Assessment of epidemic projections using recent HIV survey data in South Africa: a validation analysis of ten mathematical models of HIV epidemiology in the antiretroviral therapy era

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Summary

Background Mathematical models are widely used to simulate the effects of interventions to control HIV and to project future epidemiological trends and resource needs. We aimed to validate past model projections against data from a large household survey done in South Africa in 2012.

Methods We compared ten model projections of HIV prevalence, HIV incidence, and antiretroviral therapy (ART) coverage for South Africa with estimates from national household survey data from 2012. Model projections for 2012 were made before the publication of the 2012 household survey. We compared adult (age 15–49 years) HIV prevalence in 2012, the change in prevalence between 2008 and 2012, and prevalence, incidence, and ART coverage by sex and by age groups between model projections and the 2012 household survey.

Findings All models projected lower prevalence estimates for 2012 than the survey estimate (18·8%), with eight models' central projections being below the survey 95% CI (17·5–20·3). Eight models projected that HIV prevalence would remain unchanged (n=5) or decline (n=3) between 2008 and 2012, whereas prevalence estimates from the household surveys increased from 16·9% in 2008 to 18·8% in 2012 (difference 1·9, 95% CI –0·1 to 3·9). Model projections accurately predicted the 1·6 percentage point prevalence decline (95% CI –0·3 to 3·5) in young adults aged 15–24 years, and the 2·2 percentage point (0·5 to 3·9) increase in those aged 50 years and older. Models accurately represented the number of adults on ART in 2012; six of ten models were within the survey 95% CI of 1·54–2·12 million. However, the differential ART coverage between women and men was not fully captured; all model projections of the sex ratio of women to men on ART were lower than the survey estimate of 2·22 (95% CI 1·73–2·71).

Interpretation Projections for overall declines in HIV epidemics during the ART era might have been optimistic. Future treatment and HIV prevention needs might be greater than previously forecasted. Additional data about service provision for HIV care could help inform more accurate projections.

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Introduction

Mathematical models are widely used to generate estimates and short-term projections of HIV epidemics[1,2] and to assess the costs and effects of potential interventions to control the epidemic.[3,4] These models synthesise epidemiological information, surveillance data, infectious disease theory, and assumptions about future conditions and intervention efforts to generate HIV epidemic projections. Model projections have become increasingly central to policy decision making and resource planning and allocation.[5] For many uses, the value of these analyses for public health decision making depends on the accuracy of their projections.

The most important recent change in HIV epidemiology has been the provision of antiretroviral therapy (ART) in low-income and middle-income countries, with the number receiving ART in low-income and middle-income countries increasing from 300 000 in 2002 to an estimated 9·7 million at the end of 2012.[6] Successful ART both improves survival for HIV-positive people, potentially up to near-normal life expectancy,[7] and inhibits onward transmission of the virus.[8] This preventive effect has raised myriad questions about the future trajectory of HIV epidemics, whether existing ART programmes are sufficient to reduce incidence, whether countervailing factors will limit any effect, and what resources are needed for future ART provision in the short and long term.[9]

In response to these questions, many models have been used to quantify the short-term and long-term

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Research in context

Evidence before this study

Many mathematical models have been developed to project the epidemiological and demographic effects of antiretroviral therapy (ART) on HIV epidemics and assess different policy options for the use of ART across sub-Saharan Africa and elsewhere. However, testing of these predictions against external data had not been possible. With new data from a nationally representative household survey in South Africa, we have, for the first time, compared existing model projections with data about HIV prevalence, HIV incidence, and ART coverage.

Added value of this study

Models were consistent with new data in projecting prevalence declines among younger adults and a shift in the age distribution of HIV. However, model projections did not predict the overall increase in adult HIV prevalence since the scale-up of ART and underestimated current incidence levels.

Implications of all the available evidence

Our results suggest that existing projections for reductions in HIV incidence after the scale-up of ART might have been overly optimistic. Resources needed for future HIV treatment and prevention are probably greater than previously forecasted. Incorporating more detailed data about patterns of uptake of health services could improve future epidemiological and demographic projections for HIV and other diseases.

consequences of current and future ART provision on HIV prevalence, incidence, and mortality,[4,10,11] including assessment of the potential use of ART to substantially reduce or eliminate HIV transmission.[12–14] A comparison of models for South Africa showed that although the long-term effect of ART on incidence varied substantially, models' short-term projections of basic metrics were similar.[10] This agreement increased confidence in these projections, but assessment of the accuracy of those projections, and by implication the confidence that should be placed on the longer-term projections of these models, was not possible.

Data are now available from a large household survey done in 2012,[15] which has provided nationally representative measurements of HIV prevalence, incidence, and ART coverage in South Africa to which earlier model projections can be compared. During the period between the national surveys in 2008 and 2012, the number of people receiving ART in South Africa increased by three times—from 730 000 to 2·2 million[16]—a surge expected to bring large reductions in HIV incidence.[10] We used the 2012 household survey data[15] to undertake a validation of the previously published short-term model projections of the South African HIV epidemic in 2012.

Methods

Study design

We compared existing projections of HIV prevalence, HIV incidence, and ART coverage by age and sex from ten mathematical models of the national HIV epidemic in South Africa with empirical estimates from the South African National HIV Prevalence, Incidence and Behaviour Survey, 2012 (henceforth referred to as the 2012 household survey).[15]

Mathematical models

Ten mathematical models produced projections for adult HIV prevalence, HIV incidence, and ART coverage for the period 2002–12 (table). All models stratified the population by sex, producing projections for men and women. Eight of the models were age structured and reported results by 5-year age groups.

All of the models generated internally consistent patterns of HIV prevalence, incidence, and mortality through a non-linear dynamic transmission process in which the number of new infections was a function of the number infected and the population at risk. All models except the Estimation and Projection Package (EPP) generated new infections as a function of sexual contacts and transmission probabilities per contact over the course of the epidemic. In EPP, the rate at which infected individuals generated new infections was estimated as a flexible smooth function over time.[28] For the age-structured models, the rate of forming new sexual partnerships and sexual mixing (ie, the patterns of how sexual partnerships are formed) depended on the ages of each partner (for EPP and Goals, the HIV incidence rate ratio is a function of age). All models except pre-PopART assumed reductions in the risk of condomless sexual contacts or transmission over the course of the epidemic, mediated by increases in condom use (ASSA, Bacaër, EMOD, Goals, STDSIM, STI-HIV, and Synthesis), reductions in sexual contact (Eaton, EPP, and Goals), or improvements in the control of sexually transmitted infections (ASSA and Goals). Increases in condom use were greater among young adults than among older adults (ASSA, Bacaër, EMOD, STDSIM, and STI-HIV), resulting in greater relative reductions in the risk of condomless sexual contact over the course of the epidemic for younger adults. All models assumed reduced mortality for adults on ART and assumed that transmission by people on ART was reduced by at least 90%.

Models differed in the data used to calibrate epidemic trends, the approach to calibration, and which parameters were allowed to vary (table). Four models (EMOD, Goals, pre-PopART, and STDSIM) relied on UNAIDS prevalence estimates to calibrate the overall prevalence trend, whereas the others calibrated directly

	Model name	Type	Age structured	MTCT survival*	Time projection created and source	Main calibration data	Calibration approach
Dorrington et al (2010)[2]	ASSA	Compartmental	Yes	Yes	March, 2011[17]	Provincial age-specific and sex-specific HSRC prevalence in 2002, 2005, and 2008; ANC prevalence 1991–2008; and age-specific and sex-specific total deaths 1997–2008	Hand-tuned calibration
Bacaër et al (2010)[18]	Bacaër	Compartmental	Yes	Yes	March, 2010[10]†	Age-specific and sex-specific HSRC prevalence in 2002, 2005, and 2008; and age-specific ANC prevalence 1990–2008	Hand-tuned calibration
Eaton and Hallett (2014)[19]	Eaton	Compartmental	No	No	November, 2011[10]	Sex-specific HSRC prevalence in adults aged 15–49 years in 2002, 2005, and 2008; and ANC prevalence 1990–2010	Bayesian statistical calibration of sexual mixing and behaviour change parameters
Klein et al (2014)[20]	EMOD‡	Individual-based	Yes	Yes	December, 2012[4]	UNAIDS 2012 estimates for prevalence in adults aged 15–49 years; and HSRC for age pattern in 2005 and 2008	Hand-tuned calibration with varying transmission probability, condom use, and concurrency
Stover et al (2012)[21]	EPP§	Compartmental	Yes§	Yes	November, 2012[22]	HIV prevalence trend derived from provincial ANCs, HSRC prevalence in adults aged 15–49 years in 2002, 2005, and 2008	Bayesian statistical calibration of force of infection
Avenir Health (2015)[23]	Goals§	Compartmental	Yes§	Yes	December, 2012[4]	UNAIDS 2011 prevalence estimates	Hand-tuned calibration of model parameters
Cori et al (2014)[24]	pre-PopART	Compartmental	No	No	December, 2012[24]	UNAIDS 2008 prevalence estimates	Least-squares optimisation for sexual mixing parameters
Hontelez et al (2013)[13]	STDSIM	Individual-based	Yes	No	December, 2012[4]	UNAIDS 2012 prevalence estimates	Random sampling from ranges for number of new partners and condom use parameters
Johnson et al (2012)[25]	STI-HIV	Compartmental	Yes	Yes	November, 2011[10]	Age-specific and sex-specific HSRC prevalence in 2005 and 2008; and age-specific ANC prevalence 1997–2005	Bayesian statistical calibration of sexual mixing, transmission, and condom use parameters
Phillips et al (2011)[26] and Cambiano et al (2013)[27]	Synthesis	Individual-based	Yes	No	December, 2012[4]	Sex-specific HSRC prevalence in 15–24-year-olds and 15–49-year-olds in 2002, 2005, and 2008	Sampled from distributions for behaviour change and transmission probability parameters

References for each model provide further details regarding the assumptions about sexual behaviour, ART, and other aspects of model structure, parameters, implementation, and calibration. ANC=antenatal clinic. ART=antiretroviral therapy. EPP=Estimation and Projection Package. HSRC=Human Sciences Research Council. MTCT=mother-to-child transmission. *Whether or not models incorporated MTCT of HIV and potential survival of these infections to adolescence. †Updated in August, 2013, to simulate current numbers on ART from 2010 to 2012. ‡Version 0.8. §EPP and Goals are separate models that each produce non-age-structured HIV incidence for the 15–49 years age group. Both models are then fed into the AIDS Impact Module of the Spectrum package, which applies demographic structure and a fixed age pattern of HIV incidence.

Table: **Mathematical models included**

to prevalence estimates from antenatal clinic surveillance since 1990 and national household surveys in 2002, 2005, and 2008. ASSA, Bacaër, and STI-HIV were calibrated to age-specific and sex-specific HIV prevalence from household and antenatal clinic surveys. Synthesis was calibrated only to national survey prevalence among adults aged 15–24 years and 15–49 years by sex, and did not incorporate antenatal clinic prevalence. One model, ASSA, included the time series of corrected national all-cause mortality estimates in the model calibration. Eight models used an optimisation routine to identify parameters that produced epidemics closest to the calibration data (table). Three models (Eaton, EPP, and STI-HIV) were statistically calibrated using a Bayesian approach to estimate posterior distributions for both uncertain model parameters and outcomes of interest. These models reported 95% credible ranges for model outcomes in the analyses.

All model projections analysed were produced between 2010 and 2012 (table), before the analysis and publication of the 2012 household survey results. NB updated the Bacaër model projection to incorporate numbers of adults on ART from 2010 to 2012, but no changes were made to any other aspects of model structure or assumptions.

2012 survey data

The 2012 household survey was a stratified nationally representative household survey done between January, 2012, and November, 2012.[15] It was the fourth such survey in South Africa, following similar surveys in 2002, 2005, and 2008.[29–31] Full details of the survey design and results are described elsewhere.[15] Briefly, a nationally representative sample of 30 747 adults aged at least 15 years was randomly sampled using a two-stage cluster design, of whom 20 693 participated in an individual interview and provided a dried blood spot for HIV

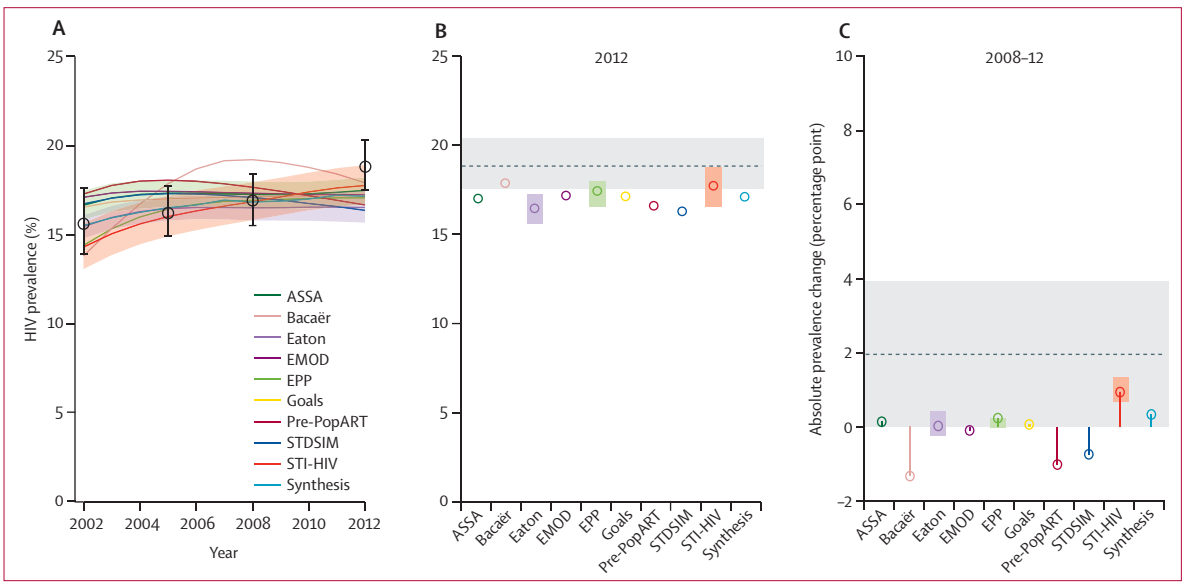

Figure 1: **Projections for HIV prevalence in adults aged 15–49 years**
(A) Projected trend for prevalence in adults aged 15–49 years from 2002 to 2012. Circles show national survey estimates in 2002, 2005, 2008, and 2012, with 95% CIs (bars). (B) Model projections for prevalence in adults aged 15–49 years in 2012 and (C) absolute (percentage point) change in HIV prevalence in adults aged 15–49 years from 2008 to 2012. Dashed horizontal lines show household survey estimates and grey regions show 95% CIs around these estimates. Shaded areas around model projections show 95% Bayesian credible regions for the three models that estimated statistical uncertainty around model estimates and projections. EPP=Estimation and Projection Package.

testing. Dried blood spots were tested for HIV antibodies using a three-assay testing algorithm. HIV-positive specimens were tested for the presence of antiretrovirals using high-performance liquid chromatography coupled with tandem mass spectrometry. HIV incidence was estimated using a testing algorithm based on the limiting-antigen avidity assay for recent infection,[32] antiretroviral testing, and viral load testing.[15] Results of the survey were published in April, 2014. Empirical adult mortality rates for 2003 to 2012 were drawn from estimates derived from the rapid mortality surveillance system.[33]

Statistical analysis

The main outcomes compared between model projections and the 2012 household survey were adult (age 15–49 years) HIV prevalence in 2012 and the change in adult (age 15–49 years) prevalence between 2008 and 2012. Changes in prevalence refer to absolute percentage point changes, not relative changes. We also compared prevalence, incidence, and ART coverage (defined as the percentage of HIV-positive adults on ART) by sex and by age groups (15–24, 25–49, and ≥50 years) for the eight models that produced age-structured estimates. We compared the change in simulated prevalence from 2005 to 2008 with the projected change in prevalence from 2008 to 2012 to assess the effect of model calibration on future model projections. We compared modelled trends in adult (15–49 years) mortality with national estimates from the rapid mortality surveillance system.[33]

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Five models projected that prevalence in adults aged 15–49 years in 2012 would change by 0·3 percentage points or less from prevalence in 2008. Three models projected prevalence declines of 0·7 to 1·3 percentage points. (figure 1). One model, STI-HIV, projected an increase in prevalence of 0·9 percentage points (95% CI 0·6–1·4; figure 1C).

However, the household surveys estimated that adult prevalence increased from 16·9% in 2008 to 18·8% in 2012 (difference 1·9, 95% CI –0·1 to 3·9; figure 1C). As a result, all models projected lower prevalence estimates for 2012 than the survey estimate (18·8%), with eight of ten models' central projections being below the survey 95% CI (17·5–20·3; figure 1B).

The disparity between the 2012 survey estimate and the ten model estimates was driven by eight models projecting that prevalence would decline among men, whereas 2012 household survey data estimated that prevalence increased by 2·9 percentage points (95% CI 0·3–5·5; figure 2A). Only STI-HIV (mean 0·5 percentage point increase) was within the survey 95% CI (figure 2A). Among women, seven models projected that prevalence

would increase, with ASSA, STI-HIV, and Synthesis projecting increases of larger than 0·9 percentage points (figure 2A). The survey data confirmed this trend, with an estimated increase of 1·9 percentage points (95% CI –0·8 to 4·6).

Despite this disparity, prevalence estimates in 2012 tended to be more accurate for men, whereas for women all models' central projections except STI-HIV were below the survey 95% CI (figure 2B). This finding was because models tended to simulate prevalence in 2008 as being higher among men and lower among women than suggested by the 2008 household survey (appendix).

All eight age-structured models projected that prevalence would decline for men and women aged 15–24 years and increase for men and women aged 50 years and older (figure 3), consistent with an overall ageing of the epidemic profile. This prediction was confirmed by the 2012 household survey data, which showed declines between 2008 and 2012 of 0·9 percentage points (95% CI –1·2 to 3·0) for young men and 2·1 percentage points (–0·6 to 4·8) for young women, and increases in prevalence among men and women aged 50 years and older of 2·0 percentage points (–0·9 to 4·8) and 2·4 percentage points (0·4 to 4·3), respectively (figure 3).

For women aged 25–49 years, all models projected that prevalence would increase by between 1·1 percentage points and 2·7 percentage points. The survey point estimate suggested a greater increase of 4·1 percentage points (95% CI 0·3–7·8). The largest discrepancy between model projections and survey point estimates was among men aged 25–49 years. Six models projected declining prevalence and EPP and STI-HIV projected slight increases, whereas point estimates from the household surveys suggested that prevalence increased by 2·0 percentage points (95% CI –2·1 to 6·2).

Most model projections closely matched the age distribution of the South African population in 2012 (appendix). The proportion of adults aged 30–50 years was under-represented in some models (Bacaër, EMOD, STDSIM, and Synthesis), which contributed to the underestimation of the overall prevalence increases among adults aged 15–49 years.

Models were similar in their representation of a rapid scale-up of ART in South Africa (figure 4A). The household survey estimated 1·83 million (95% CI 1·54–2·12 million) adults aged at least 15 years were on ART in 2012; six of ten models were within this survey 95% CI. However, all model projections of the sex ratio of women to men on ART were lower than the survey estimate of 2·22 (95% CI 1·73–2·71; figure 4B). Models were largely accurate in their projections for the age distribution of adults on ART, although three models—Bacaër, EPP, and STDSIM—overestimated the proportion of treated adults who were aged 25–34 years

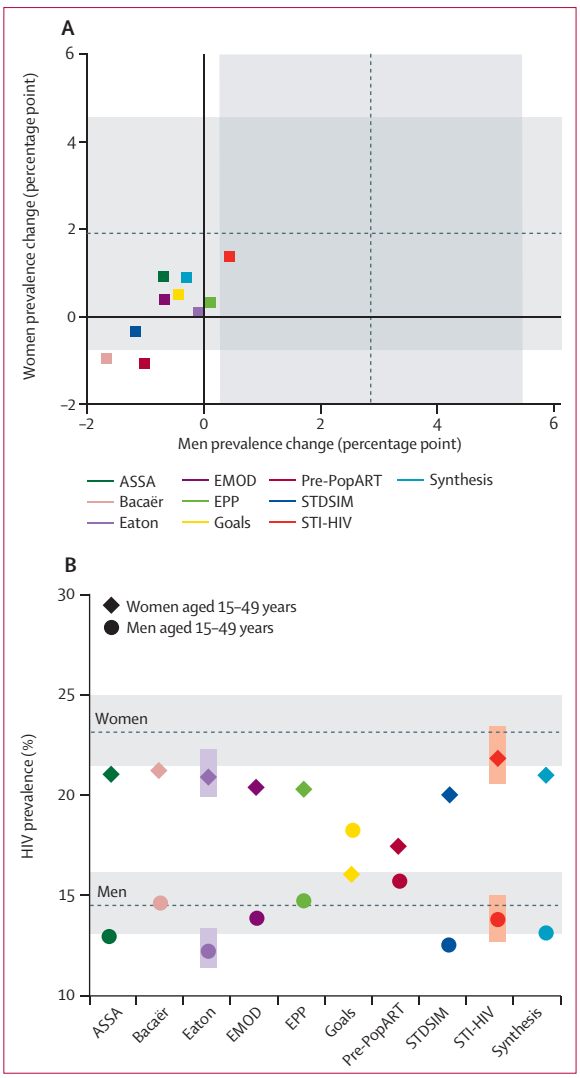

Figure 2: **HIV prevalence by sex among adults aged 15–49 years**
(A) Projected absolute (percentage point) change in prevalence between 2008 and 2012 for men (horizontal axis) and women (vertical axis). (B) HIV prevalence in 2012. Dashed lines show 2012 household survey estimates and grey shaded strips show survey 95% CIs. Shaded areas around model projections show 95% credible intervals for the two models that estimated statistical uncertainty around model estimates and projections for this outcome. EPP=Estimation and Projection Package.

(figure 4C). ART coverage was particularly overestimated among men aged 25–49 years (appendix).

Models simulated declines in HIV incidence in adults aged 15–49 years of between 40% and 54% over the decade 2002–12 (calculated using the following formula: 1–[2012 incidence rate]/[2002 incidence rate]; appendix). Projections for HIV incidence in 2012 ranged from 1·0 per 100 person-years to 1·4 per 100 person-years. These estimates were lower than the survey estimate of 1·7 per 100 person-years (95% CI 1·4–2·1), which was based on the recent infection assay. For men, the projections were consistent with the estimate of HIV incidence in the 2012 household

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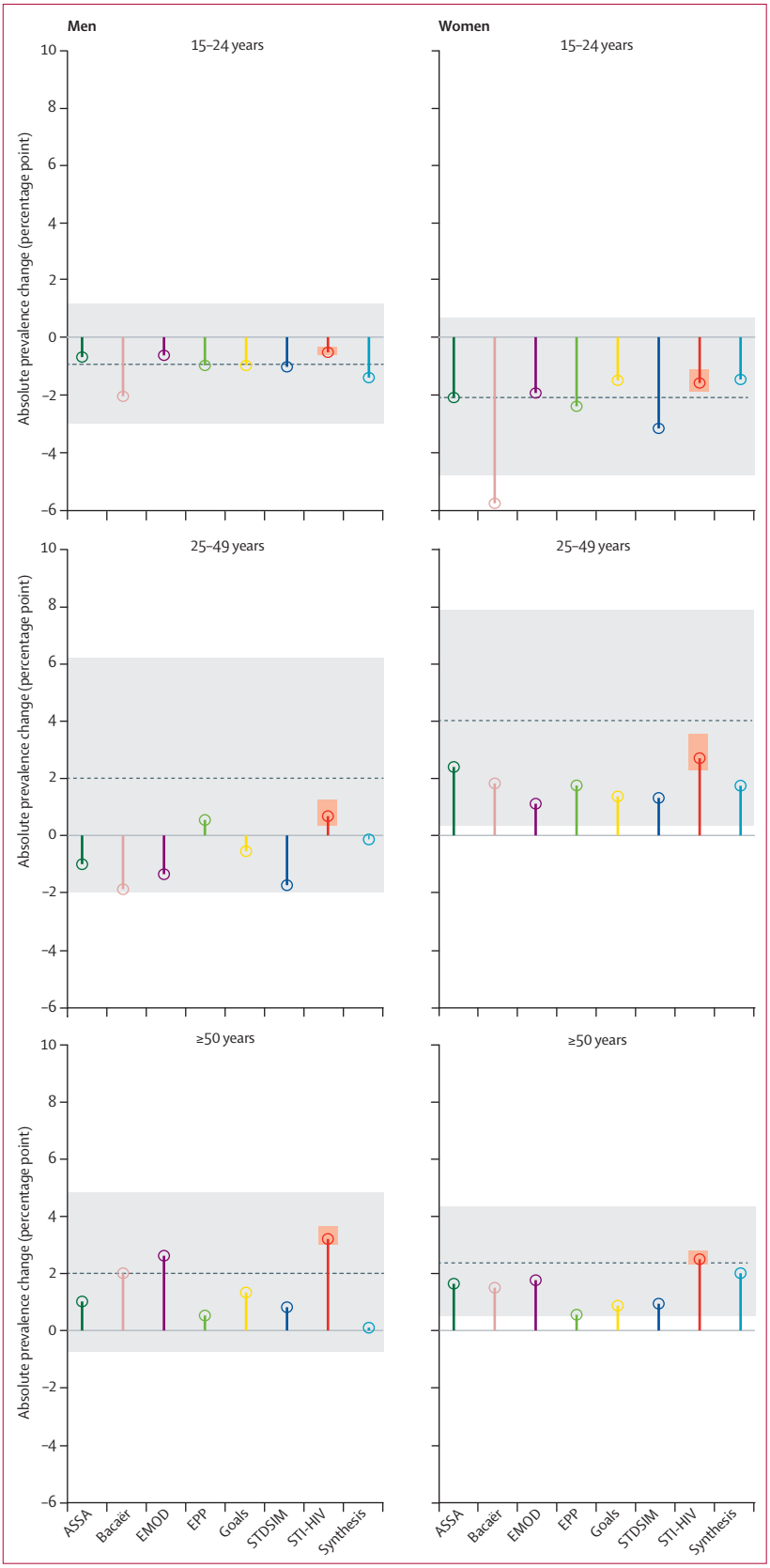

survey, but for women all model estimates of HIV incidence were substantially lower than the 2012 household survey estimate (figure 5).

Empirical estimates suggest that adult (15–49 years) mortality rates among both men and women peaked in 2005 and declined by 36% among men and by 45% among women by 2012.[33,34] Excluding one model—Bacaër—model projections simulated adult mortality peaking in 2005 or 2006 and declining by 22–37% for men and 25–45% for women (calculated as the percentage reduction in mortality rate from 2005 to 2012: (1−[2012 mx])/[2005 mx]; figure 6A). All model projections of crude mortality rates in 2012 were higher than estimates from the rapid mortality surveillance system[33] estimates (figure 6B).

In general, models calibrated to age-specific prevalence from earlier national survey data (ASSA, Bacaër, STI-HIV, and Synthesis) more closely matched reported prevalence changes between 2005 and 2008 than did models calibrated to antenatal clinic prevalence or UNAIDS prevalence estimates (appendix). Furthermore, these models tended to project larger increases in prevalence between 2008 and 2012 (appendix). Conversely, models that did not use age-structured data (Eaton and EPP) or were calibrated to UNAIDS prevalence (EMOD, Goals, pre-PopART, and STDSIM) did not capture either the earlier (2005–08) or later (2008–12) prevalence increases. The outlier to the positive association between prevalence change from 2005 to 2008 and the projected change from 2008 to 2012 was Bacaër, which compared the model fit to age-specific prevalence data during tuning of model parameters, but not in a systematic way.

Discussion

Demand for evidence-based policies and efficient allocation of resources for health have made mathematical modelling an integral component of public health decision making, with many models often being applied to the same question. We assessed the accuracy of short-term model projections from HIV transmission models in South Africa over the period of rapid ART scale-up. Mathematical models consistently predicted important epidemiological changes that were confirmed by new survey data—in particular the reduction in prevalence among young adults and increased prevalence among older adults. Models

Figure 3: **Change in HIV prevalence between 2008 and 2012 by sex and age group**

Dashed lines show estimates from successive household surveys with grey shaded regions showing survey 95% CIs. Eaton and pre-PopART models are not included because these models were not age structured. Circles show the estimate for the prevalence change for the model; coloured lines show the change from 0. Shaded areas around STI-HIV model estimates show 95% credible intervals (no other models estimated statistical uncertainty around model estimates for this outcome). EPP=Estimation and Projection Package.

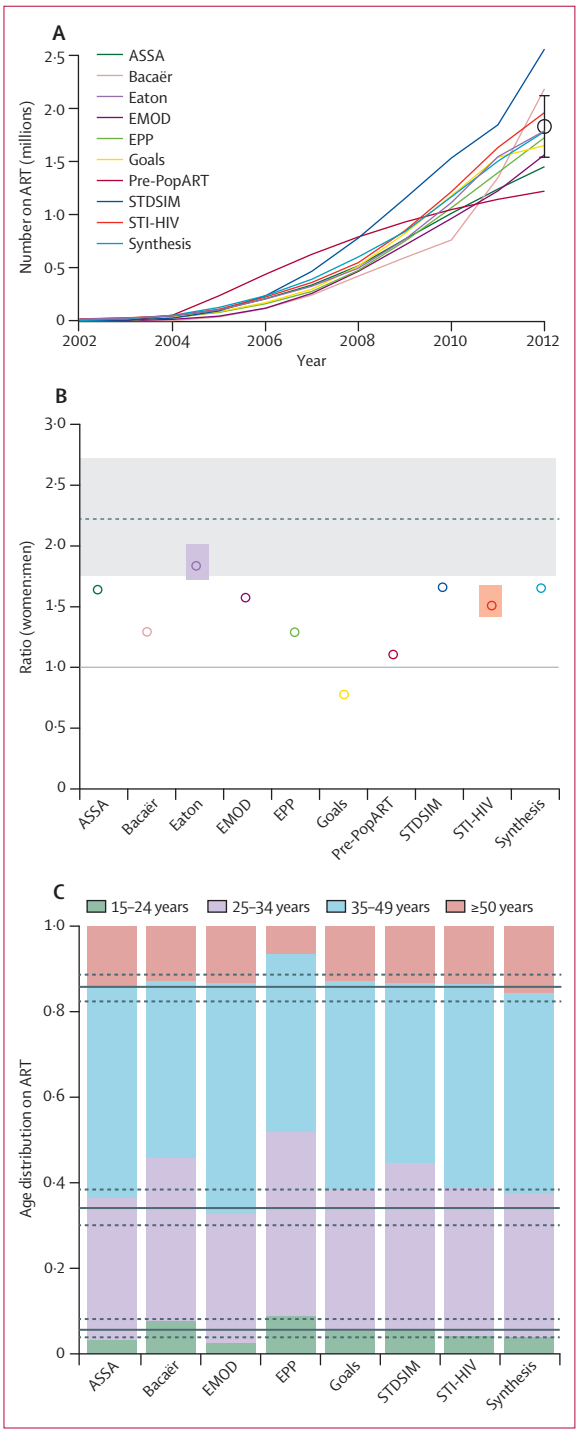

Figure 4: **Antiretroviral therapy coverage in 2012**
(A) Model projections for the number of adults aged 15 years and older on ART over time. The datapoint shows the mean 2012 household survey estimate and the error bar shows the 95% CI. (B) Sex ratio of number of adult (aged ≥15 years) women to men on ART in 2012. The dashed line shows the 2012 household survey estimate, with the 95% CI shown as a grey shaded region. For EPP and Goals, the numbers of men and women on ART is an input for the Spectrum model. Shaded areas around model projections show 95% credible intervals for the two models that estimated statistical uncertainty around model estimates for this outcome. (C) Age distribution of adults on ART in 2012 by age groups 15–24 years, 25–34 years, 35–49 years, and ≥50 years. Solid lines show 2012 household survey estimates and dashed horizontal lines show 95% CIs. ART=antiretroviral therapy. EPP=Estimation and Projection Package.

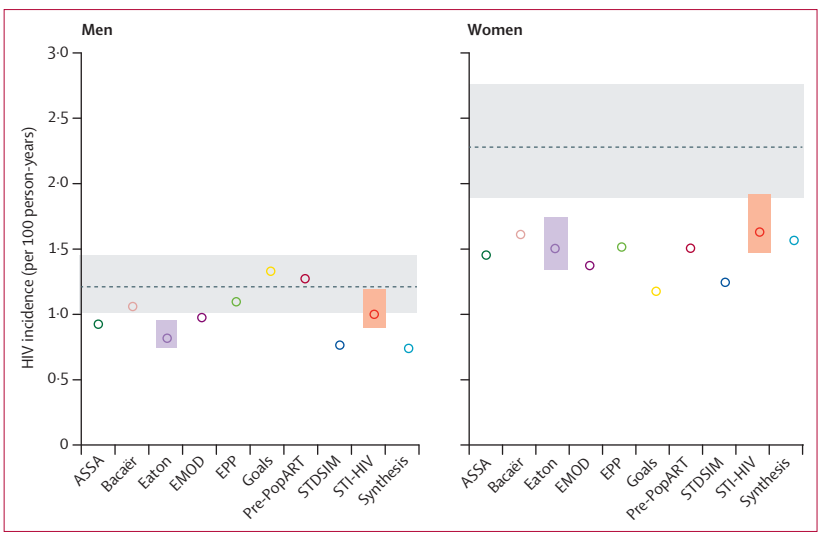

Figure 5: **HIV incidence rates in adults aged 15–49 years in 2012**
Rates are shown for men (left) and women (right). Horizontal dashed lines show estimates from the 2012 household survey and grey shaded regions show the survey 95% CIs. Shaded areas around model projections show 95% credible intervals for the two models that estimated statistical uncertainty around model estimates for this outcome. EPP=Estimation and Projection Package.

accurately projected the number and age distribution of those on ART, captured the peak in adult mortality around 2005 and declines thereafter, and were consistent or conservative about the magnitude of reductions in adult mortality. However, there were also important features of the 2012 household survey data that were not anticipated by the model projections, most importantly the magnitude of increase in adult HIV prevalence, particularly among 25–49-year-old men, and the substantially larger number of women than men on ART. These findings have implications for understanding the course of the epidemic in South Africa, and by extension other settings with large epidemics, and provide insights on issues that future projections should incorporate, in HIV and other areas of public health planning.

Some apparent discrepancies between the survey data and model projections could be the result of random sampling variation, biases in the survey data, or changes in the survey sampling procedures. 95% CIs around survey estimates were wide for prevalence changes between surveys and for some subpopulations. Among women, it seems likely that prevalence truly did increase more than was predicted by models because of the consistency of this across different outcomes—model projections were lower than survey estimates for both prevalence and incidence, and some underestimated mortality reductions. Models also overestimated ART coverage in middle-aged men and the successive surveys suggested decreases in condom use (whereas models assumed no changes in sexual risk behaviour),[15] both of which would result in models underestimating incidence among women. Furthermore, changes in

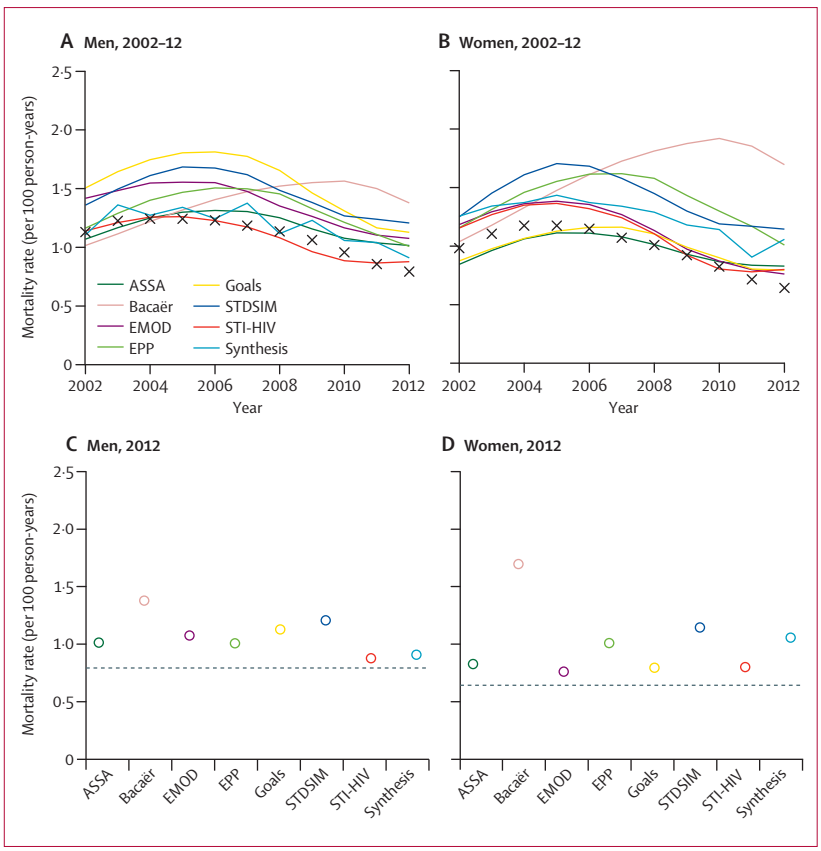

Figure 6: **Model projections of mortality rate in adults aged 15–49 years**
Projected trend for (A,B) the period 2002–12 and (C,D) in the year 2012. The crosses in (A,B) and dashed lines in (C,D) show empirical adult mortality estimates from the rapid mortality surveillance system, 2012.[33] Eaton and pre-PopART models are not included because these models do not produce total mortality estimates. EPP=Estimation and Projection Package.

age-specific prevalence estimated by the survey are consistent with age-specific trends from national antenatal clinic surveillance.[35]

However, among men, the magnitude of prevalence increases suggested by consecutive surveys seems harder to reconcile. Models did not systematically underestimate incidence in men, and models overestimated ART coverage for men, which should have led model estimates of prevalence among men to be too high and mortality too low—the opposite of what we found. One possible explanation is that the 2008 household survey underestimated prevalence in men because of random sampling error or bias, which would have affected the model projections.

Models that relied directly on age-specific household survey data were associated with a better representation of earlier trends in prevalence and more accurate projections of the trends in 2008–12 than those that used UNAIDS prevalence estimates. In particular, the STI-HIV model projection was closest to the prevalence levels and changes in the 2012 household survey. This model applied a formal statistical approach to calibration of model parameters to age-specific HIV prevalence data from two previous household surveys and age-specific antenatal clinic prevalence. Age-aggregated antenatal clinic prevalence or UNAIDS prevalence estimates, as a calibration source, are likely to have misrepresented recent epidemic prevalence trends from 2005 to 2008, and 2008 to 2012, because of downward biases in antenatal clinic prevalence as HIV prevalence shifts to older, less fertile age groups.[36] For South Africa, mortality data are another potential source for calibration models that have not been widely used, although the scope for this is probably limited in other generalised HIV epidemic settings without vital registration.

Even the models that were calibrated from previous household surveys did not match the increase in HIV prevalence in adults aged 15–49 years suggested by the 2012 household survey. There are several potential explanations for this. Models might not have captured the extent to which early ART uptake was dominated by initiation of ART in the sickest patients at high risk of dying; instead, most models considered all people with CD4 cell counts less than 200 cells per μL to have the same risk of mortality and HIV transmission and likelihood of starting ART. This assumption could result in models underestimating reductions in mortality and overestimating the infections averted because the sickest patients are unlikely to be transmitting HIV. Both factors would contribute to an underestimation of HIV prevalence.

Models might also have overestimated the effectiveness of ART at averting HIV transmission at the population level, or might have underestimated the effectiveness of ART at reducing HIV deaths. Model assumptions about the individual efficacy of ART at reducing mortality and transmission are based on randomised trial data[37–39] and supported by observational data,[40–42] which have been used to develop model assumptions. However, models might not have incorporated the persistent challenges in adherence and retention on ART that could limit the real-world effectiveness of ART at averting transmission compared with that achieved in trials. For example, models overestimated ART coverage among men aged 25–49 years, probably because they did not account for lower levels of HIV testing, treatment uptake, and retention on ART that have been consistently shown among men.[43]

Ongoing community-based trials of HIV treatment as prevention will generate evidence about the effects of large expansions of ART on population-wide HIV incidence (NCT01965470).[44,45] The ramifications of our findings for these trials depends on the underlying explanation for why prevalence and incidence were underestimated. If existing ART uptake has been more concentrated among the sickest patients and not those responsible for onward HIV transmission, then test-and-treat intervention strategies might have an even larger effect than existing projections if they can effectively

enrol people who are not accessing current treatment programmes. However, if the higher than anticipated incidence is the result of models having overestimated the real-world effectiveness of ART at preventing transmission, ART might reduce incidence less than expected based on model predictions.

Behavioural data from the 2012 household survey suggested increases in the proportion of adults who have several sexual partnerships and decreases in consistent condom use since 2008, whereas the models included in this comparison assumed that sexual behaviour would remain the same in the future. This difference represents one potential explanation for the underestimation of incidence by the models. However, increases in reported risk from the survey were largest among young adults aged 15–24 years, whereas model projections underestimated prevalence to a greater extent among older adults. Also, other recent survey data from South Africa have shown continuing reductions in risk behaviour.[46,47] Nevertheless, this survey finding emphasises the need to consider uncertainty about future changes in sexual behaviour in projections about the future course of the epidemic.

Compared with earlier eras in the HIV epidemic or other disease epidemics, all models were accurate, including capturing the overall magnitude of the epidemic, changes in the age pattern of the epidemic, and changes in mortality. This increased accuracy is largely attributable to the substantial investments in HIV surveillance and epidemiology from which these models have been developed and improved. However, aspects of our results also provide caution that consistency of a prediction by many models does not necessarily imply the correctness of the prediction, especially when models rely on the same information and the same understanding and interpretations of data and events. For example, several models calibrated to the same model-based epidemic estimates published by UNAIDS, and no model captured the magnitude of the sex differentials in uptake of ART. Epidemic estimates and short-term projections using models could be improved by (1) direct calibration to epidemiological data and careful interpretation of data from subpopulations such as pregnant women attending antenatal clinics; (2) carefully considering model assumptions underlying the effectiveness of ART at reducing transmission; and (3) incorporating information about the clinical, demographic, and epidemiological characteristics of those accessing services. Thus rapid, open, and routine reporting of clinical and programmatic data such as numbers tested, linked to care, initiated on ART, and defaulting, stratified by age and sex, are essential to improve model estimates and projections.

Although our analysis focused on the data-rich setting of South Africa, the lessons for HIV epidemiology and prevention generated are relevant more widely in generalised HIV epidemic settings in sub-Saharan Africa. Our findings do not necessarily contradict the theory that treatment could have, or has already had, a large effect on reducing transmission. They do suggest that expectations might have been overly optimistic about the extent to which HIV transmission would reduce as ART was scaled up, particularly for mid-aged (age 25–49 years) adults among whom prevalence and incidence were most consistently higher than anticipated. A further implication is that achieving targets for reductions in HIV incidence might require more intervention resources and longer time periods than previously forecasted. When HIV prevalence was assumed to be steadily increasing over the past decade, achievement of incidence reduction targets was estimated to take nearly three times as long as when prevalence was assumed to be constant.[13] As models are increasingly used to support policy planning, advocate and allocate resources, and assess programmes, surveillance and trial data must also continue to be collected to validate and improve the information that underlie these processes.

Contributors

JWE and TBH designed the study and prepared the first draft of the manuscript. JWE, NB, AB, VC, AC, RED, CF, CG, JACH, LFJ, DJK, ANP, CP, and JS did the model analyses. TMR did the data analyses. All authors edited the manuscript and approved the final version for submission.

Declaration of interests

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