Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models


Summary

Background New WHO guidelines recommend initiation of antiretroviral therapy for HIV-positive adults with CD4 counts of 500 cells per μL or less, a higher threshold than was previously recommended. Country decision makers have to decide whether to further expand eligibility for antiretroviral therapy accordingly. We aimed to assess the potential health benefits, costs, and cost-effectiveness of various eligibility criteria for adult antiretroviral therapy and expanded treatment coverage.

Methods We used several independent mathematical models in four settings—South Africa (generalised epidemic, moderate antiretroviral therapy coverage), Zambia (generalised epidemic, high antiretroviral therapy coverage), India (concentrated epidemic, moderate antiretroviral therapy coverage), and Vietnam (concentrated epidemic, low antiretroviral therapy coverage)—to assess the potential health benefits, costs, and cost-effectiveness of various eligibility criteria for adult antiretroviral therapy under scenarios of existing and expanded treatment coverage, with results projected over 20 years. Analyses assessed the extension of eligibility to include individuals with CD4 counts of 500 cells per μL or less, or all HIV-positive adults, compared with the previous (2010) recommendation of initiation with CD4 counts of 350 cells per μL or less. We assessed costs from a health-system perspective, and calculated the incremental cost (in US$) per disability-adjusted life-year (DALY) averted to compare competing strategies. Strategies were regarded very cost effective if the cost per DALY averted was less than three times the per-head gross domestic product (GDP); South Africa: $8040; Zambia: $1425; India: $1489; Vietnam: $1407) and cost effective if the cost per DALY averted was less than the country’s 2012 per-head gross domestic product (GDP; South Africa: $8040; Zambia: $1425; India: $1489; Vietnam: $1407) and cost effective if the cost per DALY averted was less than three times the per-head GDP.

Findings In South Africa, the cost per DALY averted of extending eligibility for antiretroviral therapy to adult patients with CD4 counts of 500 cells per μL or less ranged from $237 to $1691 per DALY averted compared with 2010 guidelines. In Zambia, expansion of eligibility to adults with a CD4 count threshold of 500 cells per μL ranged from improving health outcomes while reducing costs (ie, dominating the previous guidelines) to $749 per DALY averted. In both countries results were similar for expansion of eligibility to all HIV-positive adults, and when substantially expanded treatment coverage was assumed. Expansion of treatment coverage in the general population was also cost effective. In India, the cost for extending eligibility to all HIV-positive adults ranged from $131 to $241 per DALY averted, and in Vietnam extending eligibility to patients with CD4 counts of 500 cells per μL or less cost $290 per DALY averted. In concentrated epidemics, expanded access for key populations was also cost effective.

Interpretation Our estimates suggest that earlier eligibility for antiretroviral therapy is very cost effective in low-income and middle-income settings, although these estimates should be revisited when more data become available. Scaling up antiretroviral therapy through earlier eligibility and expanded coverage should be considered alongside other high-priority health interventions competing for health budgets.

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Introduction

In July, 2013, WHO issued consolidated guidelines for the use of antiretroviral drugs for the treatment and prevention of HIV infection.1 These guidelines recommended antiretroviral therapy for all HIV-positive adults whose CD4 count has fallen to 500 cells per μL or less, with treatment to be given irrespective of CD4 cell count for pregnant women, HIV-serodiscordant couples,
Evidently that antiretroviral therapy reduces HIV infectiousness suggests that increasing the number of HIV-positive adults who are on treatment could have the potential to change the course of the epidemic in highly affected regions. However, the resources necessary to implement these changes could be substantial. The recommendation for earlier initiation of antiretroviral therapy comes at a time when progress towards implementation of antiretroviral therapy is varied: at the end of 2012 only an estimated 61% of HIV-positive individuals with CD4 counts of 350 cells per μL or less in low-income and middle-income countries were receiving treatment. Even in settings where high coverage has been achieved, many patients start treatment late because of late HIV diagnosis and poor linkage to and retention in pre-antiretroviral care.

In this context, decision makers have to consider whether resources should be devoted to implementing earlier eligibility, achieving high coverage and timely initiation of antiretroviral therapy for individuals with the greatest clinical need, or expanding other health programmes that might generate greater health gains. This decision should be based on assessment of the population-level benefits and costs of strategies to expand eligibility for antiretroviral therapy or increase coverage, accounting for the additional resources that would be needed. Whereas clinical trials can be used to assess the effect of expanded eligibility criteria for individuals, mathematical models can be used to project the long-term effects of policy decisions. In the past decade, mathematical models have been useful for understanding the potential epidemiological effects, public health benefits, and costs of antiretroviral therapy in many populations.

To better inform policy for antiretroviral therapy, we assessed the potential effect of changes to adult eligibility guidelines for antiretroviral therapy and improvements in HIV testing and linkage to care in four low-income and middle-income countries. We calibrated existing, independently developed mathematical models to epidemic settings in South Africa (seven models), Zambia (four models), India (three models), and Vietnam (one model). All models were dynamic HIV transmission models that simulate HIV transmission in populations and HIV disease progression, and incorporate both the therapeutic benefits of antiretroviral therapy for reducing HIV morbidity and mortality and the preventive benefits associated with reduced HIV infectiousness (table 1).

We used model outputs that describe changes in the use of health care to estimate changes in costs borne by the HIV programme and the broader health system. We estimated the effects of intervention strategies on HIV incidence, antiretroviral therapy costs and non-antiretroviral therapy health-care costs, and disability-adjusted life-years (DALYs) averted by comparing model projections of different antiretroviral therapy eligibility and access strategies over 20 years. We calculated incremental cost-effectiveness ratios (ICERs; reported as cost per DALY averted) to compare alternative strategies.

Epidemiological modelling
The models represented three eligibility criteria by which antiretroviral therapy could be started for adult patients in care: HIV-positive adults with a CD4 count of 350 cells per μL or less (assumed to be the existing, baseline strategy); HIV-positive adults with a CD4 count of 500 cells per μL or less; and all HIV-positive adults. Each model simulated a baseline projection representing existing treatment coverage (ie, patterns of HIV testing, linkage to and retention in pre-antiretroviral care, and uptake of antiretroviral therapy), which we refer to as the status-quo access to HIV care.

All three eligibility criteria were simulated with the assumption of a continuation of status-quo access to HIV care—ie, patients started on antiretroviral therapy are those already being linked to HIV care programmes in accordance with existing patterns of access. Models also simulated each eligibility strategy with the assumption of substantial increases in routine HIV testing and linkage to care across the adult population, such that 80% of adults infected with HIV would be in care when they
became eligible for antiretroviral therapy. For concentrated-epidemic settings (India and Vietnam), models examined increased HIV testing and linkage to care in specific key populations (female sex workers, men who have sex with men, and injecting drug users), such that 80% of these populations had access to antiretroviral therapy, while access for the general population remained at the status quo.

Alternative strategies for antiretroviral therapy eligibility and coverage of HIV care were simulated for a 20 year period from the beginning of 2014 to the end of 2033. For strategies involving expanded access to HIV care, the simulated change in access was implemented gradually over 2 years from the beginning of 2014.

**Estimation of costs and cost-effectiveness**

We assessed incremental costs of each strategy from a health-system perspective, using a common costing framework across all models. The costs included were: service delivery costs necessary to identify and link HIV-positive individuals to care; service delivery costs for patients receiving antiretroviral therapy or pre-antiretroviral care; potential cost savings due to reduced use of health care in the wider health system as HIV-positive individuals start to receive care through the HIV programme; and costs associated with programmatic support and supply-chain management (table 2). All costs are in addition to the basic amount of spending needed to support the programme. Country-specific unit cost accounted for differences in prices between countries, and all costs are reported in 2012 US$. The upfront costs of infrastructure investments are spread over their useful lifetime. The costing framework and sources of cost estimates are described in the appendix (pp 9–14).

We summarised health benefits as DALYs averted, which capture improvements in both survival and quality of life that result from the direct benefits of antiretroviral therapy in extending life for HIV-positive individuals and from reduced numbers of HIV infections. Disability weights (table 3) were drawn from the Global Burden of Disease Study 2010, which assessed the value of life-years lived in different health states compared with full health.

We calculated ICERs as the incremental cost per DALY averted over 20 years by an intervention compared with a less effective, less costly alternative. Costs and health benefits were discounted by 3% per year. On the basis of WHO recommended benchmarks, an intervention was classified as very cost effective if its ICER was less than the country’s per-head gross domestic product (GDP) in 2012 (South Africa $8040; Zambia $1425; India $1489; Vietnam $1407), and cost effective if it was less than three times the per-head GDP.

**Table 1: Epidemiological models and simulated strategies**

<table>
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<tr>
<th>Setting</th>
<th>Model type*</th>
<th>Age-structured</th>
<th>Heterogeneous sexual risk in general population†</th>
<th>Key populations included in model‡</th>
<th>Notes§</th>
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<td>Female sex workers, men who have sex with men, and injecting drug users</td>
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</table>

*D = deterministic compartment model structure; M = individual-based microsimulation model. **All models for South Africa and Zambia simulate the entire adult population (age 15 years and older); the Mishra model for Belguam simulates the general adult population (age 15 years and older) of the Belguam municipality; the Pruddell model simulates only subpopulations of present and former female sex workers and their clients, and men who sex with men; the IDU-Manipur model simulates present and former male injecting drug users and their heterosexual partners; and the Pretool model for Vietnam simulates the general adult population (ages 15–45 years). ¶ Concentrated epidemic models (India and Vietnam) assess expanded testing and linkage to care among these populations. All models simulate eligibility for antiretroviral therapy for adult patients with CD4 counts of 350 cells per μL or less, and eligibility for all HIV-positive adults. ¶¶ The Mishra model was also used for a second baseline simulation in which the increases in condom usage and access to antiretroviral therapy for female sex workers that followed the implementation of the Avahan intervention programme had not occurred and access to antiretroviral therapy for HIV-positive individuals (including female sex workers) remained poor, resulting in higher HIV incidence.

**Table 1: Epidemiological models and simulated strategies**

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Sciences, University of Witwatersrand, Johannesburg, South Africa (G Meyer-Rath); Centre for Health Economics, University of York, York, UK (P Revill PhD); and Department of HIV/AIDS, WHO, Geneva, Switzerland (M Doherty PhD, N Shaffer MD), Prof P J Easterbrook MD, G Hirschl MD)

Correspondence to: Prof Timothy Hallett, Department of Infectious Disease Epidemiology, Imperial College London, London W2 1PG, UK timothy.hallett@imperial.ac.uk

See Online for appendix
Role of the funding source

Authors from WHO contributed to the design of the study, and the selection of settings investigated and strategies assessed, but had no role in the development or selection of epidemiological models, conduct of the analyses, or interpretation of results. The Bill & Melinda Gates Foundation had no role in the design of the analysis, interpretation of the results, or the decision to submit for publication. The corresponding author had final responsibility for the decision to submit for publication.

Results

We first examined whether it would be cost effective to change antiretroviral therapy eligibility criteria for adults in generalised-epidemic settings (ie, South Africa and Zambia). In South Africa, the ICER for changing the CD4 count threshold from 350 cells per μL to 500 cells per μL ranged from $273 to $1691 per DALY averted over 20 years (results from six models; figure 1). The cost per DALY averted for changing eligibility to all HIV-positive adults compared with eligibility for those with CD4 counts of 350 cells per μL or less ranged from $438 to $3790 (seven models). In Zambia, the ICER for expanding eligibility to patients with CD4 counts of 500 cells per μL or less ranged from improving health outcomes while reducing costs (ie, dominating the previous guidelines) to $749 per DALY averted (four models). For expanding eligibility to all HIV-positive adults compared with eligibility for those with CD4 counts of 500 cells per μL or less, results ranged from dominating the previous guidelines to $790 per DALY (four models).

The lower cost-effectiveness ratios in Zambia compared with South Africa are partly due to lower non-antiretroviral costs in Zambia (table 2). For South Africa and Zambia, most models showed slightly higher costs per DALY averted for expanding antiretroviral therapy eligibility to all HIV-positive adults compared with eligibility for those with CD4 counts of 350 cells per μL or less ranging from $438 to $3790 (seven models). In Zambia, the ICER for expanding eligibility to patients with CD4 counts of 500 cells per μL or less ranged from $749 to $790 per DALY averted (four models).

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Repeating the analysis for generalised epidemics with an assumption of greatly expanded HIV testing and linkage to care generated similar cost-effectiveness ratios (appendix pp 20–21). ICERs that compared costs and benefits over a shorter time period were much greater than for the full 20 year period (appendix pp 20–21); for example, in South Africa, over 5 years the highest ICER for changing the CD4 count threshold from 350 cells per μL to 500 cells per μL was $11646, compared with $1691 over a 20 year period (with the assumption of status-quo treatment coverage). This finding is because the effect of increased use of antiretroviral therapy in reducing HIV transmission tends to increase over time in the models (appendix p 18).

We next examined the cost-effectiveness of changing the eligibility criteria in concentrated-epidemic settings. In Vietnam, where the HIV epidemic is driven by female sex workers, men who have sex with men, and injecting drug users, the ICER was $290 for changing the CD4 count threshold from 350 cells per μL to 500 cells per μL and $289 for extending eligibility to all HIV-positive adults. In Bangalore, India, where the epidemic is driven by female sex workers and men who have sex with men, the ICER associated with eligibility for all HIV-positive adults compared with eligibility for those with CD4 counts of 350 cells per μL or less was $131 per DALY averted. In Manipur, India, where HIV is mainly spread by unsafe drug injection, the ICER for extending eligibility to all HIV-positive adults was $197 compared with eligibility for those with CD4 counts of 350 cells per μL or less. All of these policy changes would be very cost effective.

In Belgaum district in southern India, where the epidemic is mainly associated with female sex workers, the ICER for eligibility for all HIV-positive adults compared with eligibility for those with CD4 counts of 350 cells per μL or less was $198 per DALY averted. Belgaum has undergone substantial reductions in HIV incidence in the past decade, associated with targeted interventions that have increased condom use and access to HIV care and treatment among sex workers.\(^2,3\) In a simulated scenario in which this intervention programme did not exist, the ICER would be $241 per DALY averted. Thus, earlier eligibility for antiretroviral therapy would be very cost effective in epidemic settings similar to Belgaum with or without such programmes.

Change in eligibility for initiation of antiretroviral therapy is only one way in which decision makers could respond to the new guidelines. They could instead invest in expanding access (ie, HIV testing and linkage to care) to improve treatment coverage for individuals in greatest need (with CD4 counts of 350 cells per μL or less), or they could simultaneously adopt earlier eligibility criteria and expand testing and linkage to care. We also used the model results to compare these alternatives.

The relative effects of these competing approaches with respect to incidence reduction differed between settings (figure 2). In South Africa, where existing antiretroviral therapy coverage is moderate, expansion of eligibility to adults with CD4 counts of 500 cells per μL or less would avert only 5–12% of new infections over 20 years. By contrast, expansion of testing and linkage to care while maintaining the CD4 count threshold of 350 cells per μL would have a larger effect across the models (6–28% of infections averted). Changing eligibility to all HIV-positive adults would avert 9–32% without expansions in testing and linkage,
or 19–60% with such expansions. This relation is reversed in Zambia, which has higher coverage of antiretroviral therapy than South Africa: in all models, expansion of eligibility to all HIV-positive adults (21–40% infections averted) averted more infections than expansion of testing and linkage to care while maintaining the CD4 count threshold of 350 cells per μL (8–17%).

In both South Africa and Zambia, the additional costs of strategies that expand testing and linkage to care are much higher than the costs of strategies that only change eligibility (figure 3). Earlier initiation of antiretroviral therapy for people who are already attending the clinic has a fairly low incremental cost because the cost of the additional years of antiretroviral

Figure 2: Projected annual HIV incidence per 100 person-years for different strategies of antiretroviral therapy eligibility and access to HIV care, by country and model

In the generalised-epidemic settings (South Africa and Zambia), expanded access refers to expanded testing and linkage to care for the general population. In concentrated-epidemic settings (India and Vietnam), expanded access refers to expanded testing and linkage to care for all high-risk groups (female sex workers, men who have sex with men, and injecting drug users).
therapy are partly offset by savings in pre-antiretroviral monitoring and other averted health-care costs. By contrast, strategies that expand testing and linkage to care require additional expenditure for HIV testing, pre-antiretroviral monitoring, and antiretroviral therapy for patients diagnosed through expanded testing.

If the objective is to maximise the health returns per dollar spent, as an initial step of programme expansion, countries could prioritise the strategy that has the lowest cost per DALY averted (figure 4). All models for Zambia suggest that expanding eligibility has the lowest cost per DALY averted. This result is robust to alternative assumptions about the relative costs of HIV testing and linkage, pre-antiretroviral monitoring, and provision of antiretroviral therapy (figure 4). Four of seven models for South Africa suggest the same, but three models instead suggest that starting testing and linkage to care would have the lowest cost per DALY averted. Overall, these results suggest that in settings with moderate to high coverage, expanding eligibility might be the preferred initial strategy. But expanding testing and linkage to care while maintaining the CD4 count eligibility threshold of 350 cells per μL might be a preferred initial strategy in settings with lower coverage, especially if testing and pre-antiretroviral monitoring costs are low compared with the costs of providing antiretroviral therapy. Ultimately, both forms of expansion (i.e., eligibility and testing and linkage) would be cost effective relative to benchmarks—if a country were to proceed by initially expanding in one way, it would still be cost effective to extend services in the other way subsequently.

Whereas in generalised epidemics testing and linkage campaigns were assumed to be implemented in the general population, in concentrated epidemics it might be preferable to focus resources on specific populations. In Belgaum, India, expanding eligibility to all HIV-positive female sex workers, to all HIV-positive adults, or to all HIV-positive adults (with expanded HIV testing and linkage to care for female sex workers) would all be very cost effective. The more extensive of these strategies would lead to greater reductions in new infections, albeit at a greater cost per DALY averted (table 4). However, intervention to expand testing and linkage to care for all adults in the general population resulted in an ICER of $5648 per DALY, which would not be cost effective, although it could lead to the largest effect on HIV incidence (53% of infections averted). Each of these interventions had lower ICERs in the simulated scenario that did not include the effect of the prevention programmes in Belgaum (table 4).

For Vietnam, results were qualitatively similar to Belgaum (table 4); whereas expanding eligibility for the whole population and intervening to expand testing and linkage to care for female sex workers, men who have sex with men, and injecting drug users would be cost effective, interventions to expand testing and linkage for the whole population would not (ICER $21549).

Figure 3: Incremental costs over 20 years for different strategies of ART eligibility and access to HIV care compared with continuation of 2010 eligibility guidelines and status-quo access to care, by country

Costs are undiscounted, and reported in 2012 US$. Costs below the horizontal axis represent cost savings. In generalised-epidemic settings (South Africa and Zambia), expanded access (EA) refers to expanded testing and linkage to care for the general population. In concentrated-epidemic settings (India and Vietnam), expanded access refers to expanded testing and linkage to care for all high-risk groups (female sex workers [FSW], men who have sex with men [MSM], and injecting drug users [IDU]). For South Africa and Zambia, within each strategy each bar represents a model in the same sequence as the bars in figure 1. The models for Belgaum and Vietnam also simulated expanded testing and linkage to care for the general adult population (table 4, appendix pp 17–19 and 22–23). ART=antiretroviral therapy. SQA=status-quo access. All=all HIV-positive adults.
HIV-positive adults was very cost effective over a 20 year period. These findings reflect the fairly low cost of providing additional years of antiretroviral therapy to people in care and the assumption that expanded access to antiretroviral therapy will reduce HIV transmission in the whole population, adding to the well established clinical benefits of antiretroviral therapy in the reduction of morbidity and improvement of survival of HIV-positive individuals (panel).

In the generalised-epidemic settings we examined, all models suggested that immediate implementation of the new WHO clinical recommendations for patients with CD4 counts of 500 cells per μL or less to start treatment would be cost effective, even in settings where testing and linkage to care are still being increased to achieve universal access under the 2010 guidelines (in which patients are eligible if their CD4 cell count is 350 cells per μL or less). However, the models also show that, in settings where treatment coverage is incomplete, changing the eligibility criteria alone without an increase in access to HIV care, although cost effective, would have a smaller effect on health than would be achieved by increasing coverage of antiretroviral therapy for patients with a CD4 cell count of 350 cells per μL or less. Our modelling did not take into account cases in which resources are severely constrained, resulting in waiting lists of patients with low CD4 cell counts, or situations in which earlier eligibility would reduce access to antiretroviral therapy for patients with the greatest therapeutic need. The WHO guidelines recommend that, in such cases, treatment should be prioritised for patients with CD4 counts of 350 cells per μL or less.

In concentrated-epidemic settings, we estimated that extending eligibility for antiretroviral therapy to all HIV-positive adults or those with CD4 counts of 500 cells per μL or less already in care would be very cost effective. We also estimated that increases in HIV testing to achieve universal access to immediate antiretroviral therapy for members of specific populations—namely

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**Figure 4:** Threshold analysis showing the strategies associated with the lowest cost per DALY averted for a specific percentage change in the baseline cost assumed for pre-antiretroviral care and HIV diagnostic testing and linkage to care, by country and model.

All strategies are compared with the baseline strategy (ie, continuation of the guidelines in which patients with CD4 counts of 350 cells per μL or less are eligible for antiretroviral therapy and status-quo access to HIV care).
female sex workers, men who have sex with men, and injecting drug users would be very cost effective in India, and cost effective in Vietnam. By contrast, widespread interventions to uniformly expand access to testing and treatment services for the general population were not estimated to be cost effective in concentrated-epidemic settings. Other testing strategies not included in our analyses, such as provider-initiated testing, might be more efficient at identifying HIV-positive adults, and could potentially be cost effective in these settings.

Our results also suggest that investments in earlier eligibility for antiretroviral therapy should be regarded as a long-term investment in population health. Although upfront costs are high, the health benefits generated by expanded eligibility increase over time (appendix p 18), such that the cost of averting ill health and premature death becomes progressively lower as cost and benefits are assessed over longer time periods (appendix pp 20–23). However, by contrast with the conclusions of earlier analyses, our results did not show that the most effective interventions will be cost-saving over a 20 year period.

This analysis brought together several independent models to examine the same policy question, and their collective findings were in general agreement about the cost-effectiveness of earlier eligibility for antiretroviral therapy. The variation in some of the model results emphasises existing uncertainties and key directions for further data collection. Factors that contribute to this variation include different fundamental representations of the underlying epidemiology of HIV transmission and different expectations about future patterns of treatment uptake and effectiveness. Several studies currently in progress or planned will provide further data about other key assumptions that directly underlie our conclusions—particularly with respect to the therapeutic benefits of earlier antiretroviral therapy (NCT00867048, NCT00495651), the scaling up of the individual prevention efficacy of antiretroviral therapy to produce population-level health benefits33 and the effect of antiretroviral therapy on risk behaviours (NCT01965470, NCT01900977, and NCT01509508), and the reduction of transmission risk through use of antiretroviral therapy by men who have sex with men34 and injecting drug users.35


domestic model (without condom intervention)

Eligibility for female sex workers, status-quo access 1% 146 2 $37 1 ··†
Eligibility for all HIV-positive adults, status-quo access 1% 149 1 $36 8 ··†
Eligibility for all adults with a CD4 count ≤500 cells per μL, status-quo access 4% 175 6 $47 5 ··†
Eligibility for all HIV-positive adults, status-quo access 12% 367 1 $47 5 ··†
Eligibility for all adults with a CD4 count ≤500 cells per μL, prioritised access for female sex workers, men who have sex with men, and injecting drug users 52% 2082 5 $2485 7 $1586
Eligibility for all HIV-positive adults, prioritised access for female sex workers, men who have sex with men, and injecting drug users 52% 2082 5 $2485 7 $1586
Eligibility for all adults with a CD4 ≤500 cells per μL, expanded access 37% 2544 5 $25 692 5 ··†
Eligibility for all HIV-positive adults, expanded access 63% 3278 2 $25 725 4 $21 550

Table 4: Health benefits and costs of expanded eligibility or access to HIV care over 20 years, compared with 2010 eligibility guidelines and status-quo access to care

All costs are in 2012 US$. Proportion of infections averted, cumulative disability-adjusted life-years (DALYs) averted, and cumulative additional costs over 20 years are relative to eligibility for patients with CD4 counts of 350 cells per μL or less and status-quo access to HIV care (undiscounted). Incremental cost-effectiveness (ICER) is the incremental cost per DALY averted over 20 years relative to the next most expensive strategy (excluding dominated strategies, which produce fewer health benefits at higher cost); costs and estimated DALYs averted discounted at 3% per year. †Dominated strategy.
In concentrated-epidemic settings, increased HIV testing and linkage to care to improve programme access was cost effective and should also be considered alongside other high-priority health interventions in low-income and middle-income countries, relative to conventional WHO cost-eff ectiveness benchmarks. Adoption of these recommendations should be considered by policy makers. In concentrated-epidemic settings, broad expansions of HIV testing and linkage to care to improve programme access was cost effective and should also be considered by policy makers. In concentrated-epidemic settings, increased HIV testing and linkage to care for key populations at risk of transmitting HIV was very cost eff ective and should be considered where possible. Widespread HIV testing programmes aimed at and linkage to care services also add uncertainty to our estimates. Growing evidence suggests that unit costs of patients through care services also add uncertainty to our estimates. 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should be considered alongside other high-priority health interventions competing for health budgets in low-income and middle-income countries.

Contributors
TBH conceived the study and was responsible for the overall design. TBH, JWE, MD, NSh, PJfE, GH, and others contributed to the design of the study. JWE coordinated and analysed the results of the epidemiological model simulations. NAM led the design of the economic analysis and analysed cost data. JS, VC, IC, AC, JACH, SH, CCK, DJK, SM, KMM, BEN, and PV led the analysis of the epidemiologic models. RB, TB, AB, DEB, M-CB, STC, TC, PJd, CF, CG, JL, NRM, NAM, EMi, EMO, QDP, MP, AP, LP, CP, HJP, JAS, DAMcCvd, SJJV, BGW, BGW, DPW, and LZ contributed to the development and analysis of the epidemiologic models. JB, GM-R, BEN, MR, PR, JAS, Nsa, and FT-P contributed to the development of the economic model and the calculation of cost data. All authors approved the final version of the report for submission.

Conflicts of interest
AP has received research funds from Bristol-Myers Squibb and WHO and has received payment for consulting work from Gilead Sciences and GSK Biologicals. All other authors declare that they have no conflicts of interest.

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