Supporting information for the manuscript: Evidence for scaling up HIV treatment strategies

in sub-Saharan Africa: A call for incorporating health system constraints

**A systematic literature review of modelling studies performing prospective population level cost-effectiveness analysis of HIV treatment strategies in sub-**

**Saharan Africa**

In support of our manuscript entitled “Evidence for prioritizing HIV treatment strategies in sub-Saharan Africa: A call for incorporating health system constraints”, we conducted a systematic review to assess the degree to which health system constraints have been included in the analysis of cost-effectiveness of antiretroviral treatment interventions.

We searched for articles published until November 2015 in five databases (Cochrane library, Web of Science, PubMed, Medline, Embase). Search terms included “cost-effective analysis”, “sub-Saharan Africa”, and “ART scale-up”, and yielded a total of 1800 original papers (S1 Figure). Two independent researchers screened the titles and abstracts of these papers for relevance. Articles were selected if written in English, and if a prospective CEA was performed on resource allocation at the general population level in sub-Saharan African countries. Retrospective cohort studies, patient models were excluded. The same researchers assessed in detail the full texts of 180 articles for final inclusion of 34 articles [[1-34](#_ENREF_1)] (S1 Figure).

S1 Figure: Selection process of included articles

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Search strategy

N = 1800

PreP

N = 22

PMTCT

N = 45

Selected articles based on

title/abstract

N = 180

Antiretroviral therapy

N = 113

Included

N = 34

Each article was assessed with respect to inclusion of health system constraints both on the supply-side (e.g., financial, human, or infrastructural resource constraints) and on the demand-side (e.g., health seeking behaviour, treatment adherence, or loss-to-follow-up rates). Inclusion of health system constraints were understood as incorporating the constraints in the analysis of the reported results. The results show that 11 articles incorporated one [[2](#_ENREF_2),[8](#_ENREF_8),[14](#_ENREF_14),[15](#_ENREF_15),[18](#_ENREF_18),[23](#_ENREF_23),[29](#_ENREF_29),[31](#_ENREF_31)]or several [[7](#_ENREF_7),[13](#_ENREF_13),[19](#_ENREF_19)] demand-side constraints) in the CEA. While most of these focused on lost to follow up [[2](#_ENREF_2),[7](#_ENREF_7),[8](#_ENREF_8),[13](#_ENREF_13),[15](#_ENREF_15),[18](#_ENREF_18),[19](#_ENREF_19),[23](#_ENREF_23),[29](#_ENREF_29)], others included adherence [[14](#_ENREF_14)], acceptance [[7](#_ENREF_7),[13](#_ENREF_13)] and health seeking behaviour [[19](#_ENREF_19),[31](#_ENREF_31)]. No article incorporated more than two demand-side constraints in the analysis. Supply-side constraints were only included in four of the articles of which all performed the CEAs within financial constraints [[10](#_ENREF_10),[19](#_ENREF_19),[24](#_ENREF_24),[30](#_ENREF_30)]. Only one article [[19](#_ENREF_19)] incorporated health system constraints on both the demand – i.e. in terms of lost to follow up and health seeking behaviour - and supply-side by assessing different financial constraints to the CEA.

S1 Table: Overview of articles including health system constraints in cost-effectiveness analysis of scaling up HIV treatment in sub-Saharan countries

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| --- | --- | --- | --- | --- | --- | --- |
| Year  | Author | Title  | Aim  | Scenarios  | Location  | Health system constraints |
| Demand-side constraints | Supply-side constraints |
| 2012 | Ventelou | The Macroeconomic Consequences of Renouncing to Universal Access to Antiretroviral Treatment for HIV in Africa: A Micro-Simulation Model | To assess the consequences of macroeconomic performance in respect to different HIV treatment strategies.  | Freezing of ART programs to current level of access versus universal access (scaling up to 100% coverage by 2015 with two alternative ART strategies (CD4 ≤200 cells/µl and ≤350 cells/µl)  | Cameroon, Tanzania and Swaziland |  |  |
| 2009 | Bikilla | Cost-effectiveness of anti-retroviral therapy at a district hospital in southern Ethiopia | To assess the cost-effectiveness of ART for routine clinical practice in a district hospital setting in Ethiopia. | ART at ≤200 cells/µl versus no ART  | Ethiopia | X |  |
| 2011 | Chawana  | Risk management in HIV/AIDS: ethical and economic issues associated with restricting HAART access only to adherent patients | To describe and quantify the economic consequences and discuss some ethical issues related to adherence and non-adherence to HAART from the provider’s perspective. | Adherent versus non-adherent patients  | South Africa |  |  |
| 2006 | Cleary  | The cost-effectiveness of Antiretroviral Treatment in Khayelitsha, South Africa – a primary data analysis | To estimate HIV healthcare utilisation, the unit costs of HIV services and the cost per life year (LY) and quality adjusted life year (QALY) gained of HIV treatment interventions from a provider's perspective. | ART at 200 cells/µl versus no ART  | South Africa |  |  |
| 2006 | Marseille  | The costs and benefits of private sector provision of treatment to HIV-infected employees in Kampala, Uganda | To determine the financial incentives of companies to treat HIV infected employees | No ART versus (a) CTX starting at WHO stage 2, (b) HAART+CTX starting at WHO stage 2, (c) "hybrid": CTX at WHO stage 2 and later HAART | Uganda  |  |  |
| 2006 | Bachmann | Effectiveness and cost effectiveness of early and late prevention of HIV/AIDS progression with antiretrovirals or antibiotics in Southern African adults | To estimate the health effects, health service costs and incremental cost-effectiveness ratios of earlier or later use of antibiotics and ARV, alone and in combination in adult HIV infected people | (a) Antibiotics, (b) ART, (c) Antibiotics +ART | South Africa |  |  |
| 2012 | Palombi | Predicting Trends in HIV-1 Sexual Transmission in Sub-Saharan Africa Through the Drug Resource Enhancement Against AIDS and Malnutrition Model: Antiretrovirals for Reduction of Population Infectivity, Incidence and Prevalence at the District Level | Assess the reduction in incidence caused by ART | Universal coverage versus 45% treatment coverage in Malawi | Mozambique and Malawi | X |  |
| 2013 | Leisegang  | A Novel Markov Model Projecting Costs and Outcomes of Providing Antiretroviral Therapy to Public Patients in Private Practices versus Public Clinics in South Africa | To compare the costs and outcomes of a private-care and a public-care ART program in South Africa. | Private-care versus public-care ART program | South Africa | X |  |
| 2012 | Mbonigaba | The Cost-effectiveness of Intervening in Low and High HIV Prevalence Areas in South Africa | To assess whether HIV/AIDS interventions could be more optimal in some areas of specific prevalence levels than in others  | HIV/AIDS interventions in high versus low prevalence areas.  | South Africa |  |  |
| 2015 | Fraser  | Reorienting the HIV Response in Niger Toward Sex Work Interventions: From Better Evidence to Targeted and Expanded Practice | To assess the projected impact on the HIV epidemic of focused interventions on FSW | Focused FSW interventions versus other ART interventions  | Nigeria  |  | X |
| 2012 | Barnighausen | Economics of antiretroviral treatment vs. Circumcision for HIV prevention | To assess whether TasP is a game changer or if comparable benefits are obtainable at similar or lower costs by increasing coverage of medical circumcision (MMC) and ART at CD4 <350/μL | TasP versus a combination of male circumsision and ART at ≤350 cells/µl.  | South Africa |  |  |
| 2011 | Hallett | Optimal Uses of Antiretrovirals for Prevention in HIV-1 Serodiscordant Heterosexual Couples in South Africa: A Modelling Study | To examine the impact and cost-effectiveness of earlier initiation to ART and/or PreP for HIV-1 prevention for disconcordant counples | ART at CD4 ≤350 cells/µl versus (a) ≤500 cells/µl, (b) ART in combination with PreP or (c) exclusive PreP to disconcordant counples.  | South Africa |  |  |
| 2015 | Mitchell | Modelling the impact and cost-effectiveness of combination prevention amongst HIV serodiscordant couples in Nigeria | To estimate the impact and cost-effectiveness of treatment as prevention (TasP), pre-exposure prophylaxis (PrEP) and condom promotion for serodiscordant couples in Nigeria. | ART at ≤350 cells/µl versus (a) TasP, (b) short-term PrEP, (c) long-term PrEP, (d) condom promotion and (e) all combinations | Nigeria  | X |  |
| 2012 | Mills | Earlier Initialization of Highly Active Antiretroviral Therapy Is Associated With Long-Term Survival and Is Cost-Effective: Findings From a Deterministic Model of a 10-Year Ugandan Cohort | To examine the cost-effectiveness of raising the eligibility treshold from 200 to 350  | ART at ≤200 cells/µl versus ≤350 cells/µl | Uganda | X |  |
| 2014 | Alistar | Comparative effectiveness and cost-effectiveness of antiretroviral therapy and pre-exposure prophylaxis for HIV prevention in South Africa | To study the population health outcomes and cost-effectiveness of implementing expanded ART coverage and oral PrEP in a setting with a heavy HIV burden. | ART at ≤350 cells/µl versus (a) universal access to ART, (b) PreP to general population and (c) PreP to high-risk population  | South Africa | X |  |
| 2007 | Vijayaraghavan | Cost-Effectiveness of Alternative Strategies for Initiating and Monitoring Highly Active Antiretroviral Therapy in the Developing World | Determine the cost-effectiveness of initiating and monitoring highly active antiretroviral therapy (HAART) in developing countries according to developing world versus developed world guidelines. | Implementing developed versus developing world guidelines (ART at ≤350 cells/µl versus ≤200 cells/µl)  | Developing countries |  |  |
| 2013 | Eaton | Health benefits, costs, and cost-eff ectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models | Assess the potential health benefits, costs, and cost-effectiveness of various eligibility criteria for adult antiretroviral therapy andexpanded coverage  | ART at ≤350 cells/µl versus (a) ART at ≤500 cells/µl and (b) ART for all HIV infected indiciduals | South Africa, Zambia, India, Vietnam | \* | \* |
| 2013 | Walensky | Cost-Effectiveness of HIV Treatment as Prevention in Serodescordant Couples | Compare the cost-effectiveness between early and late initiation to ART among serodisconcordant couples | Early versus late ART initiation  | South Africa and India | X |  |
| 2011 | Hontelez | The Impact of the New WHO Antiretroviral Treatment Guidelines on HIV Epidemic Dynamics and Cost in South Africa | To estimate the long-term impact of the full WHO guidelines on the dynamics of the HIV epidemic and healthcare costs | ART at ≤200 cells/µl versus ≤350 cells/µl | The Hlabisa subdistrict of Umkhanyakunde in KZN, South Africa. | X | X |
| 2012 | Sempa | Cost-effectiveness of early initiation of first-line combination antiretroviral therapy in Uganda | To compare the cost-effectiveness of initiating cART in patients using the revised CD4 count threshold of 350 cells/μL as in the WHO 2010 guidelines versus (vs) cART initiation using a threshold of 250 cells/μL. | ART at ≤250 cells/µl versus ≤350 cells/µl | Uganda |  |  |
| 2006 | Badri | When to initiate highly active antiretroviral therapy in sub-Saharan Africa? A South African cost-effectiveness study | To assess the the impact of initiating therapy at CD4 >350/μl; 200–350/μl or <200/μl | No ART versus (a) ART at ≤350 cells/µl, (b) ART at 200–350 cells/µl and (c) ART at ≤200 cells/µl | South Africa |  |  |
| 2009 | Walensky | When to Start Antiretroviral Therapy in Resource-limited Settings | To assess the cost-effectiveness of when to start ART | No ART versus (a) ART at ≤250 cells/µl (or severe opportunistic disease) and (b) ART at ≤350 cells/µl (or severe opportunistic disease)  | South Africa |  |  |
| 2011 | Granich  | Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050 | Assess the cost-effectiveness of expanded ART  | ART at ≤200 cells/µl versus (a) ART at ≤350 cells/µl, (b) ART at ≤500 cells/µl and (c) ART at all CD4 levels | South Africa  | X |  |
| 2014 | Anderson  | Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: a modelling study | Assess the impact of focusing intervantions on geographies and key populations at high risk of HIV infection.  | (a) Female sex workers versus (a) other women, (b) men who have sex with men and (c) other men  | Kenya |  | X |
| 2006 | Goldie | Cost-Effectiveness of HIV Treatment in Resource-Poor Settings — The Case of Côte d’Ivoire | To assess the cost-effectiveness of no treatment, trimethoprim–sulfamethoxazole prophylaxis alone, antiretroviral therapyalone, and prophylaxis with antiretroviral therapy. |  No treatment versus (a) trimethoprim–sulfamethoxazole prophylaxis alone, (b) antiretroviral therapy alone, and (c) prophylaxis with antiretroviral therapy. | Côte d’Ivoire |  |  |
| 2007 | Bishai | The cost effectiveness of antiretroviral treatment strategies in resource-limited settings |  To compare costs and outcomes of different ART strategies with and without the availability of a second-line treatment regimen.  | NO ART versus (a) syndromic management without laboratory tests (ART ONLY); (b) ART plus total lymphocyte counts every 6 months (TLC); (c) ART plus CD4 cell count assessment every 6 months (CD4); (d) ART plus CD4 cell count every 6months and viral load assessment 4weeks after the initiation of treatment, then every 6 months (VL)  | Developing countries |  |  |
| 2005 | Hogan  | Achieving the millennium development goals for health. Cost effectiveness analysis of strategies to combat HIV/AIDS in developing countries | To assess the costs and health effects of a range of interventions for preventing the spread of HIV and for treating HIV infected individuals | No intervention versus (a) mass media, (b) VCT, (c) Per education and treatment of STDs for CSW, (d) School based education, (e) treatment for STDs, (f) PMTCT, (g) HAART | East Africa and South East Asia |  |  |
| 2013 | Long | Portfolios of Biomedical HIV Interventions in South Africa: A Cost-Effectiveness Analysis | To evaluate the effectiveness and cost-effectiveness of combination biomedical HIV prevention and treatment scale-up  | Expanded ART versus (a) screening and counselling, (b) voluntary male circumcision, (c) vaginal microbicide use, (d) oral PrEP | South Africa |  |  |
| 2015 | Ciaranello | Cost-effectiveness of first-line antiretroviral therapy for HIV-infected African children less than 3 years of age |  To project the long-term clinical outcomes and cost-effectiveness of first-line nevirapine and lopinavir/ritonavir for HIV-infected children below 3 years of age. | No ART versus (a) first line nevirapine followed by second-line lopinovir/ritonavir and (b) first line lopinavir/followed by second line nevirapine | South Africa and Ivory Coast | X |  |
| 2008 | Cleary  | Assessing efficiency and costs of scaling up HIV treatment | To develope an approach that simultaneously assess costs and efficiency | No ART versus (a) only first-line ART and (b) first-and second-line ART | South Africa |  | X |
| 2013 | Hontelez | Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A Model Comparison Study | To understand the impact of UTT and the possibility of elimination of HIV based on implications of different model structures and assumptions.  | ART at ≤350 cells/µl versus Universal test and treat (UTT) | South Africa  | X |  |
| 2010 | Walensky  | Scaling Up the 2010 World Health Organization HIV Treatment Guidelines in Resource-Limited Settings: A Model-Based Analysis | To determine which aspect of the new guidelines that should be implemented first in resource limited settings where immediate implementation of all the WHO trecommendations is unfeasible | No ART versus (a) ART at ≤200 cells/µl, (b) ART at ≤350 cells/µl, (c) multiple sequential ART regimens, (d) replacement of first/line stavudine with tenofovir.  | South Africa |  |  |
| 2015 | Smith | Cost-Effectiveness of Antiretroviral Therapy and Isoniazid Prophylaxis to Reduce Tuberculosis and Death in People Living With HIV in Botswana | To examine the cost-effectiveness of IPT in Botswana, where antiretroviral therapy (ART) is widely available. | Comparison of seven strategies using a ombination of ART eligibility, provision of IPT and use of TST.  | Botswana |  |  |
| 2010 | Dodd | Examining the Promise of HIV Elimination by ‘Test and Treat’ in Hyper-Endemic Settings | To investigate the impact of Test and Treat interventions under a range of epidemic contexts  | Comparison of different test and treat interventions by altering the time since infection that treatment started.  | Hyper endemic settings |  |  |

\* The study includes several models, but do not specify whether health system constraints have been incorporated.

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