Draft Working Paper

What Works to Prevent and Treat AIDS

A review of cost-effectiveness literature with a long-term perspective

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Executive Summary

This paper aims to apply recent findings regarding cost and cost-effectiveness of HIV/AIDS prevention, treatment and care activities to the current policy environment to analyze and inform a long-term strategic, efficient response, thus moving away from an emergency response to guide HIV/AIDS programming over the next 25 years.

Methodology

Our aim is to update the findings published in the chapter on HIV/AIDS Prevention and Treatment in the 2006 *Disease Control Priorities in Developing Countries (DCP)*. We conducted systematic reviews of PubMed and EconLit to examine the published and grey literature on studies of cost-effectiveness and intervention costs for prevention and HIV/AIDS care.

Findings

One striking finding of DCP was the paucity of cost-effectiveness data for both prevention and care interventions. In the three years following the publication of that chapter, 21 additional studies of cost-effectiveness of HIV prevention interventions were identified. These include new data describing cost-effectiveness of prevention interventions focusing on male circumcision and structural interventions. Progress in generating cost-effectiveness evidence for care has been substantial. The number of studies focusing on the cost-effectiveness of ARV provision in resource limited settings has grown from 2 identified in the 2006 DCP chapter to 14 by the end of 2007. This literature begins to address the nuances of when and on what basis ART should begin.

Value for money

Among prevention interventions for low-income countries, the majority of biomedical, behavioural and structural interventions are below the range of $200 per DALY and a few more are between $200 and $600, which is still very cost-effective. For middle-income countries, we find evidence that a number of interventions have been estimated to cost below $500 per DALY, and a few between $1,000 and $2,000. Overall prevention interventions for all LMIC never cost (per DALY) more than 40% of one GDP per capita (in the country of intervention) and often much less.

For care interventions in low-income countries, it is clear that co-trimoxazole prophylaxis, first-line ARV treatment and using CD4 counts to determine initiation of ARVs are cost-effective. Provision of second-line ARV regimes is also cost-effective, although with higher cost-effectiveness ratios than first-line therapy.

Affordability of interventions

When looking at the affordability of prevention interventions, it is more useful to use effectiveness evidence. Behavioral interventions of VCT, condom provision, and peer-based interventions, and bio-medical interventions of circumcision, PMTCT, and family planning (to reduce unwanted pregnancy among HIV-infected women) are all proven effective prevention strategies. Targeting interventions to those groups most at risk, especially in concentrated epidemics, can optimize the affordability of interventions.

While cost-effectiveness ratios for early (at a CD4 count of 350 cells/ul) and late (at a CD4 count of 200 cells/ul) initiation of ARVs fall within the threshold of a cost-effective intervention, initiating ART early introduces increased lifetime costs per person treated. Estimates range from 23% to 56% in increased costs.

Affordability-Efficiency Interaction

The wide range of cost effectiveness estimates per HIV infection averted indicates that there are significant differences in efficiency and quality across prevention activities. Increases in efficiency in the provision of care and reduction of costs can occur if lower prices for ARVs and laboratory assays are available.

Conclusion and recommendations

The evidence surrounding cost and cost-effectiveness of care and prevention interventions remains limited, and with significant gaps, both in terms of geographic breadth of the studies and the depth of data for specific interventions.

An optimal package of prevention and treatment interventions should be based on effectiveness and cost-effectiveness evidence at the country level, or at least by type epidemic profile. The "right mix" of interventions should be studied more carefully to maximize societal needs. These types of analyses have not been done at the country level and are urgently needed for long term HIV/AIDS strategy to have a sustained impact on the epidemic.

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List of Abbreviations

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ARV	Anti-retroviral medicines
CE	Cost-effectiveness
DALY	Disability-adjusted life years
DCP2	Disease Control Priorities in Developing Countries (2nd Edition)
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GDP	Gross domestic product
GNI	Gross national income
HIV	Human immunodeficiency virus
HAART	Highly active antiretroviral therapy
ICER	Incremental cost-effectiveness ratio
LDC	Least developed countries
LMIC	Lower- and middle-income income countries
LY	Life year
MAP	Multi-Country HIV/AIDS Program (World Bank)
MSF	Médecins sans Frontiers (Doctors without Borders)
PEPFAR	President's Emergency Plan for AIDS Relief
PLWHA	People living with HIV/AIDS
QALY	Quality-adjusted life years
TRIPS	Trade-related Aspects of Intellectual Property Rights
UMIC	Upper-middle income country
UNAIDS	United Nations Joint Program on HIV/AIDS
UNGASS	UN General Assembly Special Session on HIV and AIDS
UNICEF	The United Nations Children's Fund
VCT	Voluntary counselling and testing
VL	Viral load
WHO	World Health Organization

Introduction

The first 25 years of the response to the AIDS epidemic can be characterized as an emergency reaction. This initial response by countries and the international community has been acknowledged as unorganized and ineffective (The World Bank 1999), compounded by the problem of limited funding of HIV/AIDS activities in the early years, which was steady at an annual rate of less than $300 million per year until the late 1990s and early 2000s (UNAIDS 2007). With the beginning of a more organized response, including the establishment of UNAIDS, the Gates Foundation's prioritization of AIDS, and the World Bank's Multi-Country HIV/AIDS Program (MAP), funding began to increase. The 2001 Declaration of the Commitment on HIV/AIDS, the United National General Assembly Special Session on HIV/AIDS (UNGASS), and the most recent push to scale up antiretroviral treatment (ART) in low-resource settings mobilized donors and increased funding commitments by nearly ten-fold from 2000 to reach $10 billion in 2007.

The scope of HIV/AIDS interventions has also changed. The initial response was centered on prevention –- mostly through the dissemination of information campaigns. Interventions were designed and implemented but did not align with epidemic transmission priorities. Recently, there has been a call for "know your epidemic, know your response." Implicit in this slogan is the need for careful targeting and a move away from blanket strategies to be applied to all countries and settings.

For the first twenty years of the epidemic in low-income and many middle-income countries, treatment options for HIV-infected individuals were limited to symptom care, pain control, treatment of a limited number of opportunistic infections and co-trimoxazole prophylaxis. Antiretroviral therapy was generally unavailable in these developing country settings and limited to a few people who were able to enroll in clinical trials or who were rich enough to pay for the drugs. With the substantial drop in ARV prices, a result of the manufacture of generics, preferential pricing by pharmaceutical companies and the invocation of the TRIPS special provisions, anti-retroviral therapy became possible for many countries. The UNAIDS 2003 initiative to scale up anti-retroviral therapy, PEPFAR initiatives and funding through GFATM has resulted in a total of 3 million persons on ARVs by the end of 2007. Yet, this represents only 31% of all persons eligible for ARVS, and universal access to ARVs remains a challenge (UNAIDS 2008).

The emergency response approach to combating AIDS has led to important consequences for programs that have focused on increasing access (and reducing stigma and discrimination as an important aspect of widening access), with uneven attention given to the quality, effectiveness and efficiency of programs, and HIV prevention initiatives in general. Even though treatment of HIV is more expensive than prevention, treatment activities are more visible at the global level and are more easily quantified. Achieving measurable objectives is important for governments and international funders.

In the coming years, it is likely that interventions will need to optimize efficiency and effectiveness, as they will be implemented in a context of resource scarcity. The 2008 UNAIDS Global AIDS Report highlights an important resource gap. To maintain the current pace of scaling up activities, funding levels will need to increase by 50% by 2010. Yet funding increases of this magnitude will still fall short of the amount needed to achieve universal access by 2010 or even by 2015. The recent economic events are straining high-income country economies and the duration and impact of the global recession are still unknown at this time. The extent to which these countries will continue to fund AIDS-program implementation given potentially competing domestic budget priorities is currently unknown; a pragmatic view suggests that increases in high-income country's foreign aid budgets are unlikely in the next few budget cycles. As such, it is probable that projections for AIDS resources in the next five years will not meet the UN projections for universal access.

This paper applies findings presented in DCP2 and recent literature reviews updating DCP2 regarding cost and cost-effectiveness of HIV/AIDS prevention and treatment and care activities to the current policy environment to analyze and inform a long-term strategic, efficient response.

Specifically, the paper seeks to answer the following questions regarding HIV/AIDS interventions for prevention and care and treatment:

- What additional knowledge do we have regarding the effectiveness and cost-effectiveness of interventions since the publication of the Disease Priorities in Developing Countries in 2006?
- What is the cost-effectiveness ranking of HIV/AIDS prevention & care interventions?
- What information can we glean from the literature regarding the affordability of various interventions?
- What does the literature tell us about the intersection of affordability and efficiency?
- What evidence do we have regarding the synergy of prevention and care activities and how in the future might this synergy affect the three previous points?
- Based upon the literature and evidence available at this point, what recommendations can be made for future research on cost and cost-effectiveness of HIV/AIDS preventions and care and treatment interventions?

In order to address these questions about what we know, we rely on the data presented in three sources: the HIV/AIDS chapter in the 2006 publication of DCP2 and two subsequent literature reviews that updated this chapter.

Methodology

This paper presents in summary form and further analyzes the principal findings of DCP2 and two recently-completed literature reviews led by researchers at the Instituto Nacional de Salud Pública in Mexico on the cost-effectiveness of interventions aimed at prevention, care, and treatment of HIV/AIDS (DeMaria, Bautista-Arredondo et al. 2008; Galarraga, Colchero et al. 2009). The methodology employed to conduct the reviews for both prevention and care and treatment followed the same procedure. In general terms, we conducted systematic reviews to examine the published and grey literature on studies of cost-effectiveness of interventions for prevention and in the continuum of HIV/AIDS care. To develop the search parameters, both studies defined a broad list of search terms that were then adapted to PubMed Medical Subject Headings (MeSH) and EconLit search terms. The aim of the two reviews was to provide an update of the evidence presented in the chapter on AIDS in the 2006 publication, *Disease Control Priorities in Developing Countries*, the search was time bound from January 2005 to December 2008. We compared our findings against the HIV Care & PMTCT Bibliographic Bulletins published by the Institut de Santé Publique, d'Épidémiologie et de Développement of the Bordeaux School of Public Health[1], the bi-weekly HIV/AIDS Literature Digest published by the University of California, San Francisco, and HIV This Week published by UNAIDS[2] and also sought out relevant grey literature. A wide variety of terms were searched covering individual HIV/AIDS prevention and care interventions, antiretroviral therapy, epidemiology of OIs, and behavioral interventions (refer to tables in Annex 1). We also conducted a search of the grey literature focusing on the websites and pertinent publications from the World Health Organization and Joint United Nations Programme for HIV/AIDS that are descriptive of the scaling up process and that detail treatment guidelines.

Findings

For the following section we culled the literature reviews to tease out findings regarding effectiveness, cost-effectiveness, affordability and the affordability-efficiency interaction. We first briefly summarize the findings of the prevention and care literature reviews, highlighting the additional information we have learned since (Over, Heywood et al. 2004) the publication of DCP2. In the next section, we rank interventions in terms of cost-effectiveness. The third section discusses aspects of affordability of prevention and care interventions. We then look at affordability and efficiency, assessing the extent to which findings based on observations in the

[1] Available at: http://www.isped.u-bordeaux2.fr/CDD/BASES/HIV_Care/UK-hiv_care.htm
[2] Available at: http://hivthisweek.wordpress.com/

past are likely to be predictive of the cost-effectiveness that would be obtained as programs move forward. Finally, we analyze the interaction of prevention and care, examining potential synergies.

Summary of cost-effectiveness findings

We begin by reviewing the cost-effectiveness evidence gathered in the DCP2 chapter and in the two recent literature reviews updating it (Bertozzi, Padian et al. 2006; DeMaria, Bautista-Arredondo et al. 2008; Galarraga, Colchero et al. 2009). One striking finding of DCP2 was the paucity of cost-effectiveness data of both prevention and care and treatment interventions. In the three years following the publication of the chapter, 21 additional studies on the cost-effectiveness of HIV prevention interventions were identified. Significant additional new data on male circumcision and structural interventions aimed at prevention have been published. Table 1 presents the effectiveness, cost and cost-effectiveness evidence for the HIV prevention interventions compiled in DCP2 and the update review for prevention.

For care, progress in generating cost-effectiveness evidence has been substantial in the area of providing antiretroviral therapy. From only two studies identified in the 2006 DCP2 chapter (Marseille, Hofmann et al. 2002; Over, Heywood et al. 2004); an additional 10 articles have been published on cost-effectiveness of provision of ARVs in resource-limited settings. This recent literature begins to address the nuances of when and according to what criteria ART should begin. Table 2 summarizes the new literature regarding cost-effectiveness for care and treatment interventions.

Prevention

In the DCP2 cost-effectiveness evidence for prevention was region specific (sub-Saharan Africa), with estimates from one country per intervention study. While more cost-effectiveness evidence has become available in the years since 2006, the same pattern of a strong focus on sub-Saharan Africa and limited geographic representation per intervention can still be observed. Many interventions show wide ranges in cost-effectiveness both within and across countries.

The prevention review (Table 1) divided interventions into three types: behavioral (five articles), biomedical (17 articles) and structural (three articles). (There were 21 distinct studies, but 25 interventions were analyzed) Three main behavioral interventions were studied: voluntary counseling and testing, treatment for addiction and school-based interventions. Cost-effectiveness data for VCT taken from three studies conducted in India and Africa (Hogan, Baltussen et al. 2005; Hausler, Sinanovic et al. 2006; John, Farquhar et al. 2008) range from USD 14 to 261/DALY.

The domain of biomedical interventions included in the cost-effectiveness review includes STI screening and treatment, male circumcision, prevention of mother-to-child transmission, harm reduction, blood safety, anti-retroviral prophylaxis, microbicides, and vaccines. There was significant new data showing the effectiveness—and on a more limited basis cost-effectiveness—of male circumcision. The three recent studies on male circumcision identified through the literature review demonstrate that male circumcision, at various costs and coverage rates, ranges from cost-effective to highly cost-effective (Gray, Li et al. 2007; Martin, Bollinger et al. 2007a; Martin, Bollinger et al. 2007b).

PMTCT was shown in DCP2 to be effective and cost-effective, a finding confirmed by the more recent literature. However, this intervention remains underused in many settings. The data on effectiveness of both vaccine and microbicides was disappointing, and it will likely be a long time before scientific and technical advances make these two interventions viable options for the prevention of HIV. No harm reduction interventions were found, beyond one study of a behavioral intervention for addictions.

The domain of structural interventions for HIV prevention has received increased attention recently. While no structural interventions were included or studied in the DCP2, the follow-up literature review yielded three studies on structural interventions. For example, Sweat et al.

compared two scenarios in two cities in the Dominican Republic. In the first, implementation of laws with strong consequences and positive rewards for condom use in commercial sex locales was found to have a cost of USD 457 per DALY as opposed to USD 1,186 per DALY for the second intervention, a traditional information, education and communication campaign (Sweat, Kerrigan et al. 2006).

Care

The publication of the chapter of HIV/AIDS Prevention and Treatment in the second edition of *Disease Control Priorities in Developing Countries* reviewed the evidence available up to 2005 regarding effectiveness, costs and cost effectiveness of the various elements of HIV/AIDS care. Most conspicuous was the lack of data on cost-effectiveness of interventions for HIV/AIDS care including provision of highly-active antiretroviral therapy, prophylaxis and treatment of opportunistic infections, laboratory monitoring strategies and interventions to promote adherence.

In the literature review to update the chapter in the DCP, we found many more studies that analyzed the cost-effectiveness of ARVs, compiling a total of 10 articles that address cost-effectiveness of aspects of HIV/AIDS care (Table 2). The estimates centered on provision of ARVs, comparing both early and late starting points, first-line treatment only compared with first and second line treatment and use of clinical versus laboratory markers to determine initiation of ART.

Table 3 details the cost-effectiveness ratios of early and late initiation of ARVs, within the context of first-line only and first and second line scenarios, adjusting published data to compare all scenarios to a null case scenario (no ART). In general cost-effectiveness ratios comparing ART to a null case (no ART, curative care scenario) range from USD 296 to 1610 for early initiation and USD 302 to 1731 for late initiation in a first-line only scenario (Bachmann 2006; Bishai, Colchero et al. 2007; Freedberg, Kumarasamy et al. 2007; Vijayaraghavan, Efrusy et al. 2007). As such ARV can be considered a cost-effective strategy in a low-income country setting using the cost-effective threshold proposed by the Commission on Macroeconomics and Health of interventions with a CE ratio of 1 to 3 times the GNP per capita (World Health Organization 2001).

The other focus area of the cost-effectiveness studies is testing strategies and criteria for ART initiation. Table 4 presents the results of using clinical markers (as opportunistic infections) with laboratory markers (total lymphocyte count, CD4 cell counts or viral load monitoring) as starting and stopping criteria for first line ARV therapy.

While much progress has been made in recent years to determine the cost-effectiveness of HIV/AIDS care and treatment interventions, there are several areas for which we do not have any data. We still lack a body of effectiveness and CE data for palliative care interventions, interventions to promote adherence, provision of pain relief, as well as OI prophylaxis and treatment.

The literature review did not yield cost-effectiveness data on structural interventions for AIDS care and treatment. Structural interventions focus on health systems' capacities to boost both effectiveness and cost-effectiveness and include improving quality of care (partially defined as appropriate prescription practices, adequate and consistent drug supply), interventions to support early diagnosis of infection, adherence, monitoring and evaluation of ARV treatment and counselling for "prevention for positives".

Finally, there is a paucity of information on methods to increase the efficiency of treatment programs. These interventions could be considered the equivalent of structural interventions for prevention. ARVs, prevention of and treatment for OIs, opportune diagnosis of HIV infection are interventions which are for the most part, carried out within a health system structure; this structure can function more or less efficiently.

Interventions that offer best "value for money"

While cost-effectiveness analysis of individual interventions permits conclusions regarding those interventions that provide the greatest results for the investment, funding of prevention and care programs must adapt to the reality of constrained resources. Even for those prevention interventions such as male circumcision and PMTCT, which are highly cost-effective, scaling up to meet the prevention needs of a population can surpass the annual per capita health budgets of many low-income countries. Undoubtedly, many countries will need to continue to rely on bi- and multi-lateral transfers to fund their HIV programs, as actual local funding may not reach the needed levels. Thus it is necessary to prioritize interventions in the HIV response package, requiring constrained selectivity. Unfortunately, CE analyses rarely incorporate this type of long-term strategic thinking at the country level; one important exception is the case of India (Over et al. 2006; Dandona, Kumar, et al. 2009).

Cost-effectiveness analyses serve to identify interventions that provide optimal results for the investment made and which should therefore be implemented. Thus these analyses are a useful tool given the limited funds available for HIV/AIDS prevention and care activities. What is viewed as cost-effective varies depending on that country's level of income. According to the Commission on Macroeconomics and Health of the WHO, health interventions with an incremental cost-effectiveness ratio between 1 and 3 times the per capita gross national product per year of life gained can be considered cost-effective (World Health Organization 2001). Low-income countries are classified by the World Bank as having a gross national *per capita* income below $935; lower middle-income countries from $936-3,705; and upper-middle-income countries from $3,706-$11,455.

Prevention

In order to determine those interventions that offer best value for the investment, we analyzed the evidence available both along epidemic profile and country income level.

A ranking of the evidence for effectiveness and cost-effectiveness can be found in Table 5. To construct this table, we included both cost-effectiveness data included in the DCP2 as well as in the subsequent literature review. An asterisk marks interventions in which additional cost-effectiveness data were found in the follow-on literature review. Notably, circumcision is a new addition among the list of interventions. Additionally, new evidence since the publication of DCP2 further strengthens the qualification of VCT as cost-effective. However, these studies remain concentrated in sub-Saharan Africa settings. Specifically, voluntary counseling and testing, peer-based prevention programs, circumcision, ART to reduce mother-to-child transmission and blood safety programs can all be classified as very cost-effective interventions.

Figures 1 and 2 demonstrate the wide range of preventive interventions that can be classified as cost-effective, both in low- and middle-income countries. For low-income countries, the majority of biomedical, behavioral and structural interventions are below the range of $200 per DALY and a few more between $200 and $600, a level that is still very cost-effective. For middle-income countries, we find evidence that a number of interventions have been estimated to represent below $500 per DALY, and a few more between $1,000 and $2,000. One study of prevention of mother-to-child transmission in the Americas (specifically Mexico) is excluded as it is an outlier, with an estimated cost per DALY of $57,000. Even the relatively more expensive structural interventions are also well below the threshold of one GDP per capita. In fact, all of the prevention interventions are well below 40% of one per capita GDP when evaluated for each country of intervention (Galarraga, Colchero, et al. 2009). Dotted lines between two points in the figures depict the interval between the lowest and highest cost estimate for a specific intervention studied. Countries are ranked as low- or middle-income according to the World Bank criteria detailed above.

Figure 1. Distribution of cost per DALY of preventative interventions in low-income countries

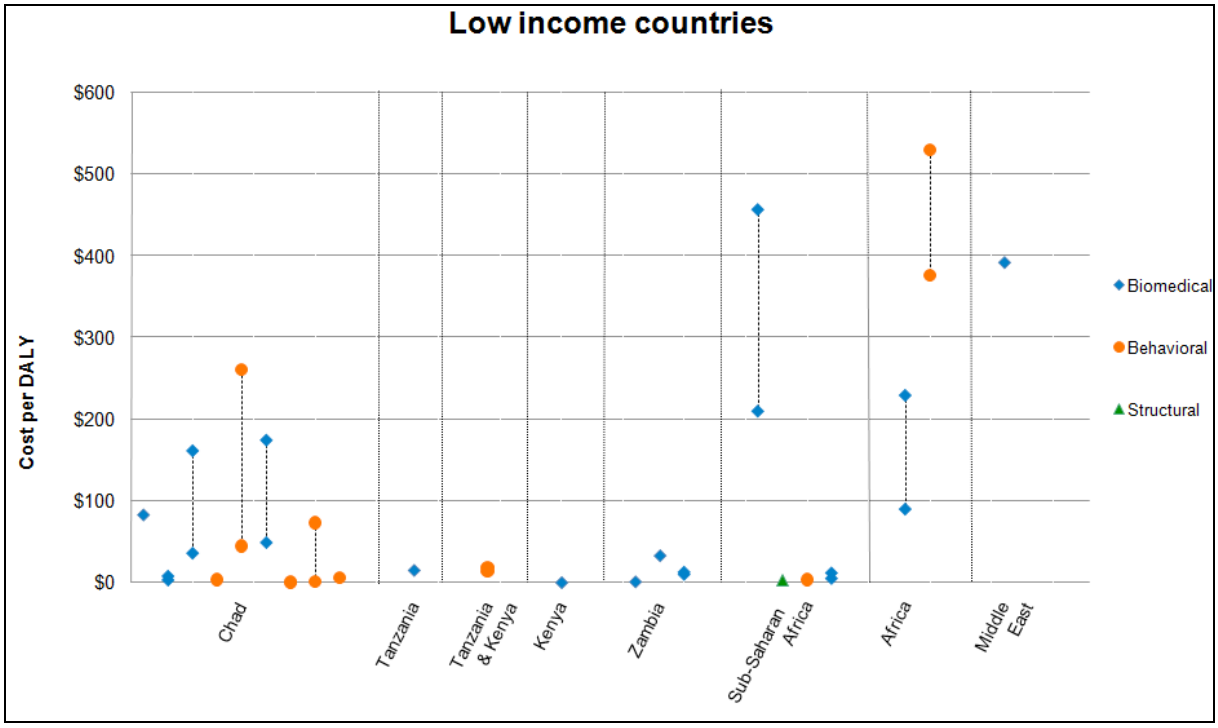
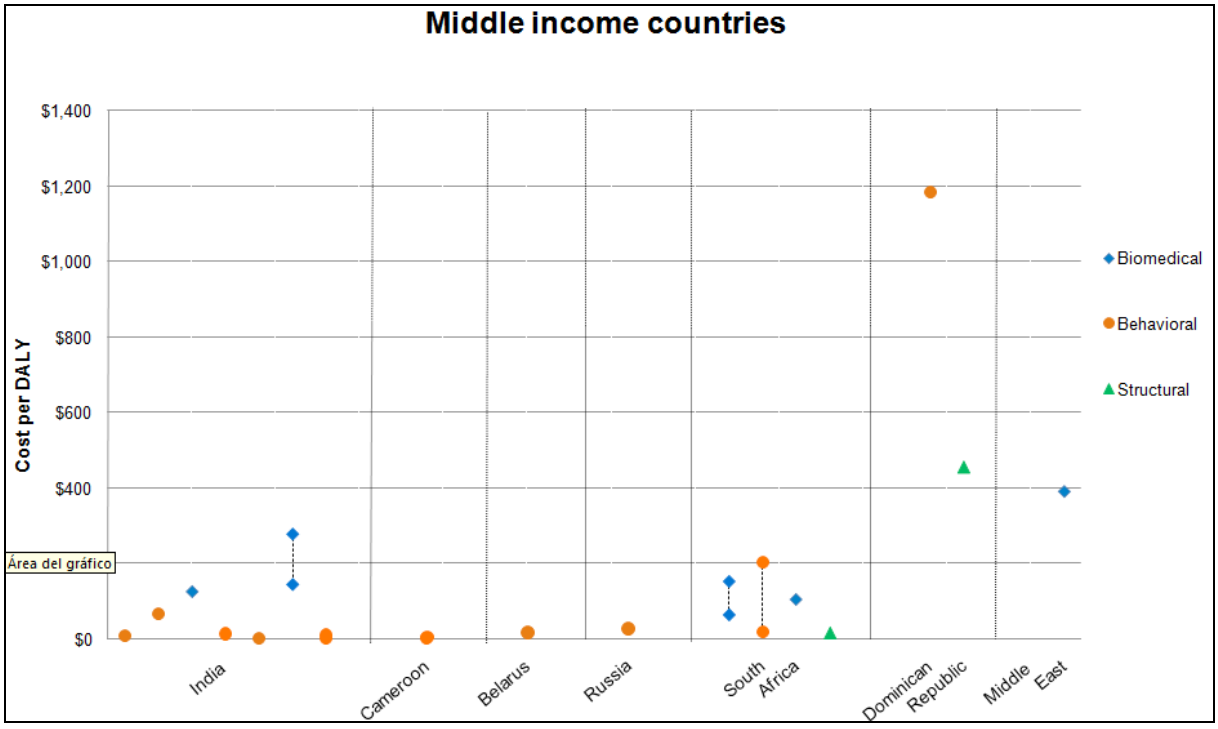


Figure 2. Distribution of cost per DALY of preventative interventions in middle-income countries



We find that there is set of interventions that has been documented as cost-effective, and that we can classify as highly cost-effective given the ratio between cost per DALY and GNI per capita in the specific setting where the estimate was made (Figures 3 and 4).

Figure 3: Cost of DALY/GNI per capita in low-income countries

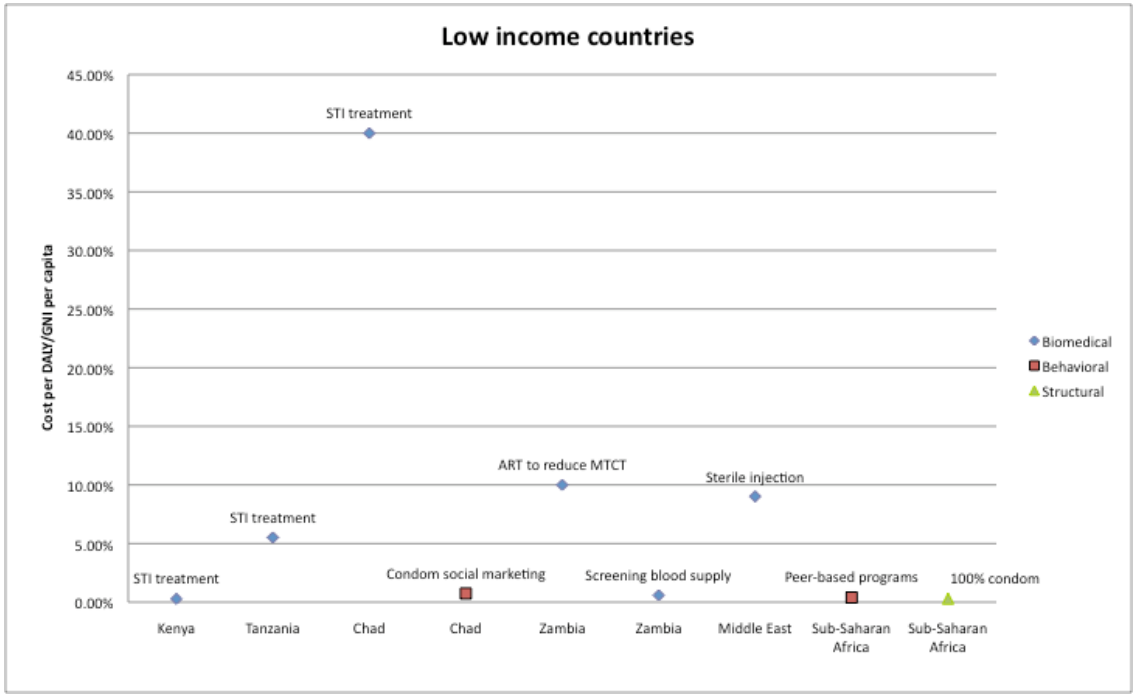
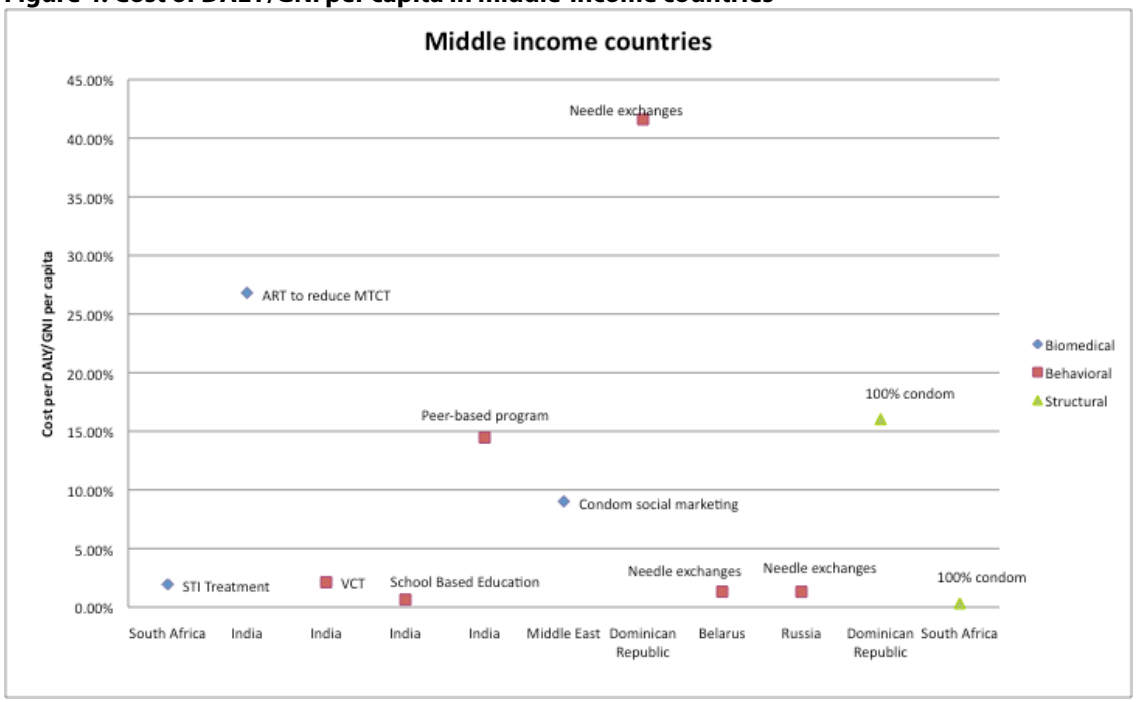


Figure 4: Cost of DALY/GNI per capita in middle-income countries



Care

We ranked the spectrum of care and treatment interventions according to level of cost-effectiveness based on the findings presented in the DCP2 chapter and the UNAIDS literature review update (Table 6).

It is clear that in low-income countries (and therefore for middle-income also) co-trimoxazole prophylaxis, first-line ARV treatment and using CD4 counts to determine initiation of ARVs are cost-effective. Provision of second-line ARV regimes are also cost-effective, although with slightly higher cost-effectiveness ratios than first-line therapy.

In the studies that we reviewed first-line and second-line therapy, salvage regimens as well as the use of CD4 and viral load testing proved highly sensitive to the price of drugs and/or laboratory testing kits and reagents. For this reason, we expect that as these prices drop, the interventions become more cost-effective. A recent analysis suggests that ART can become cost-saving at reduced ARV prices ($181 for a year's supply of first-line ARVs in the South Africa setting) (Badri, Maartens et al. 2006).

Efficiency of the HIV/AIDS response

While in the previous section, we were able to rank and identify those HIV/AIDS prevention and care interventions that provided the best value for the money, the literature shows us that there are significant variations of unit costs across countries for the same type of intervention. As such, there are important issues regarding efficiency of implementation that can contribute to a reduction in unit costs, and thus improve cost-effectiveness ratios.

Prevention

As demonstrated in the previous section, there is a range of proven HIV prevention interventions where the cost effectiveness ratios are available, which can be considered affordable for low-income countries. However, we can observe varying levels of uncertainty for both costs and effectiveness for the same intervention across countries, potentially due to differences in what methodology was used to determine costs (economic vs. financial costs), variation in estimates of effectiveness for the intervention and the individual components considered as part of each intervention.

Cost-effectiveness ratios in some cases should be carefully interpreted, particularly for those interventions for which the effectiveness evidence is questionable, such as for school-based education programs. The components of the same intervention vary; for instance, there is no one definition of what comprises a voluntary counseling and testing session.

Wide ranges of cost-effectiveness estimates for single interventions point to likely significant differences not only in how interventions are costed out, and the individual elements that comprise the intervention, but also for different levels of efficiency in implementation. Marseille, Dandona et al (2007), through the "Prevent AIDS: Network for Cost-Effectiveness Analysis" (PANCEA) project observed important variations of unit costs across countries for both voluntary counseling and testing and peer-based education programs (Marseille and et al. 2004). Another example of this variation can be found in the cost estimates of school-based education programs that range from USD 1350 in India to USD 9449 in Africa per HIV infection averted (The World Bank 1999; Hogan and Salomon 2005).

Targeting most-at-risk populations emerges as the clearest strategy in the literature to improve efficiency of the AIDS prevention response. As one of the most cost-effective interventions for sex workers, peer-based education can be highly effective if well targeted to the key populations. An economic analysis of the HIV prevention program implemented in one Indian state suggests that by reducing the importance of interventions aimed at the general population (namely mass media campaigns) and redistribution of these resources to interventions including peer-based education and VCT for key populations (including migrant workers and men who have sex with men) could avert up to 54% more HIV infections (Dandona, Kumar et al. 2009).

Care

The literature highlights a number of areas of AIDS care where improving efficiency can positively affect both affordability of treatment and outcomes. One area is improving long-term survival of people on ARVs in low- and middle-income countries, which lags behind that for people from high-income countries. When long-term survival is estimated for people in low-income countries they are still less than those enjoyed in high-income countries, although the benefits of antiretroviral therapy in low- and middle-income countries are considerable, (Beck, Santas et al. 2008). At both 6 and 12 months after initiation of antiretroviral therapy, mortality rates for

individuals in low- and middle-income countries are at least 28% higher than those for patients in high-income countries (Braitstein, Brinkhof et al. 2006). Studies have suggested that since most mortality in resource-poor settings occurs early in treatment, leading to the conclusion that the mortality gap could be reduced by efforts aimed at diagnosing HIV infection earlier, and perhaps starting earlier. One study of scaling up in Zambia found that 73% of all new patients in treatment were at WHO stage III or IV and had an average CD4 cell count of 143 cells/mm3 (Stringer, Zulu et al. 2006).

The sensitivity tests of the cost-effectiveness studies for ART provision demonstrated that CE ratios are most sensitive to prices of ARV drugs and laboratory assays (Badri, Maartens et al. 2006; Wolf, Ricketts et al. 2007). These are clearly two main areas where improved efficiency (interpreted as lower prices for drugs and assays) can greatly impact the cost-effectiveness of care and treatment.

Strategies to reduce drug costs can vary. Switching to generics in those countries not already using them would be an appropriate strategy particularly for middle-income countries that are currently using patented drugs. Wolf (2007) estimated the lifetime treatment costs of a universal access strategy for the Organization of Eastern Caribbean States, for the 1070 HIV-infected persons. The total costs for two lines of therapy when the CD4 count <350 cells/ul) plus co-trimoxazole would be $18.2 million ($2 million per year). Use of generic drugs for second line therapy would reduce this amount by 45% (Wolf, Ricketts et al. 2007).

Using markers of opportunistic disease to indicate when to switch to second-line therapy also improved cost-effectiveness, albeit with an important trade-off of decreased life expectancy (9.2 versus 8.17 years) (Goldie, Yazdanpanah et al. 2006).

Perspectives on affordability of interventions: impact of economies of scale and challenges to scaling up

This section seeks to identify issues impacting scale-up of HIV/AIDS prevention and care interventions, in particular as they relate to efficiency. Little data was included in the DCP2 chapter or in the other literature reviews on economies of scale and impacts on the costs of implementing interventions. However, for this paper we conducted a brief review of the limited literature available regarding scaling up and the impact on unit costs.

Prevention

In order to analyze the affordability of different interventions when planning an AIDS response at a national level, it is useful to have an estimate of how scaling up affects the unit cost. Cost function analysis allows measurement of how marginal and average costs vary based on implementation scale. While there is growing evidence of scale variation among interventions for HIV prevention (Kumaranayake 2008), the data is still limited and at times contradictory.

One study that analyzed scale and efficiency of prevention programs in five countries (Marseille, Dandona et al 2007) with the finding that efficiency increased with scale. Efforts to increase the scale of HIV prevention (as well as care) interventions face important infrastructure barriers which will need to be considered in the cost functions (Kumaranayake 2008).

Many of the interventions identified in the literature were carried out on a small scale by local non-governmental organizations. Thus, efficiency tends to vary among programs. One study found significant variation among programs aimed at sex workers in terms of number of contacts made by types of program staff (Dandona, Sisodia et al. 2005). As HIV prevention interventions are likely to be carried out by a combination of actors—government agencies, small local NGOs and larger international NGOs as well as other civil society organization—clear guidelines as to best practices for individual interventions can be useful to ensure that while these different organizations are individually scaling up their interventions, marginal costs can be minimized through adhering to practices and techniques for scaling up. Best practice guidelines can also help to ensure that the quality of interventions as they are scaled up. Current evidence suggests that for prevention interventions, quality may suffer as programs are scaled up, as measured in duration of counselling

session (Kumaranayake 2008). However, another found that time spent with each client, remained steady even as programs were expanded (Dandona, Kumar et al. 2008).

Beyond scaling up of individual interventions, the question remains of how to scale up the package of interventions and the appropriate combination of interventions and their potential synergies. Hogan et al. model a package of care interventions, in which mass media is the backbone (Hogan, Baltussen et al. 2005). While conceptually this is a useful model, it should be tested with different combinations of interventions and considering different epidemic profiles to identify the optimal package of prevention services. This is especially important given that the literature regarding the effectiveness of mass media on HIV prevention is mixed. Furthermore, we found no empirical evidence of interactions between the different types of interventions leading to differential prevention outcomes.

Care

The literature on the impact of economies of scale for AIDS care and treatment interventions is even sparser than the literature on prevention. Hence, we look at specific aspects of provision of antiretroviral therapy that should be taken into consideration when scaling up care in low-resource settings.

Overall, the cost-effectiveness ratios for ARV treatment demonstrate that first-line therapy is clearly affordable even in low-income countries. The results presented in Table 3 show that initiation of ARVs either early (at a CD4 count of 350 cells/ul) or late (at a CD4 count of 200 cells/ul) yield similar levels of cost-effectiveness (Bachmann 2006; Badri, Maartens et al. 2006; Cleary, McIntyre et al. 2006; Goldie, Yazdanpanah et al. 2006; Bishai, Colchero et al. 2007; Freedberg, Kumarasamy et al. 2007; Vijayaraghavan, Efrusy et al. 2007; Wolf, Ricketts et al. 2007). However, from a perspective of affordability, initiating ART early introduces important issues.

Lifetime costs of providing antiretroviral therapy increase substantially when comparing early and late initiation. Starting at a CD4 cell count of <350 cells/ul increases lifetime costs from between 23% (Vijayaraghavan, Efrusy et al. 2007) to 56% (Bachmann 2006) compared with starting at a CD4 cell count of <200 cells/ul. Thus, not only does early initiation yield greater lifetime costs per person, setting a higher CD4 threshold for initiation of ART also means that more people at the baseline are eligible for ART. We can logically assume therefore that early initiation will result both in significant increases in annual costs of AIDS programs and greater costs in the longer term. Countries will need to decide if it is fiscally viable to start HIV-infected individuals early or late. Countries with a heavy burden of HIV will likely be unable to meet the needs of all PLWHA by starting them early, while countries with a lower numbers of HIV-infected individuals may find that it is possible to start individuals earlier, and thus also reap the potential prevention benefits. Of course, early diagnosis is critical for early initiation of ARV therapy. Even in countries such as Mexico, which contemplates early initiation of ARVs, and provides universal access to treatment, most people are identified as being infected with HIV relatively late in the disease stage.

In order to analyze the costs of early versus late initiation of ARVs more precisely, it is also imperative to have clear, well-defined estimations of the need for ARV both worldwide and at the country level. Using the metric in the guidelines for construction of the UNGASS indicators, 15% of the population living with HIV is estimated to be critically ill with AIDS and requiring ARVs; roughly 5 million of the current 33 million infected (Joint United Nations Programme on HIV/AIDS 2003). Yet, this estimate is for the critically ill. The current UNAIDS estimation of people needing ARVs is close to 10 million (UNAIDS 2008). However, the construction of a denominator for this indicator is vague, and informed by sentinel surveillance in individual countries. A more refined process to determine the number of people requiring ARVs with the capacity to project into the future is clearly needed. A logical next step is then to estimate the needs for first- and second-line ARV demand in terms of active product ingredients at the global level (Galarraga, O'Brien, et al. 2007).

Laboratory costs are the other main area for analysis of affordability when discussing HIV/AIDS care. The use of clinical versus laboratory markers to base decisions about initiation of ARV

therapy has been analyzed in two studies. These two analyses found that using CD4 cell counts has a higher cost effectiveness ratio than using clinical marker or total lymphocyte counts, to guide initiation of ART. (Goldie, Yazdanpanah et al. 2006; Bishai, Colchero et al. 2007). Yet, these assays are not always available in low-resource settings and would require scaling up of laboratory capacity.

Alternative technologies for conducting CD4 cell counts and viral load play an important role. Regular viral load analyses are clearly unaffordable in low-income, and possibly many middle-income countries. Strategic decisions and policies should be made about the criteria of when to use viral load, thus optimizing the use of this test. Proposals for constrained selectivity include limiting viral load testing to diagnose infections in newborns and specifically targeting those at risk of non-adherence (Calmy, Ford et al. 2007).

Future Projections

In economic analysis, models will hold as long as the assumptions upon which they are based remain static. The assumptions of prevention are changing, especially in light of the recent push for universal access. The challenge to model the AIDS response is to develop a simple, tractable model that is nuanced enough to allow for changes in information. Evaluation (and cost and cost-effectiveness analysis) for prevention activities in particular has focused on individual interventions. Yet there is growing consensus that, especially for generalized epidemics, it is a comprehensive package of interventions that is needed for an adequate response. There is an urgent need to generate evidence regarding the effectiveness of different combinations of interventions and comprehensive packages. Rarely are there randomized controlled trials for the whole prevention package, yet we need more data on what the components of a comprehensive response should be. To take school-based interventions as an example, we have studies that show that while they are effective in imparting knowledge, there is little evidence that these types of intervention work to prevent HIV transmission (DeMaria, Galarraga et al. 2009). Few people would argue that we should not conduct school-based comprehensive sexual education, which increases knowledge about sexuality, reproduction and how to prevent HIV as well as reduces stigma and discrimination. Yet the question remains: "What is the role of school-based education in a comprehensive HIV-prevention response?"

To return to the axiom that a model is only as good as its assumptions, it is useful to examine the way that those assumptions are changing. It has become clear that there is no one response package applicable to all countries and settings; high-quality targeted interventions to most-at-risk population are more appropriate in concentrated epidemics; effective interventions to change general population behaviors and increase access to and acceptance of circumcision is called for in general epidemics (Wilson and Halperin 2008), but the appropriateness and impact of this intervention in concentrated epidemics has not been measured. For potentially mixed epidemics, we lack basic epidemiological information on routes of transmission to appropriately relate interventions to transmission sources, and achieve an appropriate balance of general population and targeted interventions (Bertozzi, Laga et al. 2008; Wilson and Halperin 2008).

If prevention interventions are better targeted and implemented more efficiently, the cost per infection averted and the cost-effectiveness ratios will likely decrease over time, as long as those interventions are effective to begin with.

There are currently some concentrated epidemics which have the potential to become generalized epidemics (Wilson and Halperin 2008). Given that it has been clearly demonstrated that prevention is far more cost-effective than care, in these settings it is critical to implement a revitalized prevention package which, if effectively implemented, will lead to future cost-savings (Canning 2006; Marseille, Hoffmann et al. 2002).

For care and treatment, we have identified several areas where assumptions may change over the next 25 years. Currently, many sub-Saharan countries are relying on paramedical personnel for the provision of first line ARVs, given the lack of physicians in many settings. It remains to be seen if

this is a viable model as patients are on ARVs longer, increasing the likelihood that they will be on second or salvage regimes. Regardless, the human resources needed to reach the goal of universal coverage by 2017 will require significant investments in human resources. One study estimates that at a minimum sub-Saharan Africa will need to double the human resources for AIDS on an annual basis to meet the increasing needs of patients (Barnighausen, Bloom et al. 2007).

Adherence rates similar to those observed in high-income countries have been documented in low- and middle-income countries (Mills, Nachega et al. 2006), as long as those drugs are provided free of charge (Mills, Nachega et al. 2006). Once patients are asked to pay even a modest price for ARVs, observed adherence begins to decline (Kiguba, Byakika-Tusiime et al. 2007). It will be important to maintain access to free ARVs to ensure that these adherence rates continue.

Similarly, the ARV pharmaceutical market dynamics continue to change in light of new negotiations and better arrangements for low-income countries. Most recently, UNITAID has arranged for second-line treatment prices to drop substantially.

Finally, as ART continues to be rolled out and survival of those infected with HIV increases, new challenges regarding the health care needs of these people will need to be met.

Prevention/care synergy

The DCP2 chapter reviewed possible effects of antiretroviral therapy on transmission dynamics, suggesting that perhaps ARV therapy would have a positive effect on the population level of HIV. Yet the level of confidence for this prediction was quite low, and the recommendation was made to continue to evaluate and monitor sexual behaviors and outcomes (Bertozzi, Padian et al. 2006).

The recently published literature regarding the synergy between prevention and care, particularly in terms of using care as an intervention for preventing future HIV infections, is non-conclusive. A recent study by Wilson et al (2007) shows that although the risk of transmission of HIV in sero-discordant couples is low, it is not likely to be zero even among those on therapy with undetectable plasma levels. If effective therapy is equated with "non-infectiousness" and as a result, condom use is neglected, a significant number of new infections could occur. Baggaley and authors (2006) employ mathematical modeling which demonstrated nearly no benefit of ART as a "direct transmission prevention measure regardless of the degree of coverage" (Baggaley, Garnett et al. 2006). As such, prevention interventions among positives focusing on condom use and partner reduction will need to be reinforced.

One study calculated the cost-effectiveness ratios of ART provision for two scenarios: index cases only and index cases plus HIV transmission to partners. Cost-effectiveness ratios declined from $5314 for patient only scenarios to $3956 for index patient and sexual partners scenario (both estimations comparing treatment according to US vs. WHO guidelines (null case) (Vijayaraghavan, Efrusy et al. 2007). Assuming that in South Africa all HIV patients are treated according to US standards versus WHO guidelines, and including the lifetime costs of index patients and their sexual partners, the authors found that ARV may even be cost-saving (Vijayaraghavan, Efrusy et al. 2007).

Recommendations and Conclusions

A quarter century into the AIDS epidemic, we are still falling short of delivering an adequate response, particularly in low-income settings. This is evidenced in the reports published in 2008—at the mid-point between the implementation of UNGASS Millennium Development Goals (MDGs)—which show that 40% of young men and 38% of young women were reported to have "accurate and comprehensive knowledge of HIV and how to avoid transmission," falling short of the goal of 95%.

Only 34% of HIV-infected pregnant women received antiretrovirals to prevent mother to child transmission (global goal of 80%). The data also clearly indicate that key populations for HIV prevention activities are not being reached; in fact coverage of prevention services to key

populations is low. According to aggregated UNGASS country reports, nearly 63% of countries have legislation and/or policies which present obstacles to information and services for men who have sex with men, sex workers and injecting drug users (UNAIDS 2008).

In the coming years, it is likely that these interventions will need to optimize efficiency and effectiveness as they will be implemented in a context of resource scarcity. The 2008 UNAIDS Global AIDS Report highlights an important resource gap. To maintain the current pace of scaling up activities, funding levels will need to increase 50% by 2010. Yet funding increases of this magnitude will still fall short of the amount needed to achieve universal access by 2010 or even by 2015. The recent economic crises are straining high-income country economies and the duration and impact of the global recession are still unknown at this time. The extent to which these countries will continue to fund AIDS programs given potentially competing domestic budget priorities is currently unknown. A pragmatic view suggests that increases in high-income country's foreign aid budgets are unlikely in the next few budget cycles. Hence, it is probable that projections for AIDS resources in the next five years will not meet the UN projections for universal access.

While we still lack critical data on how to optimize the cost-effectiveness of many prevention interventions, particularly for large-scale implementation, we have learned a substantial amount about the effects and costs of prevention strategies in developing countries over the past decade. The current challenge is two-fold: 1) the HIV/AIDS community must utilize existing data to the fullest extent and prioritize programs with a clear benefit; and 2) we must press to include rigorous program evaluations with the implementation of new and existing interventions to inform resource allocation, potential scale-up, and program design.

Comparing the costs of both prevention and care interventions leads to one striking conclusion: the utility and necessity of prevention activities cannot be under-valued. Prevention activities are much more cost-effective over the long run than any care/treatment package.

Reallocation of resources between interventions

Allocation of resources should be made according to the country's epidemic profile. In broad terms, those countries with generalized epidemics should invest more in circumcision and in partner reduction as the core of a comprehensive and affordable package of interventions that includes VCT, and condom promotion should be implemented.

In concentrated epidemics, prevention interventions need to be targeted according to the type of epidemic and profile of most-at-risk populations. In many countries, this will also imply efforts to assure the political will and policy environment to deliver services. Estimates of these critical "enabling environment" interventions are estimated to require relatively low funding levels; approximately 10% of total prevention program budget (Commission on AIDS in Asia 2008).

Needs for data, information and research

There is a clear need for long-term estimates of cost, beyond the 2015 projections estimated in the 2007 UNAIDS Financial Needs Assessment of various epidemiological aspects of the epidemic (UNAIDS 2007). Epidemiological surveillance, both among the general population and most-at-risk groups, needs to be strengthened in nearly all countries. Sentinel surveillance of those already infected is needed to better forecast ARV needs.

Finally, and perhaps most importantly, the optimal allocation of resources for HIV/AIDS needs to be balanced with the needs of society. By a simple utility maximization exercise at the global level, preventing future HIV infections is clearly the most cost-effective approach. While a 100% prevention approach would be appropriate in Year Zero of the epidemic, it is an untenable strategy 25 years into the epidemic. Although some theoretical work has been proposed (Gersovitz 2006), there are no calibrations available at the country level to balance the investment between care and treatment and arrive at a ratio of how funds should be divided to maximize total societal welfare. How to balance the funding needs of care programs for the 33 million currently

infected with the needs of the many more millions at risk of future infections is a debate that must extend beyond the discussion of costs and cost-effectiveness and include human rights and the political budgetary realities of policy making.

An optimal package of prevention and treatment interventions should be based on effectiveness and cost-effectiveness evidence at the country level, or at least by type of epidemic profile. The "right mix" of interventions should be studied more carefully to maximize societal needs. These sorts of analyses have not been done at the country level. Yet to maximize effectiveness, any long-term strategy urgently needs this information.

Table 1. Summary of findings on HIV/AIDS prevention: effectiveness, cost and cost-effectiveness			Epi. profile of CE study population				
Category and specific intervention	Effects	Cost-effectiveness (USD per HIV infection or DALY averted) NOTE: THESE VALUES HAVE NOT BEEN ADJUSTED TO 2008 USD, MAY REFLECT DIFFERENT YEARS OF CURRENCY	Low	Conc.	Gen. low	Gen. high	Citations
BEHAVIORAL INTERVENTIONS							
School-based education	Later sexual debut[a,b], fewer sex partners[a,c], higher condom use[a-d,f,g], reduced frequency of sex[f,g], less unprotected sex[f,g] No impact found on HIV incidence[a] or STI incidence[a]	India: $1350 per HIV infection; $68 per DALY[h] Africa: $6704-9448 per HIV infection; $376–530 per DALY[e]	✓		✓	✓	a) Hayes et al. 2003, b)Stanton et al 1998, c) Fawole et al 1999, d)Harvey, Stuart, and Swan 2000, e) Hogan, et al. 2005, f)Kirby et al. 2006, g) Kirby et al. 2007 h) World Bank 1999
Abstinence education	No impact found on condom use or early sexual debut[a,b]						a) Jemmott, Jemmott, and Fong 1998, b) Meekers 2000
VCT	Higher condom use[a-g], lower HIV incidence[b,n] and STI incidence[d,f,n], less unprotected sex[c,g,h] No impact found on number of partners[h]	South Africa: $67-112 per HIV infection[i] India: $196 per HIV infection; $10 per DALY[j] Chad: $891-5,213 per HIV infection; $45-261 per DALY[k] Kenya and Tanzania: $270-376 per HIV infection; $14-19 per DALY[l] Russia (cost only): $1.5 per full VCT per person[m] Mexico (cost only): $668 per full VCT per person[m]		✓ ✓ ✓	 ✓ ✓	✓	a) Bentley et al. 1998, b) Bhave et al. 1995, c) Dechamps et al. 1996, d) Jackson et al. 1997, e) Kamenga et al. 1991, f) Levine et al. 1998, g) VCT Efficacy Study Group 2000, h) Denison et al. 2007, i) Hausler et al. 2006, j) World Bank 1999, k) Hutton, Wyss, N´Diekhor 2003, l) Sweat et al. 2000, m) Marseille et al. 2007, n) Celentano et al. 2000
Peer-based programs	Higher condom use[a-d, o], lower HIV[h,i] and STI incidence[h], less unprotected sex[a,c,e,f,], improved communication with sexual partner[g]	Chad: $6-1,476+ per HIV infection; $1-74+ per DALY[j] Cameroon: $67-137 per HIV infection; $3-7 per DALY[k] India: $52-303 per HIV infection; $3-15 per DALY[l] India: $56-219 per HIV infection; $3-12 per DALY[m] Sub-Saharan Africa: $68 per HIV infection; $4 per DALY[n]	 ✓ ✓		✓ ✓	 ✓	a) Kelly et al. 1997, b) Norr et al. 2004, c) Sikkema et al. 2000, d) Stanton et al. 1996, e) Basu et al. 2004, f) Kegeles, Hays and Coates 1996, g) Lauby et al. 2000, h) Ghys et al. 2002, i) Katzenstein et al. 1998, j) Hutton, Wyss, N´Diekhor 2003, k) Kumaranayake et al. 1998, l) World Bank 1999, m) Fung et al. 2007, n) Hogan et al. 2005 o) Coates 1996
Condom promotion and distribution	Higher condom use[a-k], lower HIV incidence [b,h,l,] and STI incidence[b, h,i,l,n]	South Africa (female condom): $378-4,094 per HIV infection; $19-205 per DALY[m]				✓	a) Bentley et al. 1998, b) Bhave et al. 1995, c) Egger et al. 2000, d) Fordet al. 1996, e) Jackson et al. 1997, f) Jemmott, Jemmott, and Fong 1998, g) Kagimu et al. 1998, h) Laga et al. 1994, i) Levine et al. 1998, j) Ngugi et al. 1988, k) Pauw et al. 1996, l) Celentano et al. 2000, m) Marseille et al. 2001 n) Jackson et al. 1997
Condom social marketing	Mixed results on condom use[a,b]; increased knowledge of HIV, interpersonal communication, and health provider awareness [c,d]; improved self-efficacy in condom use[c,d] No impact on early sexual debut	Dominican Republic: $28,208 per HIV infection; $1,186 per DALY[e] Chad: $77 per HIV infection; $4 per DALY[f]			✓ ✓		a) Agha, Karlyn, and Meekers 2001, b) Meekers 2000, c) Bertrand and Anhang 2006, d) Bertrand, O'Reilly et al. 2006, e) Sweat et al. 2006, f) Hutton, Wyss, N´Diekhor 2003

Table 1. Summary of recent findings on HIV/AIDS prevention (continued)			Epi. profile of CE study population				
Category and specific intervention	Effects	Cost-effectiveness (USD per HIV infection or DALY averted)	Low	Conc.	Gen. low	Gen. high	Citations
BIOMEDICAL INTERVENTIONS							
STI treatment	Lower STI incidence[b-i] Mixed findings on influence on HIV incidence[a-d], reduction in HIV incidence found among sex workers and their clients[o]	Chad: $1,675 per HIV infection; $84 per DALY[j] Tanzania: $326 per HIV infection; $16 per DALY[k] Kenya: $11-16 per HIV infection; $1 per DALY[l] South Africa: $2,093 per HIV infection; $78 per DALY[n] Nicaragua: $118-200 per STI cured[p] Malawi: $12 per HIV infection[q]		 ✓ 	✓ ✓ ✓ 	 ✓ ✓	a) Grosskurth et al. 1995, b) Kamali et al. 2003, c) Laga et al. 1994, d) Wawer et al. 1999, e) Jackson et al. 1997, f) Kamali et al. 2003, g) Laga et al. 1994, h) Mayaud et al. 1997, i) Wawer et al. 1999, j) Hutton, Wyss, and N'Diekhor 2003, k) Gilson et al. 1997, l) Moses et al. 1991, m) Vickerman et al. 2005, n) Vickerman et al. 2006, o) Fung et al. 2007, p) Borghi et al. 2005, q) Price et al. 2006
Male circumcision	Large reduction in HIV incidence[a-c]	South Africa: $181 per HIV infection[d] Sub-Saharan Africa: $551 per HIV infection[d]			✓	 ✓	a) Auvert et al. 2005, b) Bailey et al. 2007, c) Gray et al. 2007, d) Kahn et al. 2006
PMTCT							
ART to reduce MTCT	Large reduction in MTCT[a-h]	Mexico: $39,230-42,528 per HIV infection; $2,124-2,303 per DALY[j] India: $2,527 per HIV infection; $126 per DALY[i] Zambia: $848 per HIV infection; $34 per DALY[k] Chad: $924-4,044 per HIV infection; $37-162 per DALY[l] South Africa: $1,650-3,844 per HIV infection; $66-154 per DALY[m] Sub-Saharan Africa: $142-11,444 per HIV infection; $6-458 per DALY[n,p]		✓ ✓ 	 ✓ ✓ 	 ✓ ✓	a) Ayouba et al. 2003, b) Connor et al. 1994, c) Dabis et al. 1999, d) Guay et al. 1999, e) Jackson et al. 2003, f) PETRA Study Team 2002, g) Shaffer et al. 1999, h) Wiktor et al. 1999, i) World Bank 1999, j) Rely et al. 2003, k) Stringer et al. 2003, l) 54k, m) Wilkinson, Floyd, and Gilks 1998, n) Marseille, Kahn, and Saba 1998, o) Marseille et al. 1999, p) Reynolds et al. 2006
Feeding substitution	Reduction in MTCT and improved overall survival[a]	Chad (breastfeeding advice): $1,241-4,382 per HIV infection; $50 -175 per DALY[b]			✓		a) Nduati et al. 2000, b) Hutton, Wyss, and N'Diekhor 2003, c) Foss, Watts et al. 2007
Harm reduction							
Needle exchanges	Lower HIV incidence[a,b], reduction in needle sharing[c-f]	Belarus: $353 per HIV infection; $18 per DALY[g] Russia: $564 per HIV infection; $28 per DALY[h]		✓ ✓			a) Des Jarlais and Friedman 1996, b) Hurley, Jolley, and Kaldor 1997, c) Jenkins et al. 2001, d) Ksobiech 2003, e) Peak et al. 1995, f) Vlahov et al. 1997, g) Kumaranayake et al. 2004, h) Bobrik 2004
Drug substitution and addiction treatment	Lower rate of drug use[a]	Ukraine: $97 per HIV infection[b]		✓			a) Metzger, Navaline, and Woody 1998, b) Vickerman et al. 2006
Blood safety							
Screening blood supply	Reduction in HIV infections[a,b] and units of HIV infected blood[c]	Low-level epidemic countries : $374-45,173 per HIV infection; $19 -2,259 per DALY[d] Chad: $75-151 per HIV infection; $4-8 per DALY[e] Zambia: $41-262 per HIV infection; $2-13 per DALY[f,g] Zimbabwe: $166-1,010 per HIV infection; $8-51 per DALY[h]	✓		 ✓ ✓	 ✓	a) Foster and Buve 1995, b) Laleman et al. 1992, c) Jacobs and Mercer 1999, d) Over and Piot 1996, e) Hutton, Wyss, and N'Diekhor 2003, f) Watts, Goodman, and Kumaranayake 2000, g) Foster and Buve 1995, h) McFarland and others 1995

Table 1. Summary of recent findings on HIV/AIDS prevention (continued)			Epi. profile of CE study population				
Category and specific intervention	Effects	Cost-effectiveness (USD per HIV infection or DALY averted)	Low	Conc.	Gen. low	Gen. high	Citations
Sterile injection		Middle East: $393 per DALY[a] Southeast Asia: $143-593 per DALY[a] Americas: $1,851-56,642 per DALY[a] Western Pacific: $953 per DALY[a] Africa: $91-230 per DALY[a]	✓	 ✓ ✓ ✓	 ✓	 ✓	a) Dziekan and others 2003
Universal precautions	Use of gloves reduced volume of blood transferred in needlestick injury[a]						a) Mast, Woolwine, and Gerberding 1993
ART for prevention or post-exposure prophylaxis	Lower seroconversion rate[a]	United States: $76,584 per HIV infection; $3,829 per DALY[b] India: $145-280 per DALY[c]		✓ ✓			a) Cardo and others 1997, b) Pinkerton, Holtgrave, and Bloom 1998, c) Over et al. 2006, d) Freedberg et al. 2007, Bachman 2006
STRUCTURAL INTERVENTIONS							
Prices, taxes, subsidies, vouchers	Reduced teen pregnancies[a], increased rate of STI treatment[b]	Kenya (subsidies to increase PMTCT ART): $441 per HIV infection[c]			✓		a) Duflo et al. 2006, b) Borghi, Gorter et al. 2005, c) Dupas 2005
Access to credit	Control over own money associated with HIV-related negotiations[a]		✓				a) Ashburn et al. 2007
Conditional economic incentives	Increased return rate for testing services[a]	Malawi (incentive to return for test result): $1136 per HIV infection				✓	a) Thornton 2006
100% condom	Reduced STI incidence[d]	Brazil: $20,683 per HIV infection[c] Dominican Republic: $10,856 per HIV infection; $457 per DALY[a] Sub-Saharan Africa: $58 per HIV infection; $3 per DALY[b] South Africa: $985 per HIV infection; $18 per DALY[c]		✓	✓	 ✓ ✓	a) Sweat et al. 2006, b) Hogan et al. 2005, c) Dowdy et al. 2006 d) Kerrigan et al. 2006

Table 2. Summary of Recent Findings on Cost-effectiveness of HIV Care and Treatment Interventions

Source	Country /Setting	Scenarios considered	Lines of inquiry	Analytic Methods
Bishai, D., A. Colchero, and D.T. Durack (2007)	General sub-Saharan Africa (low income)	1. No treatment strategy. 2. Syndromic management without laboratory tests. 3. Syndromic management plus total lymphocyte counts every 6 months. 4. Syndromic management plus CD4 cell count assessment every 6 months. 5. Syndromic management plus CD4 cell count every 6months and viral load assessment 4weeks after the initiation of treatment, then every 6 months. In two settings: (a)no second-line treatment available and (b) second-line treatment available.	*Laboratory monitoring strategies *One and Two lines of ARVs	- Markov-type modelling using joint normal distributions of CD4 and viral load (for natural hist & for effectiveness of Tx) - All parameters from the literature
Freedberg, K.A., et al. (2007)	India (middle income)	1) No treatment strategy. 2) Starting ARVs by CD4 count or by occurance of opportunistic infection 3) Early and late initiation of ART by CD4 cell count threshholds: <200 cel/µl, <250 cel/µl and <350 cel/µl. 3) Cotrimoxazole prophylaxis only. In two settings: (a)no second-line treatment available and (b) second-line treatment available.	*Clinical criteria for starting ARV; *Laboratory monitoring for starting ARVs *Early and late initiation of ARVs *One and Two lines of ARVs *Cotrimoxazole prophylaxis, with and without ARVs	- CEPAC model - Costs: from the international literature (mostly Indian)
Badri, M., et al. (2006)	Cape Town South Africa (Upper Middle Income)	HAART drug-price scenarios presented were: 1) present public sector prices, ($730 per year), 2) anticipated public sector price for locally manufactured drugs, ($181 per year), for the WHO-recommended regimen.	*One and Two lines of ARVs *Reduced prices for second-line ARVs	- Quasi experimental design: matching at baseline (CD4, age and SE status) - Costs: SA sources
(Long,	St Petersburg, Russia.	1. IDU-targeted treatment strategy: 80%	*Targeting ARV strategies to	

Brandeau et al. 2006)	(Upper middle Income)	treatment-eligible IDUs and 1% of treatment-eligible non-IDUs receive HAART 2. Non-IDU targeted treatment strategy: no infected IDUs and 80% of treatment-eligible non-IDUs receive HAART; 3. Untargeted treatment strategy: 50% of all treatment-eligible IDUs and non-IDUs receive HAART 4. Optimistic untargeted treatment strategy: 80% of all infected, treatment-eligible IDUs and non-IDUs receive HAART.	IDUs and/or general HIV+ population	
Cleary, S.M., D. McIntyre, and A.M. Boulle (2006)	Khayelitsha, Cape Town, South Africa.	Comparison of treatment and prophylaxis of opportunistic and HIV-related illnesses without antiretrovirals ("No-ART") to costs and effects when ARVs are used ("ART") based on primary unit cost, utilisation, health-related quality of life (HRQoL) and outcome data.	*Costs and cost-effectiveness of HAART	- Quasi experimental design: before and after - Empirical - Costs: mostly SA data
Goldie, S.J., et al. (2006)	Abidjan, Côte d'Ivoire	1) No treatment. 2) Trimethoprim–sulfamethoxazole prophylaxis alone; 3) Antiretroviral therapy alone, 4) Prophylaxis with antiretroviral therapy. 22 strategies in which thresholds for initiating and discontinuing a single line of antiretroviral therapy were based on clinical criteria alone or on both the CD4 cell count and clinical criteria.	*Laboratory monitoring strategies for starting and stopping ART. *Use of antibiotic prophylaxis with and without ART *Comparison of clinical and laboratory markers for starting and stopping ART	- CEPAC Model - Costs: From the literature
Bachmann, MO (2006)	South Africa	No prevention Late isoniazid Early isoniazid and isoniazid withcotrimoxazole Late cotrimoxazole Early isoniazid /cotrimoxazole Early cotrimoxazole Late ARV Late ARV & both antibiotics Early ARV	*Early and late initiation of ARVs *Cotrimoxazole prophylaxis, with and without ARVs *Isoniazid prophylaxis, with and without ARVs *Combined antibiotic prophylaxis, with and without ARVs *Early and late initiation of	- TreeAge Markov Model with 7 transition states - First order Montecarlo simulation - Assumes early detection for all - Costs: SA sources

		Early ARV & both antibiotics	antibiotic prophylaxis *Willingness to pay for treatment	
Vijayaraghavan (2007)	South Africa	1) Starting HAART at CD4 count of ≤350 cells/µl or viral load of >100,000 copies/ml and CD4 cell counts and viral load every 3 months (US DHHS guidelines). 2) Starting HAART at CD4 count of ≤200 cells/µl with CD4 monitoring every six months (WHO guidelines).	*Early vs. late initiation of HAART *Laboratory monitoring strategies for starting and stopping ART.	- Markov with 11 transition states - Probably second order simulation, but not specified - Costs: utilization based in guidelines and then used SA unit costs
(Pitter, Kahn et al. 2007)	Uganda (rural setting)	Cotrimoxazole prophylaxis for: 1) All HIV infected individuals 2) WHO Stage 2 or more advanced disease 3) CD4 cell count of <500 cells/µl 4) Individals in groups 2 and 3 (current WHO recommendation)	*Criteria for initiating contrimoxazole prophylaxis	
Yazdanpanah Y et al (2005)	Cote d'Ivoire	Cotrimoxazole prophylaxis according to clinical or immunologic status: 1) WHO stage ≥ 3 2) WHO stage ≥ 2 3) CD4 count ≤ 50 cells/ cells/µl 4) CD4 count ≤ 200 cells/ cells/µl 5) CD4 count ≤ 500 cells/ cells/µl 6) All HIV infected individuals	*Criteria for initiating contrimoxazole prophylaxis	-CEPAC model -First order Montecarlo simulation -Costs: Abidjan hospital unit costs -Clinical data based on RCT conducted in Cote d'Ivoire

Table 3. Comparison of cost-effectiveness of first line therapy starting points, first line only versus first-line and salvage regimes versus no ART scenario (2005 US Dollars) Discounted values unless otherwise specified

	First line therapy only ICER/LY unless noted (life expectancy)	**First-line and second-line** ICER/LY unless noted (life expectancy)
Starting late (CD4 < 200 cells/µl)		
Sub-Saharan Africa (Bishai, Colchero et al. 2007)	$629 (2.3 QALYs)	$684 (2.3 QALYs)
India (Freedberg, Kumarasamy et al. 2007)	$296-298[a] (5.2-5-3 LE)	$704-711[a] (7.1-7.2 LE)
Cote d'Ivoire (Goldie et al 2006)	$590[b] (5.8 LE)	
South Africa (Vijayaraghavan, Efrusy et al. 2007)	$1,168 (9.9 LE)	
South Africa (Bachmann 2006)	$1,564-1,610[b] (8.2-8-4 LE)	
Starting early (CD4 < 350 cells/µl)		
Caribbean (Wolf, Ricketts et al. 2007)	$687-689[b] (8.0-8.2 LE)	$1,850 (9.2 LE)
India (Freedberg, Kumarasamy et al. 2007)	$302[b] (5.4 LE)	$733 (7.4 LE)
South Africa (Bachmann 2006)	$1,720-1,731[b] (11.4-12.1 LE)	
South Africa (Vijayaraghavan, Efrusy et al. 2007)	$1,465 (9.66 LE)	
South Africa (Cleary et al. 2006)	$938-993[c] (9.70-12.9 LE)	

[a] Starting at <250 cells/µl

[b] With prophylaxis

[c] Alternative scenario: Increased probability of dying (+37%), adjusting ART and No ART visits; inpatient care at secondary level hospitals (not tertiary).

Indicates scenario not analyzed.

LE= life expectancy, reported in years

Table 4. Comparison of cost-effectiveness of laboratory monitoring strategies (2005 US Dollars) Discounted values unless otherwise specified

Monitoring Strategy	ICER/Qaly (Unless otherwise indicated)	Setting
Clinical Markers		
2 OIs[3] to guide initiation and 1 OI for stopping of ART	$590/YLG	Cote d'Ivoire (Goldie, Yazdanpanah et al. 2006)
1 OI to guide initiation and 5 OIs for stopping of ART	$1060/YLG	Cote d'Ivoire (Goldie, Yazdanpanah et al. 2006)
Laboratory Markers		
CD4 counts and one OI to guide initiation and stopping of ART	$1,180/YLG	Cote d'Ivoire (Goldie, Yazdanpanah et al. 2006)
ART with TLC monitoring vs ART with no monitoring	$238 (first-line only)	Sub-Saharan Africa (Bishai, Colchero et al. 2007)
ART with TLC monitoring vs ART with no monitoring	$1,117 (salvage regime available) (TLC less cost-effective than CD4 with no salvage regime)	Sub-Saharan Africa (Bishai, Colchero et al. 2007)
ART with CD4 monitoring vs ART with TLC monitoring	$8,636 (salvage regime available)	Sub-Saharan Africa (Bishai, Colchero et al. 2007)
ART with VL monitoring vs ART with CD4	$14,670 -$16,139 (w/ & w/o salvage regime available)	Sub-Saharan Africa (Bishai, Colchero et al. 2007)

YLG=Year of life gained

[3] OIs included in the base case for ART starting criteria were severe fungal infection, isosporiasis, toxoplasmosis, nontuberculous mycobacteriosis, and other severe illness.

Table 5. Recommended interventions for HIV prevention by epidemiologic profile

Recommendation	Intervention	Epidemiologic profile			
		Low	Conc.	Gen. low	Gen. high
Cost-effective interventions that should clearly be prioritized for implementation	• Peer based education among high risk groups	✓	✓	✓	✓
	• School-based education programs			✓	✓
	• VCT		✓	✓	
	• Condom promotion and distribution	✓	✓	✓	✓
	• Social marketing			✓	✓
	• STI screening and treatment among sex workers	✓	✓	✓	✓
	• Avoidance of unintended pregnancies	✓	✓	✓	✓
	• ART to prevent mother-to-child transmission	✓	✓	✓	✓
	• Male circumcision			✓	✓
	• Needle exchanges for IDUs	✓	✓	✓	✓
	• Drug substitution and addiction treatment	✓			
	• Exclusive formula feeding to prevent MTCT	✓			
	• Exclusive breast feeding and early weaning			✓	✓
	• 100% condom		✓	✓	✓
	• Blood supply screening	✓	✓	✓	✓
	• Sterile injection	✓	✓	✓	✓
Interventions that are not effective in their current state or prohibitively expensive for developing countries	• Microbicides	✓	✓	✓	✓
	• Post-exposure ARV prophylaxis			✓	✓
	• Universal precautions			✓	✓
	• Abstinence education	✓	✓	✓	✓
Interventions still lacking some key data required to formulate a firm recommendation	• School-based education programs	✓	✓		
	• VCT	✓	✓		
	• Non-targeted STI screening and treatment	✓	✓	✓	✓
	• Counseling mothers on feeding practices			✓	✓
	• Price strategies, conditional economic incentives	✓	✓		
	• Methods to reduce use of injectable medications			✓	✓
Interventions that are understudied and merit prioritization on the research agenda	• Vaccines	✓	✓	✓	✓
	• Female-controlled prevention strategies, such as microbicides	✓	✓	✓	✓
	• Inexpensive universal precautions	✓	✓	✓	✓

Table 6. Value for money: Categorizations of cost-effectiveness of treatment and care interventions

Highly cost-effective or cost-saving

- Co-trimoxazole prophylaxis for *P. jiroveci* pneumonia, malaria, diarrhea, toxoplasmosis, and *Mycobacterium Avium* complex
- Early initiation of co-trimoxazole prophylaxis in areas with high prevalence of malaria
- Treatment of oral and esophageal candidiasis
- First-line ARVs (starting at CD4 count of 200 cells/ul)
- Micro-nutrient supplementation (no cost-effectiveness data, but low-cost treatments)
- Prophylaxis and treatment of tuberculosis
- Pain and symptom control (no cost-effectiveness data, but low-cost treatments)

Moderately cost-effective:

- Early initiation of first-line ARVs (starting at CD4 count of 350 cells/ul) (solid data)
- CD4 testing to determine initiation of ARVs (solid data)

Borderline cost-effective:

- Viral load testing to determine initiation of ARVs (solid data)

Not cost-effective:

- Treatment of Kaposi's sarcoma, cytomegalovirus, MAC (fair data)
- Hospital-based end-of-life care (assumption, no data)

No cost-effectiveness data:

- Interventions to boost adherence to ARVs
- Palliative care (either home/community or hospice-based)

Annex 1

Table 1-A. Search Terms for Review of HIV Prevention Literature

Domain	*Description*	Search terms
Economic / evaluation	*Economic and Impact evaluation*	Cost, costing, effectiveness, cost-effectiveness, prevention, impact, HIV, AIDS
	Setting	developing countries, third world countries, low income countries, middle income countries, limited resource settings
Intervention	*Prevention interventions*	HIV/AIDS; school-based education; abstinence education; voluntary counseling and testing; peer based programs; condom promotion and distribution; information, education and communication; condom social marketing; sexually transmitted infection treatment; antiretroviral treatment/therapy; mother-to-child HIV transmission interventions; feeding substitution; harm reduction; needle exchange; drug substitution; blood safety; universal precautions; post-exposure prophylaxis; behavior-change programs; efficacy; and effectiveness. Structural interventions, social interventions

Table 1-B. Overview of search terms for HIV/AIDS Care and Treatment Literature Review

Domain	*Description*	Search terms (MeSH Headings)
Economic / evaluation	*Economic and Impact evaluation*	Cost-benefit analysis, Cost and cost analysis, Health expenditures; Markov chains
	Setting	Developing countries; Africa, South America, Central America, Mexico, Asia, Eastern Europe
ART	*Treatment of HIV with ART: Cost effectiveness considerations.*	HIV Infections; drug therapy; antiretroviral therapy, highly active; Guideline adherence; HIV Infections/*drug therapy/immunology
Adherence to ART	*Importance of adherence to prescribed therapy*	Patient compliance; Patient acceptance of health care; treatment refusal, access, quality, intervention studies, guideline adherence.
OI Prophylaxis	*Primary prophylaxis for OI*	AIDS-related opportunistic infections; antibiotic prophylaxis; cerebral toxoplasmosis, cryptoccocal meningitis; pneumocytis pneumonia; Mycobacterium tuberculosis; toxoplasmosis.
OI Treatment	*Role of ART in relation to OI and management of OI*	Tuberculosis and HIV, efficacy of ARV, preventive therapy, management of opportunistic infections, secondary prophylaxis. viral load.
Palliative Care	*Control of pain and other symptoms.*	Palliative care, pain; narcotics; analgesics, opioid; counseling; Terminal care; Hospice care.
Monitoring	*Laboratory monitoring of immune function to guide therapy*	Viral load, CD4; CD4 lymphocyte count; lymphocyte count, medication therapy measurement; Drug resistance; withdrawing treatment; disease progression.
Monitoring toxicity		Drug toxicity; drug monitoring.
Nutrition Programs		Dietary supplementation; nutritional support.
Psychosocial support		Social support; Community Health Services/counseling;.
Health Systems		Quality Assurance, health care; quality of health care; quality-adjusted life years; Delivery of Health Care/economics/utilization; Outcome Assessment (Health Care)/*economics
Dates	*January 2005 to October 2007*	

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