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

Jeffrey W Eaton, Nicolas A Menzies*, John Stover, Valentina Cambiano, Leonid Chindelevitch, Anne Cori, Jan A C Hontelez, Salal Humair, Cliff C Kerr, Daniel J Klein, Sharmistha Mishra, Kate M Mitchell, Brooke E Nichols, Peter Vickerman, Roel Bakker, Till Bärnighausen, Anna Bershteyn, David E Bloom, Marie-Claude Boily, Stewart T Chang, Ted Cohen, Peter J Dodd, Christophe Fraser, Chaitra Gopalappa, Jens Lundgren, Natasha K Martin, Evelinn Mikkelsen, Elisa Mountain, Quang D Pham, Michael Pickles, Andrew Phillips, Lucy Platt, Carel Pretorius, Holly J Prudden, Joshua A Salomon, David A M C van de Vijver, Sake J de Vlas, Bradley G Wagner, Richard G White, David P Wilson, Lei Zhang, John Blandford, Gesine Meyer-Rath, Michelle Remme, Paul Revill, Nalinee Sangrujee, Fern Terris-Prestholt, Meg Doherty, Nathan Shaffer, Philippa J Easterbrook, Gottfried Hirnschall, Timothy B Hallett*

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 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.

Funding Bill & Melinda Gates Foundation, WHO.

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,

Lancet Glob Health 2014; 2: e23–34

Published Online December 10, 2013 http://dx.doi.org/10.1016/S2214-109X(13)70172-4

See Comment page e2

See Online for an audio interview with Tim Hallett

*Contributed equally

MRC Centre for Outbreak Analysis and Modelling (A Cori PhD, Prof C Fraser PhD), **Department of Infectious Disease Epidemiology** (J W Eaton PhD, S Mishra MD, M-C Boily PhD, E Mountain MSc, M Pickles PhD, Prof T B Hallett PhD), **Imperial College London, London, UK; Center for Health Decision Science** (N A Menzies MPH, Prof J A Salomon PhD), **Department of Global Health and Population** (L Chindelevitch PhD, J A Salomon, S Humair PhD, T Bärnighausen DSc, Prof D E Bloom PhD), **and Department of Epidemiology** (T Cohen DPH), **Harvard School of Public Health, Boston, MA, USA; Futures Institute, Glastonbury, CT, USA** (J Stover MA, C Gopalappa PhD, C Pretorius PhD); **Research Department of Infection and Population Health, University College London, London, UK** (V Cambiano MS, Prof A Phillips PhD); **Department of Public Health** (J A C Hontelez PhD, R Bakker PhD, S J de Vlas PhD) **and Department of Virology**

(B E Nichols MS, D A M C van de Vijver PhD), **Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands; Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Mtubatuba, South Africa** (J A C Hontelez, T Bärnighausen)**; Nijmegen International Center for Health System Analysis and Education (NICHE), Department of Primary and Community Care, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands** (J A C Hontelez, E Mikkelsen MSc)**; Kirby Institute, University of New South Wales, Sydney, Australia** (C C Kerr PhD, Q D Pham MD, D P Wilson PhD, L Zhang PhD)**; Institute for Disease Modelling, Intellectual Ventures Laboratory, Bellevue, WA, USA** (D J Klein PhD, A Bershteyn PhD, S T Chang PhD, B G Wagner PhD)**; Division of Infectious Diseases, St Michael's Hospital, University of Toronto, Toronto, ON, Canada** (S Mishra)**; Social and Mathematical Epidemiology Group** (K M Mitchell PhD, Prof P Vickerman DPhil, N K Martin DPhil, L Platt PhD, H J Prudden MSc, M Remme MSc, F Terris-Prestholt PhD) **and Department of Infectious Disease Epidemiology** (P J Dodd PhD, R G White PhD)**, London School of Hygiene & Tropical Medicine, London, UK; Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA** (T Cohen)**; Centre for Viral Diseases, Department of Infectious Diseases, Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark** (Prof J Lundgren DMSc)**; Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark** (J Lundgren)**; School of Social and Community Medicine, University of Bristol, Bristol, UK** (N K Martin)**; Division of Global HIV/AIDS, US Centers for Disease Control and Prevention, Atlanta, GA, USA** (J Blandford PhD, N Sangrujee PhD)**; Center for Global Health and Development, Boston University, Boston, MA, USA** (G Meyer-Rath PhD)**; Health Economics and Epidemiology Research Office, Department of Medicine, Faculty of Health**

and individuals with active tuberculosis or hepatitis-B-associated severe chronic liver disease. The decision to increase the threshold CD4 count from the 350 cells per µL recommended in 2010 was reached through a structured GRADE (Grading of Recommendations Assessment, Development and Evaluation) review process that assessed evidence for the clinical and epidemiological benefits of earlier HIV initiation.[2]

Evidence that antiretroviral therapy reduces HIV infectiousness[3,4] 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.[5,6] However, the resources necessary to implement these changes could be substantial.[1] 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.[7] 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.[8–10]

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.[11] 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.[5,11–14]

To better inform policy for antiretroviral therapy, we assembled 12 independently developed HIV epidemic models to generate estimates for the health benefits, costs, and cost-effectiveness of earlier eligibility for antiretroviral therapy using the most recent available evidence. We also assessed the cost-effectiveness of increasing HIV testing and linkage to care to improve coverage of antiretroviral therapy. The use of several models allows for the identification of conclusions that can be robustly reproduced across models, which is crucial in view of the wide range of results seen in previous analyses.[6] Because optimum strategies might be expected to differ in settings with different epidemic types, existing coverage of antiretroviral therapy, and income, we selected four countries with existing models of the effect of antiretroviral therapy as case studies in an effort to produce guidance applicable to a broad set of epidemic 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).

Methods

Overview

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,[28] 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.[29] 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),[30] and cost effective if it was less than three times the per-head GDP.[29]

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 Hirnschall 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

	Setting	Model type*	Age-structured	Heterogeneous sexual risk in general population†	Key populations included in model‡	Notes§
Goals[15]	South Africa and Zambia	D	Yes	Yes	Female sex workers and men who have sex with men	Incorporates tuberculosis disease
STDSIM[16]	South Africa	M	Yes	Yes	Female sex workers	..
EMOD[17]	South Africa and Zambia	M	Yes	Yes	..	..
BBH[18]	South Africa	D	No	No	Female sex workers and men who have sex with men	..
PopART[19]	South Africa and Zambia	D	No	Yes	..	Incorporates tuberculosis disease
Synthesis[20]	South Africa	M	Yes	Yes	..	Includes WHO stage 4 HIV disease as a criteria for antiretroviral therapy
Menzies[21]	South Africa	D	No	No	..	Incorporates tuberculosis disease; does not include threshold CD4 count of 500 cells per μL
Macha[22]	Zambia	D	No	No	..	..
Pruddell[23]	Bangalore, India	D	No	NA	Female sex workers and men who have sex with men	Does not include threshold CD4 count of 500 cells per μL
Mishra[24]	Belgaum, India¶	D	No	No	Female sex workers	Does not include threshold CD4 count of 500 cells per μL
IDU-Manipur[26]	Churachandpur, India	D	No	NA	Present and former injecting drug users	Incorporates hepatitis C disease; does not include threshold CD4 count of 500 cells per μL
Prevtool[27]	Vietnam	D	No	No	Female sex workers, men who have sex with men, and injecting drug users	..

*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 Belgaum simulates the general adult population (age 15 years and older) of the Belgaum 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 Prevtool model for Vietnam simulates the general adult population (ages 15–49 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[25] 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**

	South Africa	Zambia	India	Vietnam
Costs of ART provision				
Antiretroviral drug cost (per person-year)	$143	$141	$91	$105
Non-antiretroviral cost (per person-year)	$422	$217	$128	$198
ART initiation for patients in pre-ART care (per initiation)	$95	$49	$29	$45
ART initiation for patients not in pre-ART care (per initiation)	$126	$65	$38	$59
Cost of pre-ART care (per person-year)				
CD4 count >350 cells per μL	$205	$127	$73	$145
CD4 count >200–350 cells per μL	$238	$139	$81	$150
CD4 count ≤200 cells per μL	$359	$185	$109	$169
Cost of HIV testing and linkage (per diagnostic test done)				
General population	$20	$10	$6	$9
Female sex workers, men who have sex with men, and injecting drug users	$67	$34	$20	$31
Costs of health-care use				
CD4 count >350 cells per μL, not in HIV care (per person-year)	$13	$5	$3	$2
CD4 count >200–350 cells per μL, not in HIV care (per person-year)	$46	$17	$11	$7
CD4 count ≤200 cells per μL, not in HIV care (per person-year)	$167	$63	$39	$26
End-of-life care (per death)	$160	$50	$34	$32
Tuberculosis treatment (per case treated)	$364	$188	$110	$172
Supply-chain management and programmatic support (% mark-up)				
Supply-chain management*	20%	20%	20%	20%
Programmatic support†	50%	50%	50%	50%

All costs are in 2012 US$. ART=antiretroviral therapy. *Mark-up assessed on the basis of antiretroviral drug costs. †Mark-up assessed on the basis of all costs apart from antiretroviral drugs.

***Table 2*: Unit costs**

	Disability weight
HIV-positive, CD4 count >350 cells per μL (untreated)*	0·053
HIV-positive, CD4 count >200–350 cells per μL (untreated)	0·221
HIV-positive, CD4 count ≤200 cell per μL (untreated)	0·547
HIV-positive, on antiretroviral therapy	0·053
Tuberculosis disease	0·331

Disability weights are based on reference 26. For individuals with comorbidity (eg, concurrent HIV and tuberculosis disease), disability weights were compounded multiplicatively. *HIV infection with a CD4 count of 350 cells per μL or greater was assumed to cause the same disability (0·053) as is incurred by individuals receiving antiretroviral therapy.

***Table 3*: Disability weights by health state**

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 350 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 expansion to those with CD4 counts of 500 cells per μL or less (five of six models for South Africa and two of four for Zambia). However, these models also showed that the expansion of eligibility from a CD4 threshold of 500 cells per μL to all HIV-positive adults was still either cost effective or very cost effective (figure 1).

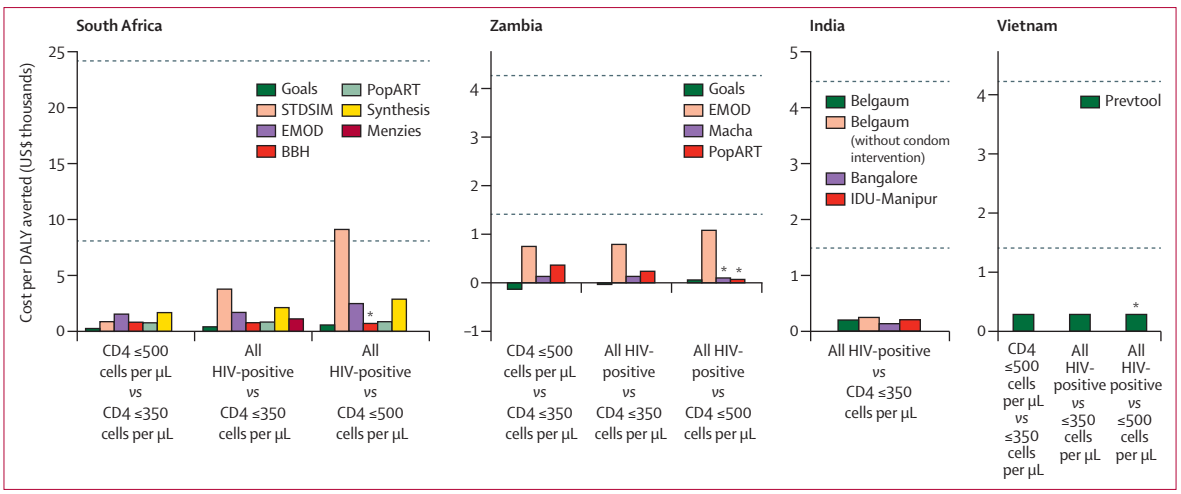

Figure 1: **Incremental cost per DALY averted for expanding eligibility criteria for antiretroviral therapy, by country and model**
Results calculated over 20 years, with all costs and health benefits discounted at 3% per year. All costs are in 2012 US$. Values below the upper dashed line (three-times per-head gross domestic product [GDP]) are defined as cost effective; those below the lower dashed line (per-head GDP) are defined as very cost effective. The Menzies model (South Africa) and all models for India simulated only expanding eligibility to all HIV-positive adults. For the Goals model in Zambia, the estimated incremental cost-effectiveness ratio (cost per disability-adjusted life-year [DALY] averted) is negative because over 20 years the strategy produces health benefits and is estimated to be cost-saving because of the reduced treatment and care burden, including savings due to averted cost of tuberculosis treatment. *Indicates that eligibility for patients with CD4 counts of 500 cells per μL or less is dominated by the other strategy (ie, produces fewer health benefits at higher cost).

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 $11 646, 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.[25,31] 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,

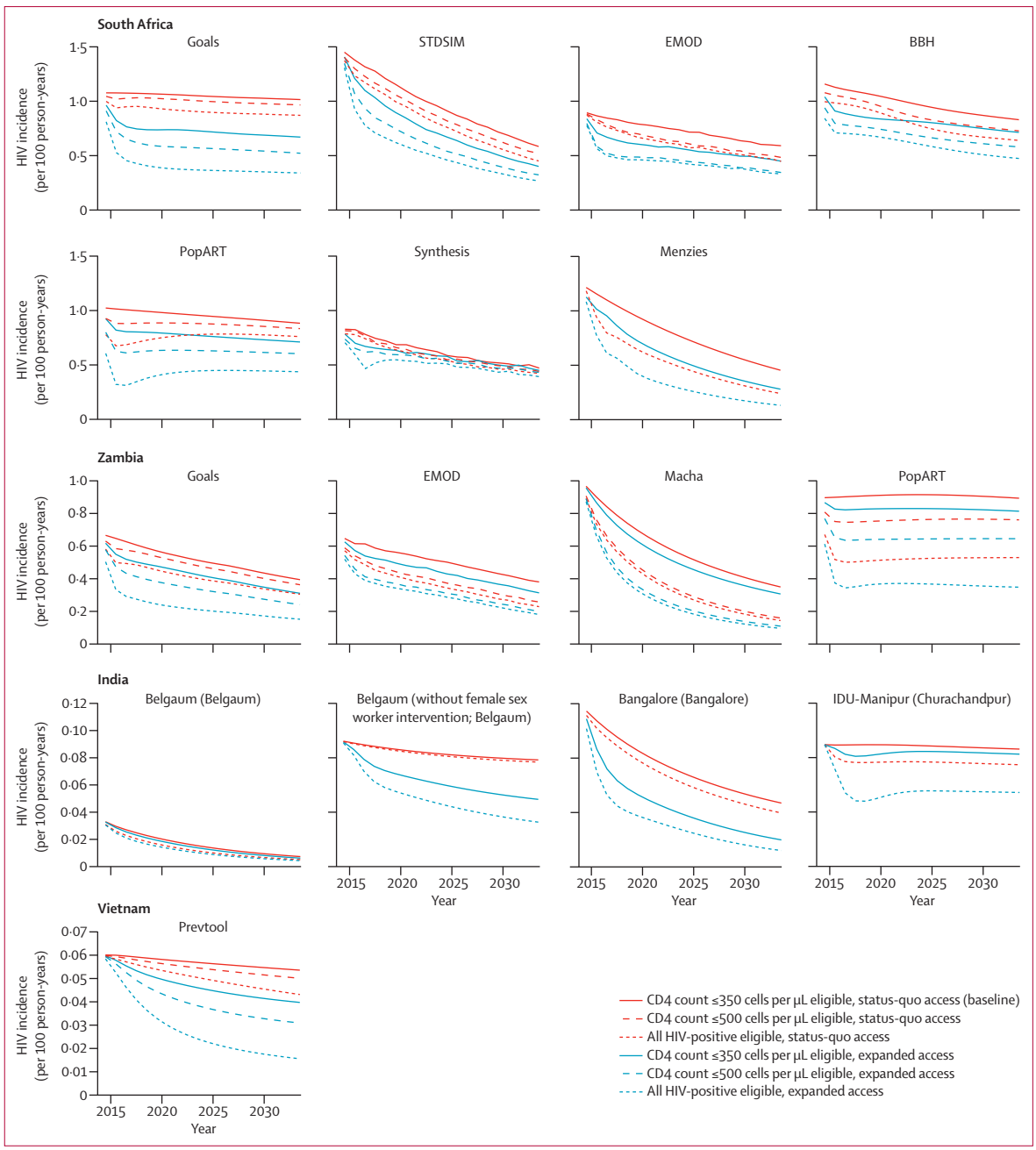

Figure 2: **Projected annual HIV incidence per 100 person-years for different stategies of antiretroviral therapy eligibility and access to HIV care, by country and model**

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).

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

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 expanding 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 (ie, 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 $21 549).

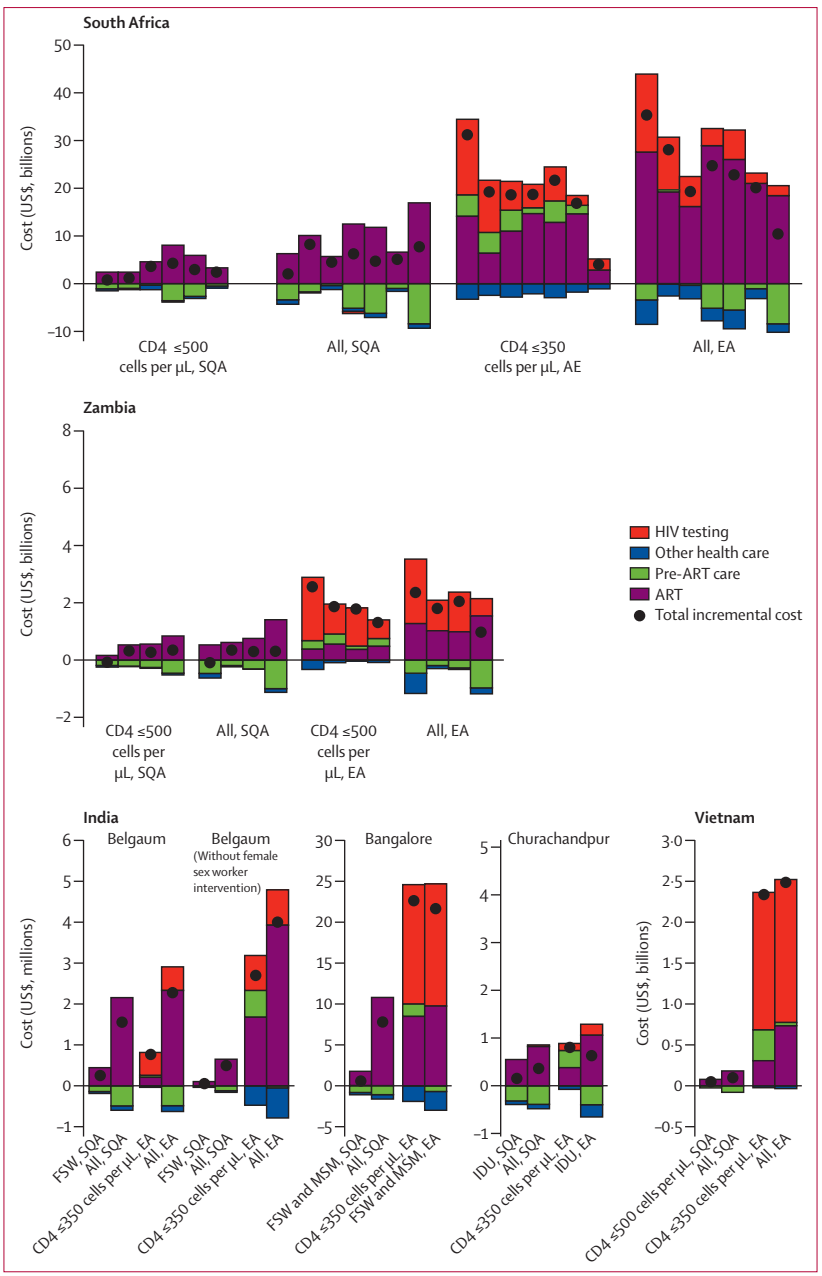

Figure 3: **Incremental costs over 20 years for different strategies of ART eligibility and access to HIV care compared with continuation of 2010 eligibility guidelines and status-quo access to care, by country**
Costs are undiscounted, and reported in 2012 US$. Costs below the horizontal axis represent 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.

Discussion

In all settings and across all models, extension of adult eligibility for antiretroviral therapy to people already in care with CD4 counts of 500 cells per µL or less, or to all

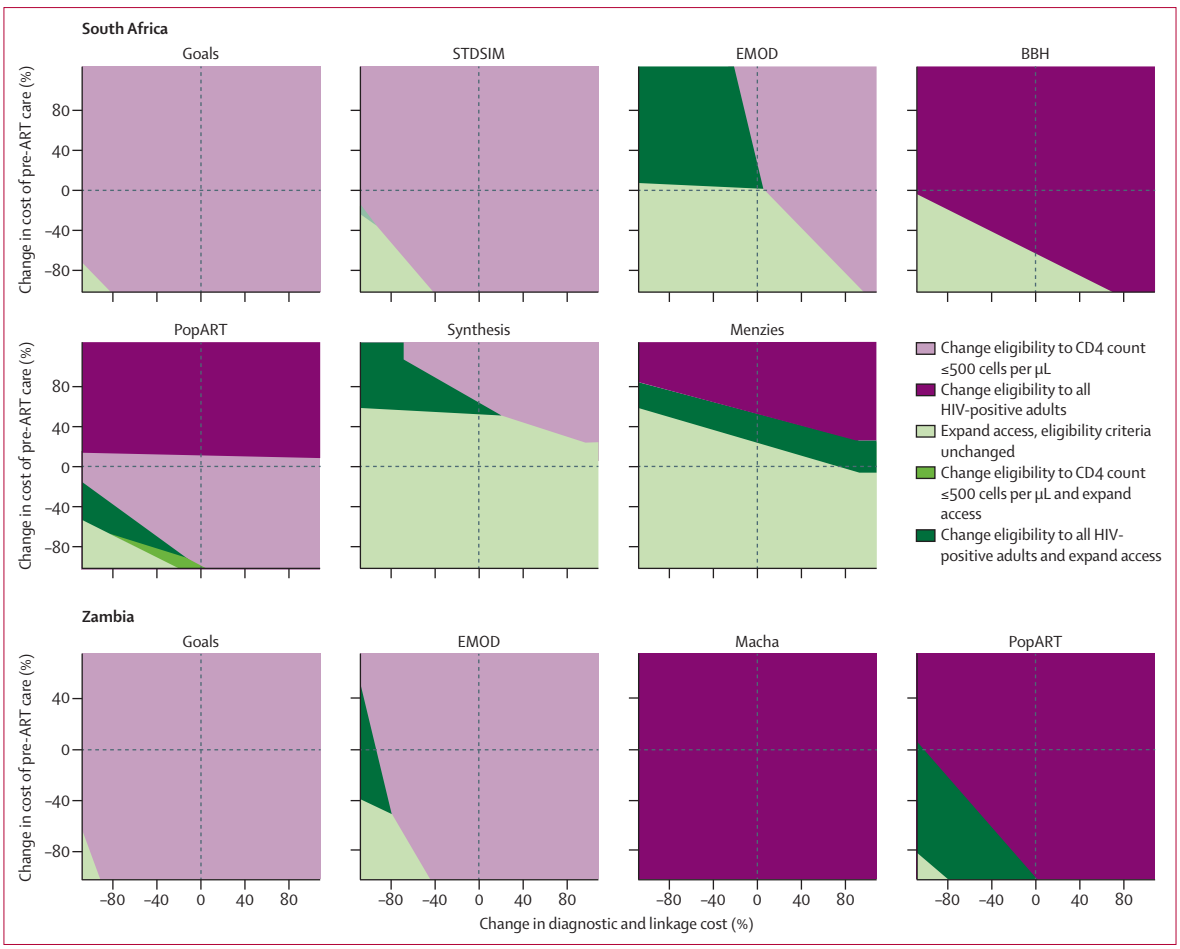

Figure 4: **Threshold analysis showing the strategies associated with the lowest cost per DALY averted for a specific percentage change in the baseline cost assumed for pre-antiretroviral care and HIV diagnostic testing and linkage to care, by country and model**
All strategies are compared with the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

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[1] 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

	Infections averted (%)	DALYs averted (thousands)	Additional cost (US$, millions)	ICER (US$)*
India				
Belgaum model				
Eligibility for female sex workers, status-quo access	13%	3·5	$0·2	$85
Eligibility for all HIV-positive adults, status-quo access	21%	9·0	$1·6	$268
Eligibility for all HIV-positive adults, prioritised access for female sex workers	29%	11·0	$2·3	$395
All HIV-positive adults, expanded access	52%	33·8	$123·9	$5648
Belgaum model (without condom intervention)				
Eligibility for female sex workers, status-quo access	1%	0·9	$0·1	$73
Eligibility for all HIV-positive adults, status-quo access	1%	2·2	$0·5	..†
Eligibility for all HIV-positive adults, prioritised access for female sex workers	41%	37·6	$4·0	$123
Eligibility for all HIV-positive adults, expanded access	66%	108·9	$138·7	$2054
Vietnam				
Prevtool model				
Eligibility for female sex workers, status-quo access	2%	41·5	$5·9	$161
Eligibility for men who have sex with men, status-quo access	5%	146·2	$37·1	..†
Eligibility for injecting drug users, status-quo access	5%	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	$96·4	$305
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	30%	1497·5	$2442·6	..†
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

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.

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**

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,[5,12,32] 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 benefits[33] 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 men[34] and injecting drug users.[35]

Comparisons of model predictions with observational data can be useful. The epidemiological effects of high antiretroviral therapy coverage in high-income countries have seemingly been mixed,[36–41] but one observational

***Panel:* Research in context**

Systematic review

Recently WHO issued revised guidance for the use of antiretroviral therapy that includes the recommendation that HIV-positive adults should start receiving antiretroviral therapy when their CD4 count falls to 500 cells per μL or less.[1] Countries now have to decide whether to adopt and implement these recommendations. Reductions in HIV infectiousness for people who start antiretroviral therapy earlier[3] mean that both the individual therapeutic benefits and prevention benefits have to be taken into account when assessing the public health benefits of earlier eligibility for antiretroviral therapy. Many mathematical models have been developed to examine the population-level health benefits and costs of different strategies for antiretroviral therapy in low-income and middle-income country settings, and previous work has shown that results from different analyses can vary widely.[6] This finding suggests that taking into account results across different models and epidemic settings is essential for assessing the health effect and cost-effectiveness of earlier eligibility to inform policy decisions.

Interpretation

Expanding eligibility for antiretroviral therapy to adult patients with CD4 counts of 500 cells per μL or less, or to all HIV-positive adults was cost effective over 20 years in low-income and middle-income countries, relative to conventional WHO cost-effectiveness benchmarks. Adoption of these recommendations should be considered alongside other high-priority health interventions in low-income and middle-income countries. In generalised-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 effective and should be considered where possible. Widespread HIV testing programmes aimed at the entire adult population did not seem to be cost effective in concentrated-epidemic settings, suggesting that health resources might be better allocated elsewhere.

study[39] in rural South Africa showed that the risk of HIV infection was lower for individuals living in areas with higher coverage of antiretroviral therapy,[42] and studies have not shown increases in sexual risk behaviour by people given early antiretroviral therapy[43,44] or the general population.[45] As in all scientific endeavours, the conclusions of this analysis should be reassessed as new data become available.

The paucity of data for the costs of managing and supporting front-line services, the costs of scaling up and maintaining expanded testing programmes, and the flow of patients through care services also add uncertainty to our estimates. Growing evidence suggests that unit costs will decrease as service provision sites expand and mature.[46–48] However, how this effect will translate to scale-up within a national programme context, which would probably involve expansion of existing sites as well as creation of new treatment sites and possibly novel care platforms, is unclear. Therefore, the experiences in countries that rapidly adopt earlier treatment and achieve high coverage should be used to provide better information about the epidemiological and economic effects that might be encountered by other countries.

We assessed cost-effectiveness using a convention that approximates the social willingness to pay to achieve health gains with a country's per-head GDP. Interventions shown to be cost effective on the basis of this benchmark can be taken to be a reasonable investment, relative to a country's present level of income.[29] However, this suggestion does not mean that the present amount or distribution of health spending is optimum, or that other interventions (for HIV or other health issues) might not produce greater health gains per dollar spent. For example, analyses of medical male circumcision suggest that expansion of access to circumcision might have a lower ICER than expansion of access to antiretroviral therapy,[18] and might even be cost-saving in the long term.[49] National policy making will require explicit comparisons of alternative spending portfolios, which might include other interventions and a broader array of antiretroviral therapy and HIV-testing strategies. Similarly, countries will need to weigh affordability and feasibility when considering large expansions in access to or eligibility for antiretroviral therapy. Implementing these strategies could require large, one-time investments in the years immediately after a policy change. In view of these costs and the uncertainties involved, some countries—especially those with low coverage of antiretroviral therapy at present—could decide to take a gradual approach to changing the eligibility criteria.

For this study we adopted an analytical approach that assesses total health attainment (total DALYs averted) and is indifferent to how these health benefits are distributed. For this reason, our results do not take into account other considerations for decisions makers, such as equity of treatment access. The conclusions of this analysis could therefore differ from those of a narrower analysis focused only on the health benefits for people receiving antiretroviral therapy, especially since studies are still in progress to quantify the direct health benefits of antiretroviral therapy at high CD4 cell counts.[50] For the economic analysis we adopted a health-systems perspective, which excludes some economic outcomes that might be valued by decision makers, such as reduced orphanhood, improved productivity, and survival of working-age adults. For all of these reasons, the general guidance from the four country case studies undertaken in this analysis should be regarded as an input into a decision-making process that weighs all locally relevant considerations, rather than a policy prescription.

The revised WHO recommendations[1] have required decision makers to reconsider policies around antiretroviral therapy eligibility and treatment coverage, even while trials and demonstration projects are underway to quantify the consequences of expanded HIV treatment. As a result, uncertainties persist about key outcomes of these policies.[51] However, informed by currently available epidemiological, biological, and economic information, the consensus finding of this study is that extending eligibility for antiretroviral therapy to all adults with CD4 counts of 500 cells per μL or less, and potentially to all HIV-positive adults, would be cost effective and

should be considered alongside other high-priority health interventions competing for health budgets in low-income and middle-income countries.

Contributors

TBH conceived of the study and was responsible for the overall design. TBH, JWE, MD, NSh, PJE, 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, LC, 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, NKM, NAM, EMi, EMo, QDP, MP, AP, LP, CP, HJP, JAS, DAMCvdV, SJdV, BGW, RGW, 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 collation 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.

Acknowledgments

The study was funded by the Bill & Melinda Gates Foundation and WHO. We thank Ellen McRobie and Annick Borquez from Imperial College London (London, UK) for coordinating the HIV Modelling Consortium ART Eligibility Guidelines modelling project. We thank Mary Mahy from UNAIDS (Geneva, Switzerland) for providing additional information about UNAIDS' country-level epidemiological estimates. We thank Emmanuela Gakidou and Herbert Duber from the Institute for Health Metrics and Evaluation at the University of Washington (Seattle, WA, USA) for providing information about antiretroviral therapy programmes in South Africa and Zambia. We thank Elliot Raizes from the US Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA) for input on supply-chain management costs for antiretroviral drugs. We thank the Clinton Health Access Initiative (New York, NY, USA) and the Division of Global HIV/AIDS of the CDC for access to unpublished cost estimates. VC and AP acknowledge the University College London Research Computing Services (Legion Cluster; London, UK) and input to the synthesis model from Deborah Ford, Alec Miners, Paul Revill, Fumiyo Nakagawa, and Deenan Pillay. DJK, AB, STC, and BGW thank Bill and Melinda Gates for their active support of this work and their sponsorship through the Global Good Fund. M-CB, SM, EMo, and MP thank all other members of the Strategic Epi-ART in India Modeling team for their contribution to data and model inputs. M-CB, SM, EMo, and MP acknowledge the Canadian Foundation for AIDS (CANFAR, research grant number 023-015) for funding the Belgaum modelling. KMM and HJP acknowledge funding from the Wellcome Trust (086431/Z/08/Z). TC received funding from the US National Institute of General Medical Sciences (U54GM088558; the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of General Medical Sciences or the National Institutes of Health). DPW, CCK, QDP, and LZ acknowledge funding from the World Bank, Australian Research Council, University of New South Wales, and AusAID. QDP acknowledges scholarship support from AusAID. RGW acknowledges research funding from the UK Medical Research Council (Methodology Research Fellowship G0802414 and grant MR/J005088/1) and the Bill & Melinda Gates Foundation (Consortium to Respond Effectively to the AIDS/TB Epidemic [19790.01] and TB Modelling and Analysis Consortium [21675]). BEN and DAMCvdV acknowledge research funding from the Aids Fonds (grant 2010-035) in Amsterdam, Netherlands, and the European Union FP7 CHAIN grant (223131). NKM acknowledges funding from a UK National Institute for Health Research postdoctoral fellowship. PV acknowledges funding support from UNAIDS India for modelling work in northeast India. The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the CDC or WHO.

References

1 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection—recommendations for a public health approach. Geneva: World Health Organization, 2013.

2 WHO. Consolidated ARV guidelines 2013. Chapter 7—web annexes. Geneva: World Health Organization, 2013. http://www.who.int/hiv/pub/guidelines/arv2013/annexes/en/index2.html (accessed Nov 28, 2013).

3 Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365:** 493–505.

4 Anglemyer A, Rutherford GW, Horvath T, Baggaley RC, Egger M, Siegfried N. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. *Cochrane Database Syst Rev* 2013; **4:** CD009153.

5 Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009; **373:** 48–57.

6 Eaton JW, Johnson LF, Salomon JA, et al. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Med* 2012; **9:** e1001245.

7 UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2013. Geneva: UNAIDS, 2013. http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf (accessed Nov 28, 2013).

8 Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. *PLoS Med* 2011; **8:** e1001056.

9 Kranzer K, Govindasamy D, Ford N, Johnston V, Lawn SD. Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review. *J Int AIDS Soc* 2012; **15:** 17383.

10 Lahuerta M, Lima J, Nuwagaba-Biribonwoha H, et al. Factors associated with late antiretroviral therapy initiation among adults in Mozambique. *PLoS One* 2012; **7:** e37125.

11 Schwartländer B, Stover J, Hallett T, et al. Towards an improved investment approach for an effective response to HIV/AIDS. *Lancet* 2011; **377:** 2031–41.

12 Granich R, Kahn JG, Bennett R, et al. Expanding ART for treatment and prevention of HIV in South Africa: estimated cost and cost-effectiveness 2011–2050. *PLoS One* 2012; **7:** e30216.

13 Hecht R, Stover J, Bollinger L, Muhib F, Case K, di Ferranti D. Financing of HIV / AIDS programme scale-up in low-income and middle-income countries, 2009–31. *Lancet* 2010; **376:** 1254–60.

14 Walensky RP, Wood R, Fofana MO, et al. The clinical impact and cost-effectiveness of routine, voluntary HIV screening in South Africa. *J Acquir Immune Defic Syndr* 2011; **56:** 26–35.

15 Futures Institute. Goals manual: a model for estimating the effects of interventions and resource allocation on HIV infections and deaths. Glastonbury: Futures Institute, 2011.

16 Hontelez JAC, Lurie MN, Bärnighausen T, Bakker R, Baltussen R. Elimination of HIV in South Africa through expanded access to antiretroviral therapy: a model comparison study. *PLoS Med* 2013; **10:** e1001534.

17 Bershteyn A, Klein DJ, Eckhoff PA. Age-dependent partnering and the HIV transmission chain: a microsimulation analysis. *J R Soc Interface* 2013; **10:** 20130613.

18 Bärnighausen T, Bloom DE, Humair S. Economics of antiretroviral treatment *vs* circumcision for HIV prevention. *Proc Natl Acad Sci USA* 2012; **109:** 21271–76.

19 Cori A, Ayles H, Beyers N, et al, and the HPTN 071 (PopART) study team. HPTN 071 (PopART): a cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: mathematical model. *PLoS One* (in press).

20 Cambiano V, Bertagnolio S, Jordan MR, Lundgren JD, Phillips A. Transmission of drug resistant HIV and its potential impact on mortality and treatment outcomes in resource-limited settings. *J Infect Dis* 2013; **207** (suppl 2): S57–62.

21 Menzies NA, Cohen T, Lin H-H, Murray M, Salomon JA. Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. *PLoS Med* 2012; **9:** e1001347.

22 Nichols BE, Boucher CAB, van de Vijver DAMC. HIV testing and antiretroviral treatment strategies for prevention of HIV infection: impact on antiretroviral drug resistance. *J Intern Med* 2011; **270:** 532–49.

23 Anon. Pruddell model description. http://www.hivmodelling.org/sites/default/files/Pruddell%20model%20description.pdf (accessed Nov 28, 2013).

24 Mishra S, Mountain E, Pickles M, et al. Exploring the impact of antiretroviral treatment in south India: the influence of baseline intervention context. *AIDS* (in press).

25 Boily MC, Pickles M, Lowndes CM, et al. Positive impact of a large-scale HIV prevention program among female sex workers and clients in Karnataka state, India. *AIDS* 2013; **27:** 1449–60.

26 Vickerman P, Martin NK, Hickman M. Understanding the trends in HIV and hepatitis C prevalence amongst injecting drug users in different settings—implications for intervention impact. *Drug Alcohol Depend* 2012; **123:** 122–31.

27 Zhang L, Pham QD, Do MH, Kerr C, Wilson DP. Return on investment of HIV prevention in Vietnam: technical report for the World Bank and Vietnam Administration for AIDS Control. Sydney: University of New South Wales, 2013.

28 Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2129–43.

29 Edejer TT-T, Baltussen R, Adam T, et al. Making choices in health: WHO guide to cost effectiveness analysis. Geneva: World Health Organization, 2003.

30 World Bank. World Development Indicators. Washington, DC: World Bank, 2012. http://data.worldbank.org/indicator/NY.GDP.MKTP.CD (accessed Feb 13, 2013).

31 Pickles M, Boily M-C, Vickerman P, et al. Assessment of the population-level effectiveness of the Avahan HIV-prevention programme in South India: a preplanned, causal-pathway-based modelling analysis. *Lancet Glob Health* 2013; **1:** e289–99.

32 Hontelez JAC, de Vlas SJ, Tanser F, et al. The impact of the new WHO antiretroviral treatment guidelines on HIV epidemic dynamics and cost in South Africa. *PLoS One* 2011; **6:** e21919.

33 Boily M-C, Mâsse B, Alsallaq R, et al. HIV treatment as prevention: considerations in the design, conduct, and analysis of cluster randomized controlled trials of combination HIV prevention. *PLoS Med* 2012; **9:** e1001250.

34 Rodger A, Bruun T, Weait M, et al. Partners of people on ART—a New Evaluation of the Risks (The PARTNER study): design and methods. *BMC Public Health* 2012; **12:** 296.

35 HPTN studies in development. http://www.hptn.org/research_studies/Developing.asp (accessed Dec 2, 2013).

36 Das M, Chu PL, Santos G-M, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PLoS One* 2010; **5:** e11068.

37 Montaner JSG, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet* 2010; **376:** 532–39.

38 Wilson DP. HIV treatment as prevention: natural experiments highlight limits of antiretroviral treatment as HIV prevention. *PLoS Med* 2012; **9:** e1001231.

39 Van Sighem A, Jansen I, Bezemer D, et al. Increasing sexual risk behaviour among Dutch men who have sex with men: mathematical models versus prospective cohort data. *AIDS* 2012; **26:** 1840–43.

40 Birrell PJ, Gill ON, Delpech VC, et al. HIV incidence in men who have sex with men in England and Wales 2001–10: a nationwide population study. *Lancet Infect Dis* 2013; **13:** 313–18.

41 Phillips AN, Cambiano V, Nakagawa F, et al. Increased HIV incidence in men who have sex with men despite high levels of ART-induced viral suppression: analysis of an extensively documented epidemic. *PLoS One* 2013; **8:** e55312.

42 Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell M-L. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science* 2013; **339:** 966–71.

43 Venkatesh KK, Flanigan TP, Mayer KH. Is expanded HIV treatment preventing new infections? Impact of antiretroviral therapy on sexual risk behaviors in the developing world. *AIDS* 2011; **25:** 1939–49.

44 Jean K, Gabillard D, Moh R, et al. Effect of early antiretroviral therapy on sexual behaviors and HIV-1 transmission risk among adults with diverse heterosexual partnership statuses in Côte d'Ivoire. *J Infect Dis* 2013; published online Aug 29. DOI:10.1093/infdis/jit470.

45 McGrath N, Eaton JW, Bärnighausen TW, Tanser F, Newell M-L. Sexual behaviour in a rural high HIV prevalence South African community: time trends in the antiretroviral treatment era. *AIDS* 2013; **27:** 2461–70.

46 Menzies NA, Berruti AA, Blandford JM. The determinants of HIV treatment costs in resource limited settings. *PLoS One* 2012; **7:** e48726.

47 Menzies NA, Berruti AA, Berzon R, et al. The cost of providing comprehensive HIV treatment in PEPFAR-supported programs. *AIDS* 2011; **25:** 1753–60.

48 Marseille E, Giganti MJ, Mwango A, et al. Taking ART to scale: determinants of the cost and cost-effectiveness of antiretroviral therapy in 45 clinical sites in Zambia. *PLoS One* 2012; **7:** e51993.

49 Njeuhmeli E, Forsythe S, Reed J, et al. Voluntary medical male circumcision: modeling the impact and cost of expanding male circumcision for HIV prevention in eastern and southern Africa. *PLoS Med* 2011; **8:** e1001132.

50 Sabin CA, Cooper DA, Collins S, Schechter M. Rating evidence in treatment guidelines: a case example of when to initiate combination antiretroviral therapy (cART) in HIV-positive asymptomatic persons. *AIDS* 2013; **27:** 1839–46.

51 De Cock KM, El-Sadr WM. When to start ART in Africa—an urgent research priority. *N Engl J Med* 2013; **368:** 886–89.