risk and less rapid disease progression compared to individuals not in care, including those who are lost from care.²⁸ Finally, individuals lost from care experience natural history disease progression, including death, and are not eligible for re-entry into clinical care. This simplifying assumption was chosen to reflect the high risk of mortality documented among patients lost from ART programs in resource-limited settings,²⁹ as well as lack of data on reentry into care. In the longer term, this assumption may result in a conservative estimate of the number on ART, while overestimating mortality. In the relative short-term, similar to the current model's 10-year analytic time horizon, this assumption may not have considerable effect. However, the model's flexible structure allows for revisiting this assumption as data on re-entry into care become available.

Internal validation and calibration to patient-level data

In a first stage of model development, we internally validated the model by comparing model predictions to outcomes from the patient-level data used to parameterize the model.¹³ All patient-level data were collected by the clinic of the Haitian Study Group for Kaposi's Sarcoma and Opportunistic Infections (GHESKIO), which has provided free HIV counseling, testing, treatment, and other services to the Port-au-Prince, Haiti, population since 1983. Patient-level data came from three Haitian observational cohorts and a randomized trial of early versus delayed ART conducted in Haiti.

The patient-level data were used to derive model input parameters for untreated and treated disease progression (Table 1, Panel A).^{14–20} For disease progression of HIV-infected adults in care but not receiving ART, we used prospective longitudinal cohort data on 476 patients, including 41 seroconverters, recruited between September 1985 and September 1998.^{14,15,17} Study subjects were evaluated by a physician quarterly or upon becoming symptomatic, were staged at each visit according to the U.S. Centers for Disease Control and Prevention Classification System,^{30,31} and received biannual CD4 cell counts beginning in 1993. Mean

age was 32.7 years (SD 9.0 years) and 38.2% of the cohort was male. Median CD4 count at upon recruitment was 650 cells/ μ L (interquartile range (IQR) 380 cells/ μ L, 725 cells/ μ L), with median follow-up 27.7 months (IQR 14.0, 50.6). Median time to symptomatic HIV disease (CDC categories B or C) was 3.8 years (95% confidence interval (CI) 3.3 – 4.5 years), while median time to AIDS (CDC category C) was 5.1 years (95% CI 4.5 – 6.0 years). To derive model inputs for treated disease progression among HIV-infected individuals initiating ART with AIDS, we used prospective longitudinal cohort data collected by GHESKIO on 910 HIV-infected adults and adolescents between March 2003 and May 2009.^{16,19,20} Study subjects were seen monthly, CD4 counts determined every 6 months, and ART eligibility and treatment regimen failure and switching determined according to World Health Organization guidelines.⁵ Of the 910 patients, 504 (55.3%) were female and had a median CD4 count of 131 cells/ μ L (IQR 55, 211), with 472 (51.9%) having a history of an AIDS-defining illness. At 60 months, 208 of the 910 patients (23%) had died and 70 (8%) were lost to follow-up. Estimates related to 1st-line ART clinical or immunologic failure and subsequent switching to 2nd-line ART came from 3,126 patients initiating ART at GHESKIO between March 2003 and July 2008.²⁰ Among the full cohort, 482 (15%) met WHO criteria for clinical or immunologic failure, with 195 (41%) of those meeting failure criteria switching to 2nd-line ART. For individuals initiating ART with intermediate HIV, data came from 408 patients in the early treatment group of a randomized trial of early versus delayed ART conducted at GHESKIO. Subjects were seen by a clinician monthly, CD4 counts repeated biannually, and 1st-line ART consisting of lamivudine, zidovudine, and efavirenz administered.¹⁸ Of the 816 subjects for a median of 21 months (range 1 – 44 months), 470 (58%) were women and median CD4 count at enrollment was 281 cells/ μ L. Of the 408 receiving delayed treatment, 160 (39%) met criteria for ART initiation. Kaplan-Meier analysis showed 98% (early treatment group) versus 93% (delayed) alive at 36 months. The unadjusted hazard ratio for risk death was 4.0 (95% CI 1.6 – 9.8) for delayed compared to early treatment.

Model input parameters were derived from the patient-level data by using incidence density analysis to estimate event rates; analyses were conducted with Stata/MP 12 (College Station, TX). Assuming constant event rates and an exponential distribution, we converted the event rates to transition probabilities for use in the model. Details of this process have been described elsewhere.¹³

To internally validate the model, we compared Kaplan-Meier event-free survival estimates from the patient-level data to model predictions for 19 model pathways. Pathways were defined as transitions between health states and could consist of one or more probabilistic transitions in order to reach a health state of interest. To examine goodness of fit between model predictions and the patient-level data, we compared the fraction remaining event-free over 5- and/or 10-year time horizons. We used an acceptance window approach to visually compare event-free survival predicted by the model to event-free survival estimated from the patient-level data; acceptance windows were defined by the 95% confidence intervals of the patient-level data.³² We also calculated the mean of the percentage deviation between the model output and the target data at each available time point.³³

We then developed an internal calibration algorithm to improve the fit of relevant model endpoints to the patient-level data. Internal calibration was performed when, due to model structural simplifications, model predictions for a particular pathway were outside the acceptance window defined by the 95% confidence intervals and did not visually approximate event-free survival estimated from the patient-level data; internal calibration was also performed if mean percentage deviation between model predictions and the empiric data exceeded 15%. For each parameter pathway requiring calibration, we defined clinically plausible ranges over which to evaluate parameter values. Manual adjustment of the model inputs in absolute increments of 0.05 were then made over this range, first singly and then in combination. We evaluated each single- and multi-parameter pathway in terms of event-free survival relevant to the particular pathway. For example, for the multi-parameter pathway Asymptomatic, In Care to AIDS, In Care, we used the model to predict the fraction event-free (i.e., not having experienced AIDS) over time of a single cohort entering the model in the Asymptomatic, In Care health state, passing through the Intermediate, In Care health state, and transitioning to the AIDS, In Care health state. Similar to the internal validation process, we then compared model predictions of event-free survival to event-free survival estimated from the patient-level data. We selected final inputs using an acceptance window approach in which we visually compared event-free survival curves predicted by the model to those derived from the patient-level data. As in the internal validation process, the acceptance window was defined by the 95% confidence intervals of the patient-level data.³² We confirmed our results by evaluating the mean percentage deviation between predicted event-free survival and the patient-level data using the thresholds described above.

External calibration to population-level data

In a subsequent stage of model development, we derived unknown model inputs for rates of diagnosis and linkage to care, pre-treatment loss to follow-up, and ART enrollment through an external calibration process. We simultaneously varied **25** model parameters across simulated cohorts and selected model inputs based on the fit of model predictions to population-level Haitian data not used to parameterize the model. The primary external calibration target was the number receiving ART annually between 2005 and 2009³⁴ (Table 1, Panel B), which was used to confirm that model projections corresponded with country-level reports on the number receiving ART in Haiti over the calibration time horizon.

External calibration involved a multi-stage, iterative process. First, from country-level reports and demographic and health survey data, we assigned values to the prevalent cohort for the number on ART, total number HIV-infected, and fraction not in treatment or care (Table 1, Panel A).^{34,35} Second, we identified the uncertain model parameters and made assumptions about the relationships among these parameters. For example, we assumed the annual probability of being diagnosed and linked to care was greater for HIV-infected individuals with AIDS than for individuals with Intermediate HIV disease; we assumed the inverse with regard to pre-ART loss from care. Third, we assigned ranges over which to sample model input values for each parameter. For example, between 2005 and 2009, the number of newly infected individuals annually varied within the upper and lower bounds estimated by the World Health Organization and the Joint United Nations Programme on

HIV/AIDS (UNAIDS).² If data were not available from the literature, clinically plausible ranges were identified and evaluated iteratively during the calibration process.

Values for uncertain model inputs were randomly selected from a uniform distribution over the identified range. Simultaneous selection of multiple input values generated unique parameter sets. Model outcomes using each unique parameter set were then estimated over a 6-year time horizon. This process was repeated for 150,000 unique parameter sets and automated in Excel using simple Visual Basic code (see Appendix). We defined good-fitting sets as those sets where the predicted number on ART did not deviate more than 15% annually from observed data. Among these good-fitting sets, we identified the top sets of input values that minimized the percentage deviation between model predictions and the empiric data of the number on ART between 2004 and 2009.^{33,34} We explored alternative thresholds for the number of good-fitting sets by evaluating the top 5, top 10, top 50, and top 75 sets minimizing the percentage deviation. We also varied the threshold for a good-fitting set between 5% and 30%. For further model verification, we corroborated model results by performing visual assessment of trend for secondary outcomes compared to results from another model, including total number of individuals with HIV and ART coverage for CD4 count <350 cells/ μ L.³⁴

The multi-stage, external calibration process involved multiple iterations. When model predictions did not correspond with visual trends of both primary and secondary outcomes, we re-evaluated our assumptions or allowed some model inputs to vary over time in order to improve model fit. For example, we allowed the probability of ART initiation to vary annually throughout the external calibration process; the probability of diagnosis and linkage to care were varied over longer intervals, rather than over constant over the calibration period, to improve model fit.

RESULTS

Model fit to patient-level data

We evaluated the model's internal validity by comparing model predictions to the empiric patient-level data for 19 model pathways representing both untreated and treated disease progression. Pre-calibration, visual assessment of trend was confirmed in 12/13 pathways involving a single transition between health states and 4/6 pathways involving more than one transition among health states. Among the 16 pathways that visually approximated the empiric data, the fraction of model predictions outside the 95% confidence intervals of the empiric data ranged from 0.0 (10 of 16, or 63% of parameter pathways assessed) to 0.29 (1 of 16, or 6% of parameter pathways assessed).

For the two multi-parameter pathways in which event-free survival was over-estimated, we improved model fit by internally calibrating two single-transition pathways related to untreated HIV disease progression: the transition from Asymptomatic to Intermediate and the transition from Intermediate to AIDS (Figure 3). After internal calibration of the two pathways, 16 of 17 of the remaining single-transition or multi-parameter pathways (94%) had a mean percentage deviation between model predictions and the patient-level data of <6% over both 5- and 10-year time horizons. The remaining transition pathway was from

untreated AIDS to death, for which there were limited reliable data available in the observational data sets.

We further evaluated the model's internal validity for several real-world treatment and care scenarios. For example, we assessed model outcomes for a cohort of HIV-infected individuals initiating ART at CD4 <200, when the vast majority of HIV-infected patients present for care in Haiti.¹⁹ By 5 years, model predictions for loss from care, 2nd-line ART initiation, and death fell within the 95% confidence intervals of the patient-level data.

Model fit to population-level data

There were 25 uncertain parameters for which unique sets of model input values were generated during the external calibration process (Table 2). Uncertain parameters were mainly related to early engagement with clinical care, including the probability of testing and linkage to care, the probability of pre-ART loss from care, and the probability of ART initiation; data to inform these parameters in Haiti and other resource-limited settings are limited. Other uncertain model inputs considered in the external calibration process included the distribution of HIV-infected individuals across health states in the prevalent cohort and the number of newly HIV-infected individuals annually for which only other modeled estimates exist.³⁴ For each input parameter generated during the external calibration process, the mean and the median of the top 25 values were similar, suggesting few outliers.

Figure 4 shows model predictions of the number on ART when using the top 25 good-fitting sets compared to historical ART scale-up data.³⁴ Between 2004 and 2009, predicted estimates were within 7% for each year of the reported data.³⁴ The mean percentage deviation of the number on ART over the analytic time horizon for the top 25 good-fitting sets compared to country-level reports of the number on ART was less than 1%. While mean percentage deviation was less than 1% across the range of good-fitting thresholds assessed (e.g., 5 good-fitting sets, 25 sets, 75 sets), the maximum deviation in any one year increased as the number of good-fitting sets increased above a threshold of 25 sets. A sample unique parameter set of the top 25 good-fitting sets is shown in the Appendix.

We corroborated model results by comparing alternative targets, including the number of HIV-infected individuals alive and antiretroviral coverage, to the upper and lower estimated bounds of these targets from an alternative model.³⁴ Model projections generally fell within the estimated bounds of the two alternative modeled targets, with the model having a reasonable fit to both alternative targets (Figure 5). However, the rate of increase in ART coverage begins to decrease in the later years of the calibration time period in our model compared to estimates from the alternative model.

Illustrative example of projected future outcomes

To illustrate the practical and policy relevance of the model for projecting future outcomes, we forecast two outcomes — deaths averted and number on ART — requested by decision makers in Haiti for programmatic planning. We predicted outcomes for each of the top 25 sets of externally calibrated parameter inputs individually and report the mean outcomes. Between 2010 and 2020, the model predicts as many as 5,900 deaths can be averted and 10,300 more individuals will need ART when implementing simultaneous policies to

improve engagement in clinical care, including further ART expansion, compared to the status quo.

DISCUSSION

Motivated to assist decision makers in projecting treatment need for ART,¹³ we used available local data to develop a multi-cohort state-transition model of treated and untreated HIV disease in Haiti. To achieve transparency, we used a conceptually simple model structure that considers levels of engagement across the continuum of HIV treatment and care. At each stage of the model development process, we assessed model performance. Straightforward validation and calibration techniques were implemented in a series of iterative steps in order to improve the fit of the model to patient- and population-level data and to improve overall model performance.

In evaluating model fit to the patient-level data, outcomes forecast by the model generally approximated empiric data for both single- and multi-parameter model pathways. Systematic, manual adjustment of select model inputs (i.e., internal calibration) improved model fit when model simplifications resulted in over-estimation of event-free survival. After internal calibration, parameter pathways visually approximated the shape of the event-free curve estimated from the empiric data; 16 of 17 parameter pathways (94%) had a mean percentage deviation between model predictions and the empiric data of less than 6% over policy-relevant time horizons.

In evaluating model fit to the population-level data, model output generated after the external calibration process approximated the number on ART reported at the country-level. Between 2004 and 2009, the percentage deviation between model predictions of the number on ART and the population-level data at each time point did not exceed 7% and was less than 1% over the calibrated time horizon. Results after external calibration were also similar to estimates from another model, including the total number of HIV-infected and ART coverage,³⁴ and to a recent analysis conducted by GHESKIO on loss to follow-up in Haiti.³⁶

Increasing emphasis has been placed on assessing mathematical model performance as a component of the model-building process. In addition to practical applications,^{25,32,37–39} the literature has outlined frameworks for mathematical model evaluation,⁴⁰ approaches for model calibration,^{41–43} and guidelines for reporting calibration methods.⁴⁴ The ISPOR-SMDM Modeling Good Research Practices Task Force recently published recommendations for achieving model transparency and assessing model performance, including face validity checks, internal validation, corroboration, and calibration.⁴⁵ The approach used to develop the model in the current study followed all these criteria, although we did not examine the model's external validity due to lack of data.

This study has several limitations related to the model structure, methods for assessing model performance, and data used to calibrate and corroborate the model. First, the model does not explicitly incorporate population-level disease transmission dynamics, in particular the reduced risk of transmission among individuals receiving ART.^{6,7} While it is unlikely that ART-related transmission dynamics would play out over the short analytic time horizon

intended for the model's policy projections (i.e., 5–10 years), disease transmission effects could be incorporated into the model structure in the future by allowing model projections to reflect reductions in incident infections. In contrast to models incorporating transmission dynamics that are well-suited to evaluating policies to reduce new HIV infections, the current model addresses policy questions related to demand for HIV treatment and the capacity required to further expand ART. An additional important contribution of the current model is in its ability to evaluate policy questions regarding the impact of potential improvements in clinical engagement along the HIV care continuum. The model is designed to predict outcomes along the care continuum — including testing and linkage to care, pre-treatment retention, ART enrollment by regimen, treatment retention — by stage of disease progression. Moreover, because the model accommodates multiple cohorts and is calibrated to historical data, it is capable of predicting population-level outcomes due not only to individually targeted policies along the HIV care cascade but also simultaneous implementation of multiple policies. The results arising from this model can assist donors in targeting available funds. Results are also critical for country-level programmatic planning as decision makers implement programs to further expand HIV clinical care in countries like Haiti. However, while simple conceptually and implemented in Microsoft Excel, the model in its current form may be too complex for use by untrained users.

Second, the model assumes the effectiveness of first- and second-line ART regimens did not improve over the retrospective time horizon between 2004 and 2009. However, the model's flexible framework could allow for changes in treatment effectiveness to be incorporated into model projections. In addition, it is possible that an annual cycle length may not adequately capture transitions (e.g., ART initiation, death) that may occur throughout the cycle. An annual cycle length was chosen to reflect HIV-related decision making and programmatic planning at the national level in Haiti, as well as to reflect clinically meaningful events during the time interval.⁴⁶ Third, while the literature on the methods for assessing model performance is increasing, no consensus exists regarding adequate fit of model predictions to patient- or population-level data. The choice of method for evaluating model fit, therefore, is determined through an analytic decision making process specific to the research question, individual model, and available empiric data. The current analysis relied on visual assessment of trend, acceptance window (95% confidence interval of patient-level data), and percentage deviation from the mean, all of which are consistent with practical applications in the literature and can be implemented in settings with limited computing capacity and statistical support.^{25,32,33,38,39}

Fourth, when externally calibrating the model, limited pre-treatment data resulted in a simultaneous search for multiple uncertain parameters, an extensive search space, and possible model over-specification. Local decision making required predicted outcomes along the entire HIV care continuum rather than aggregate estimates of the number on ART and/or cumulative deaths that might entail fewer health states. However, model parameter estimates can be updated as new data emerge and will allow for comparison of the previously calibrated parameters to the new data. In addition, no guidelines exist regarding determining how to best search the parameter space and when it has been adequately searched. While more efficient algorithms (e.g., Nelder-Mead) could have been used,^{33,47}

we preferred to use methods that were straightforward, were reproducible, and used fewer computer resources, but also that performed comparably to more sophisticated methods.³³

Fifth, patient-level data from Haiti were from one center, GHESKIO, that may not be nationally representative. HIV natural history data from GHESKIO, however, are comparable to those reported for other low-income settings. For example, adjusting for age at seroconversion, survival outcomes reported by GHESKIO for Haitian HIV-infected individuals are similar to survival in several East and Southern African countries.^{14,48} It is also possible that the population-level data that were available for calibration were based on limited surveillance or were subject to over-reporting. To account for this, we chose a relative measure of deviation from the calibration target (i.e., mean percentage deviation of the reported number on ART) to evaluate goodness of fit. This approach avoided over-fitting the data compared to an exact measure (e.g., mean absolute deviation) that might more closely approximate the surveillance data.

Development of the current model relied on detailed patient-level data of treated and untreated HIV in Haiti. Data required to derive model parameters included longitudinal CD4 cell count (for disease progression in the absence of treatment and disease stage at ART initiation), accurate classification of key events along the care continuum (e.g., 1st- or 2nd-line ART initiation, loss to follow-up, or death), and calendar dates associated with each event. The current model benefited in particular from close tracking of individual patients receiving care at the GHESKIO clinic, allowing for more precise identification of patients as either lost from care, transferred to another care facility, or having died. Detailed patient-level data similar to the data used to develop the current model are increasingly accessible through international research consortiums, such as the International Epidemiologic Databases to Evaluate AIDS (IeDEA network). While reports suggest difficulty in maintaining accurate patient death records due to loss to follow-up, methods to correct mortality estimates have been developed.⁴⁹ In addition to patient-level data, model development and policy analysis benefits from strong partnerships with in-country decision makers in order to access and interpret the data, as well as design and implement the policy analyses.

Findings from this analysis suggest that a conceptually simple model structure coupled with model validation and calibration techniques can generate predicted clinical outcomes that reasonably fit local patient- and population-level data. These types of models are sufficient for forecasting health-related outcomes that can inform clinical decision making over a 5–10 year time horizon, and using local data in the model-building and assessment process is feasible. This process of model development, validation, and calibration can be applied in other resource-limited settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Role of the funding source

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Figure 1. Process for evaluating model performance

Figure 2. Model schematic of disease progression and engagement in clinical care for individual cohorts

For each cohort of HIV-infected individuals in the model, individuals may experience untreated disease progression in one of three mutually exclusive and collectively exhaustive stages of HIV disease. Within each disease stage, a fraction of the cohort may engage with clinical care through HIV case detection and linkage to care, ART initiation, or loss from treatment or care. Two sequential ART regimens are available to individuals eligible for ART. Disease progression and movement through different clinical care-related events occurs according to transition probabilities, denoted by arrows. HIV-infected individuals with intermediate disease (i.e., CD4 count 200–350 cells/ μ L) or who have AIDS (i.e., CD4 count <200 cells/ μ L) are eligible for ART according to current World Health Organization guidelines.⁵ Continuation in the same health state over time is not shown. Death (also not shown) can occur from HIV- or non-HIV-related causes. Abbreviations: ART = antiretroviral therapy; Lost = loss from treatment or care.

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Figure 3. Internal calibration of HIV disease progression

Shown is Kaplan-Meier AIDS-free survival in a cohort of newly HIV-infected individuals with no access to treatment. Time, in years, is on the x-axis; the proportion AIDS-free is on the y-axis. The dark blue line represents empiric survival from the patient-level data, and the shaded blue region represents the 95% confidence intervals of the empiric data. Model predictions of median AIDS-free survival — represented by the dashed orange line — were 9.0 years prior to internal calibration. After internal calibration, median survival was 6.6 years compared to 5.8 years in the empiric data. The model prediction of 6.6 years falls within the 95% confidence intervals of the empiric data.

Figure 4. Model performance: External calibration to population-level data of the number on ART, 2004–2009

Shown are results of the multi-cohort calibration process where the predicted number on ART across multiple cohorts was compared to country-level reports of the number on ART. On the horizontal axis is time, by year; the vertical axis shows the number on ART. The thick black line represents the reported data. The thin red lines represent the top 25 good-fitting sets of outcomes predicted by the model. Across the calibration time horizon, mean percentage deviation between model predictions for the top 25 good-fitting sets and the population-level data was less than 1 percent.

Figure 5. Model performance: Corroboration of model projections to other modeled estimates
 In a final stage of model performance assessment, model predictions of the total number of HIV-infected individuals alive (Panel A) and ART coverage (Panel B) were compared to other modeled estimates. The thick black lines represent the 95% confidence intervals of estimates from UNAIDS³⁴; the thin red lines represent the top 25 good-fitting sets of outcomes predicted by the model.

Table 1
Selected Model Input Parameters from the Patient-level Data and External Calibration Targets Used to Assess Model Performance

Parameter	Value*	Range*	Source(s)
Panel A. Selected parameter inputs			
Prevalent HIV-infected Cohort (2004)			
Total HIV-infected population (number)	110,000		UNAIDS ³⁴
Number on ART (number)	3,000		UNAIDS ³⁴
Fraction not in care or treatment	0.750		DHS 2006 ³⁵
Disease Progression (Prevalent and Incident Cohorts)			
Untreated and in care			
Progression to Symptomatic if Asymptomatic	0.200	0.150 – 0.250 [§]	Internal calibration
Progression to AIDS if Symptomatic (not lost)	0.300	0.225 – 0.375 [§]	Internal calibration
Death if Asymptomatic	0.017	0.009 – 0.031	Deschamps et al., ¹⁴ Pape et al., ¹⁷ Fitzgerald et al. ¹⁵
Death if Intermediate	0.026	0.010 – 0.068	Deschamps et al., ¹⁴ Pape et al., ¹⁷ Fitzgerald et al. ¹⁵
Death if AIDS	0.385	0.315 – 0.466	Deschamps et al., ¹⁴ Pape et al., ¹⁷ Fitzgerald et al. ¹⁵
Treated			
2 nd -line ART if Intermediate 1 st -line ART Initiation	0.009	0.004 – 0.014	Severe et al. ¹⁸
2 nd -line ART if AIDS 1 st -line ART Initiation	0.031	0.025 – 0.038	Severe et al., ¹⁹ Leger et al. ¹⁶
Death if Intermediate 1 st -line Initiation or 2 nd -line ART	0.005	0.002 – 0.010	Severe et al. ¹⁸
Death if AIDS 1 st -line ART Initiation 12 mo	0.148	0.126 – 0.174	Severe et al., ¹⁹ Leger et al. ¹⁶
Death if AIDS 1 st -line ART Initiation >12 mo	0.026	0.021 – 0.032	Severe et al., ¹⁹ Leger et al. ¹⁶
Death if AIDS 2 nd -line ART	0.094	0.068 – 0.131	Charles et al. ²⁰
Loss from ART (Prevalent and Incident Cohorts)			
Loss from 1 st - or 2 nd -line ART if Intermediate ART Initiation	0.014	0.008 – 0.021	Severe et al. ¹⁸
Loss from 1 st -line ART if AIDS ART Initiation and on ART 12 mo	0.032	0.022 – 0.047	Severe et al., ¹⁹ Leger et al. ¹⁶
Loss from 1 st -line ART if AIDS ART Initiation and on ART >12 mo	0.011	0.008 – 0.016	Severe et al., ¹⁹ Leger et al. ¹⁶
Loss from 2 nd -line ART if AIDS ART Initiation	0.027	0.014 – 0.052	Charles et al. ²⁰
panel B. Primary external calibration targets			
Number on ATR			
2005	6,896		UNAIDS ³⁴

Parameter	Value*	Range*	Source(s)
<i>Panel A. Selected parameter inputs</i>			
Prevalent HIV-infected Cohort (2004)			
2006	8,796		UNAIDS ³⁴
2007	14,514		UNAIDS ³⁴
2008	19,990		UNAIDS ³⁴
2009	26,007		UNAIDS ³⁴

Adapted with permission from Kimmel et al. Lives saved by expanding HIV treatment availability in resource-limited settings: the example of Haiti. JAIDS 2013; 63:e40–48.¹³

Abbreviations: ART = antiretroviral therapy; N/A = not applicable; Asymptomatic = CD4 count >350 cells/ μ L; Intermediate = CD4 count 200–350 cells/ μ L; AIDS = CD4 count <200 cells/ μ L; Loss = lost from HIV treatment or care.

* Values shown for disease progression and loss from treatment are annual probabilities. Unless otherwise indicated, ranges for the model inputs reflect the upper and lower bounds derived from the incidence density analysis, which are then converted to probabilities.

Table 2

Model Inputs Resulting from External Calibration to Population-level Data

Parameter	Mean (SD)*	Median (IQR)*
Prevalent HIV-infected Cohort (2004)		
Fraction of total on ART, CD4 count 200 – 350 cells/ μ L	0.166 (0.019)	0.167 (0.150, 0.180)
Initial health stage distribution		
Asymptomatic	0.452 (0.125)	0.463 (0.208, 0.687)
Intermediate	0.303 (0.148)	0.305 (0.232, 0.396)
AIDS	0.245 (0.071)	0.234 (0.183, 0.286)
Incident Cohorts (2005 – 2009)[†]		
Newly infected, 2005 (number)	11,000 (1,400)	11,300 (9,500, 12,100)
Newly infected, 2006 (number)	10,100 (1,200)	10,500 (9,400, 11,000)
Newly infected, 2007 (number)	10,200 (1,400)	10,600 (9,600, 11,200)
Newly infected, 2008 (number)	9,200 (1,600)	9,700 (7,500, 10,700)
Newly infected, 2009 (number)	8,600 (1,200)	8,500 (7,600, 9,700)
Disease Progression		
Untreated		
Progression to AIDS if Lost, Intermediate	0.240 (0.043)	0.261 (0.190, 0.277)
Death (multiplier), not in care	1.066 (0.052)	1.058 (1.017, 1.099)
Linkage to Care and Treatment		
Testing and Linkage from No Care to In Care, off ART (2004 – 2006)		
Linkage if Asymptomatic	0.056 (0.015)	0.060 (0.048, 0.066)
Linkage if Intermediate	0.075 (0.020)	0.080 (0.065, 0.087)
Linkage if AIDS	0.094 (0.025)	0.100 (0.081, 0.109)
Testing and Linkage from No Care to In Care, off ART (2007 – 2009)		
Linkage if Asymptomatic	0.074 (0.008)	0.074 (0.068, 0.078)
Linkage if Intermediate	0.099 (0.010)	0.099 (0.091, 0.105)
Linkage if AIDS	0.469 (0.049)	0.471 (0.433, 0.497)
Linkage from In Care, off ART to ART		
Linkage to ART if Intermediate	0.128 (0.052)	0.140 (0.098, 0.169)
Linkage to ART if AIDS (2005)	0.360 (0.147)	0.377 (0.251, 0.490)

Parameter	Mean (SD) [*]	Median (IQR) [*]
Linkage to ART if AIDS (2006)	0.130 (0.096)	0.130 (0.062, 0.179)
Linkage to ART if AIDS (2007)	0.384 (0.122)	0.431 (0.279, 0.459)
Linkage to ART if AIDS (2008)	0.420 (0.087)	0.426 (0.359, 0.490)
Linkage to ART if AIDS (2009)	0.433 (0.087)	0.426 (0.359, 0.490)
Pre-Treatment Loss from Care		
Loss if Asymptomatic	0.307 (0.188)	0.223 (0.162, 0.389)
Loss if Intermediate	0.182 (0.105)	0.155 (0.114, 0.249)
Loss if AIDS	0.059 (0.038)	0.056 (0.028, 0.073)

Adapted with permission from Kimmel et al. Lives saved by expanding HIV treatment availability in resource-limited settings: the example of Haiti. JAIDS 2013; 63:e40–48.¹³

Abbreviations: ART = antiretroviral therapy; N/A = not applicable; Asymptomatic = CD4 count >350 cells/μL; Intermediate = CD4 count 200–350 cells/μL; AIDS = CD4 count <200 cells/μL; Loss = lost from HIV treatment or care.

^{*} Values shown are annual probabilities unless otherwise indicated.

[†] The upper and lower bounds of the number newly infected annually estimated in the external calibration process were defined by estimates from the World Health Organization. The ranges assessed included: 8,100 – 13,000 (2005); 7,700 – 12,000 (2006); 7,000 – 12,000 (2007); 6,800 – 12,000 (2008); and 6,500 – 11,000 (2009).²