

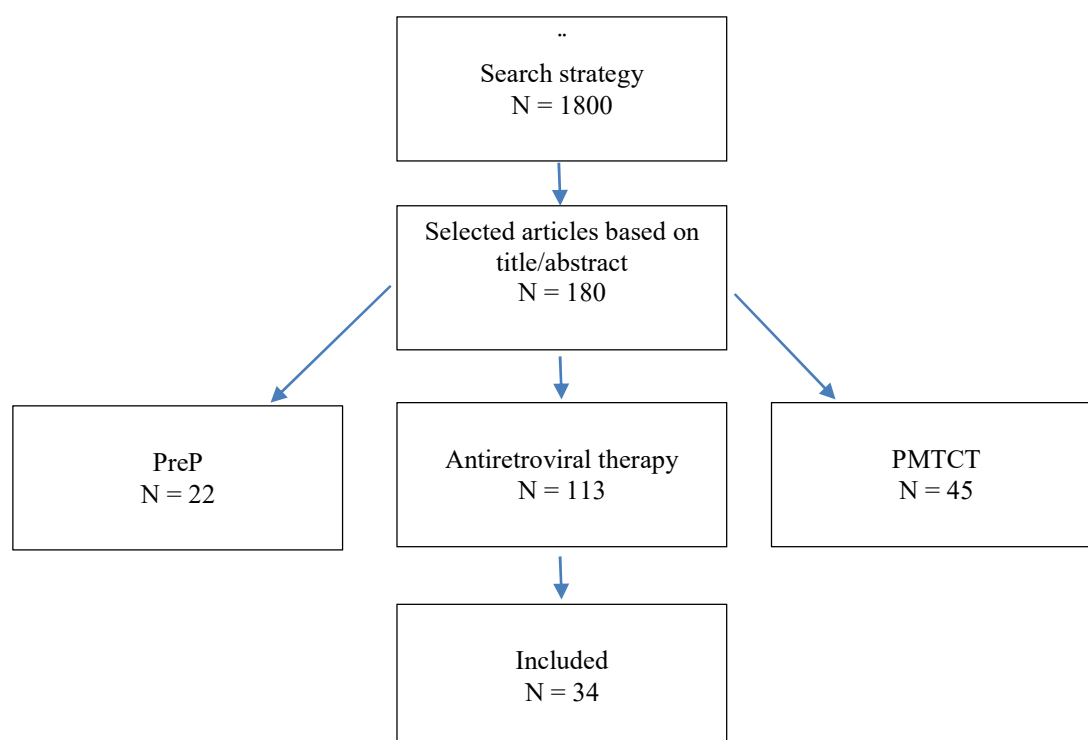
Supporting information for the manuscript: *Evidence for scaling up HIV treatment strategies in sub-Saharan Africa: A call for incorporating health system constraints*

## 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 (Figure 1). 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<sup>1-34</sup> (Figure 1).

Figure 1: Selection process of included articles



The results show that 11 articles incorporated one<sup>2,8,14,15,18,23,29,31</sup> or several<sup>7,13,19</sup> demand-side constraints (i.e. demand of HIV-infected people to receive care) in the CEA. While most of these focused on lost to follow up<sup>2,7,8,13,15,18,19,23,29</sup>, others included adherence<sup>14</sup>, acceptance<sup>7,13</sup> and health seeking behaviour<sup>19,31</sup>. No article incorporated more than two demand-side constraints in the analysis. and adherence to treatment. Supply-side constraints (i.e. the capacity of the health system) were only included in four of the articles of which all performed the CEAs within financial constraints.<sup>10,19,24,30</sup> Only one article<sup>19</sup> 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.

Table 1: Overview of articles including health system constraints in cost-effectiveness analysis of scaling up HIV treatment in sub-Saharan countries

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 $\leq$ 200 cells/ $\mu$ l and $\leq$ 350 cells/ $\mu$ l)	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 $\leq$ 200 cells/ $\mu$ l 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/ $\mu$ l 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/ $\mu$ L	TasP versus a combination of male circumcision and ART at $\leq 350$ cells/ $\mu$ l.	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 discordant couples	ART at CD4 $\leq 350$ cells/ $\mu$ l versus (a) $\leq 500$ cells/ $\mu$ l, (b) ART in combination with PreP or (c) exclusive PreP to discordant couples.	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 $\leq 350$ cells/ $\mu$ l 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 threshold from 200 to 350	ART at $\leq 200$ cells/ $\mu$ l versus $\leq 350$ cells/ $\mu$ l	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 $\leq 350$ cells/ $\mu$ l 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 $\leq 350$ cells/ $\mu$ l versus $\leq 200$ cells/ $\mu$ l)	Developing countries		
2013	Eaton	Health benefits, costs, and cost-effectiveness 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 and expanded coverage	ART at $\leq 350$ cells/ $\mu$ l versus (a) ART at $\leq 500$ cells/ $\mu$ l and (b) <b>ART for all HIV infected individuals</b>	South Africa, Zambia, India, Vietnam		* *
2013	Walensky	Cost-Effectiveness of HIV Treatment as Prevention in Serodiscordant Couples	Compare the cost-effectiveness between early and late initiation to ART among serodiscordant 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 $\leq 200$ cells/ $\mu$ l versus $\leq 350$ cells/ $\mu$ l	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/ $\mu$ L as in the WHO 2010 guidelines versus (vs) cART initiation using a threshold of 250 cells/ $\mu$ L.	ART at $\leq 250$ cells/ $\mu$ l versus $\leq 350$ cells/ $\mu$ l	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	
2012	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 interventions 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 therapy alone, 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 lopinavir/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 develop 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 $\leq 350$ cells/ $\mu$ l 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 recommendations is unfeasible	No ART versus (a) ART at $\leq 200$ cells/ $\mu$ l, (b) ART at $\leq 350$ cells/ $\mu$ l, (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 combination 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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