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The Evidence Base of Interventions in the Care and Management of AIDS In Low And Middle Income Countries

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INTRODUCTION

Suffering and loss of production and life due to the AIDS pandemic is felt worldwide. However, it is in low and middle income countries where an estimated 96% of humanity's 36.1 million HIV infected people live, that the greatest challenges are being faced. Many of the world's HIV positive population are economically vulnerable including 16.4 million women and 1.4 million children[1]. Shockingly in many African countries, the risk of dying of AIDS within a lifetime is better than one in three[2].

As there are no immediate prospects for cure of HIV/AIDS, interventions that increase the length and quality of life for HIV positive people in low to middle income countries are sorely needed. However, resources are limited. These resources need to be used strategically to provide the greatest increases in longevity and well being possible. Thus there is an urgent need to understand what interventions achieve the most for the money spent. Further, a balance must be struck between resources allocated for research, prevention and care.

This paper will describe the clinical stages of HIV/AIDS, the scope of the problem of care, potential interventions and evidence of their effectiveness and cost-effectiveness, and constraints to scaling up the effective interventions. In order to properly manage the needs of people with HIV/AIDS, it is important to be aware of the phases of the HIV disease process.

HIV DISEASE PROGRESSION

Initial Infection

The human immunodeficiency virus is transmitted from human to human through blood, semen, vaginal fluid or breast milk. The development of antibody or seroconversion occurs from 2 to 6 weeks after initial exposure. This stage may last for only 2 to 3 weeks[3] and cause symptoms such as fever, night sweats, and weight loss[4]. HIV infection initiates complex and poorly understood processes that ultimately lead to the decline of the immune system[5]. For the most part, illness and death results from impairment of the immune system.

Clinical Staging

One of the major difficulties in addressing the care of people with HIV/AIDS is the highly unpredictable disease course that follows the initial infection. The Centers for Disease Control and Prevention[6] describe three states to explain the stages of HIV disease progression in adults. Initially, there is a period of time when there are no symptoms at all (CDC category A). This latent period lasts from a few months to years and is characterized by a CD4 and T-Lymphocyte measurement of greater than 500 cells/microliter (ul). Although the clinical signs of HIV are not yet evident at this stage, the antibodies can usually be detected within the first 1-3 months[7]. Furthermore the virus is present in the blood and secretions of these individuals and they are infectious to their contacts.

The severity of illness depends upon the extent of damage to the immune system by the virus. When the disease has progressed to the point when CD4 T-Lymphocyte counts dip below 500 cells/ul, minor symptoms begin to occur. This second stage (CDC category B) is characterized by a CD4/ T-lymphocyte measurement of 200- 499 cells/ul. At this point, symptoms such as candidiasis, fever, diarrhea, enlarged lymph nodes, dermatalogic conditions and oral lesions may occur[6]. Without antiretroviral therapy (ARV therapy), there is a 20- 30% probability that progression to an AIDS-defining condition or death will occur within the next 18 to 24 months[8].

The third stage (CDC category C) involves a progression to more severe opportunistic infections as the CD4 and T-Lymphocyte measurement drops below 200 cells/ul. Since the frequency of AIDS-defining conditions rises dramatically with a CD4 count of less than 200, this has become the cut-off point for the definition of "AIDS". In this advanced stage of HIV infection, opportunistic infections (including tuberculosis, *Pneumocystis carinii* pneumonia, toxoplasmosis, cytomegalovirus infection, cryptosporidiosis, cryptococcal meningitis), opportunistic malignancies (invasive cervical cancer, Kaposi's sarcoma, non-Hodgkins lymphoma) and the wasting syndrome begin to occur.

Rate of Progression to AIDS

The natural history of HIV has been well documented [3,8,910,11]. The incubation time from initial infection to the onset of AIDS is highly variable, for reasons that are not completely understood. From the available body of evidence, it is difficult to make generalizations about the differences in progression between the industrialized and developed worlds. However, some evidence has suggested that there may be geographic variation in the median times from HIV seroconversion to AIDS diagnosis, seroconversion to death, and survival after AIDS diagnosis[12,13,14,15,16,17,18]. Some studies in developing countries found that while their progression rates from HIV to AIDS were similar to those found in industrialized countries, their all-cause mortality was much higher and the rate of progression from AIDS to death was more rapid[19,20,21].

The variation in disease progression may depend on factors such as gender[22], HIV subtypes[21], immunologic response of the individuals, nutritional status[23,24], and chronic immune activation by helminths[25]. It is most likely that the accelerated progression to disease or death is caused by exposure to opportunistic infections for which there is inadequate care[19]. However empiric evidence for an effect of these factors is lacking and additional research is necessary. From studies that measured the progression of HIV in African descendents in the United States[26] and United Kingdom[27], it appears that race is not likely to be an explanatory factor. Frequent infections may alter immunologic responses to the virus resulting in more rapid disease progression in some population subgroups, such as sex workers[16,28].

It should be noted that the above discussion is centered on knowledge about HIV-1. The effect of HIV-2 infection on progression to AIDS and death is not comparable. HIV-2 was originally detected in West Africa[29] where the epicenter of this less virulent[30] virus still remains[31]. There is strong evidence to suggest that survival and asymptomatic times are much greater with HIV-2 than HIV-1[32,33]. A study in Guinea-Bissau found that overall, HIV-2 infected adults had only twice as high mortality as those who were not infected with any HIV[34].

Opportunistic Infections

As the HIV/AIDS disease progresses, the immune systems's capacity to combat infections decreases, leaving the infected person vulnerable to the more than one hundred

different AIDS-related pathogens[35]. There is great regional variation in the frequency of these Opportunistic Infections (OIs) depending upon the prevalence of pathogens and the quality and extent of treatment that is available.

In Africa, some of the most common opportunistic infections include tuberculosis and bacterial infections (particularly pneumococcal and salmonella infections) but the full range of fungal, parasitic and viral opportunistic infections occurs[36,37, 38,39,40,41]. Prevalent opportunistic infections in Asia include tuberculosis, cryptococcosis, *Penicillium marneffei* infection, *Pneumocysitis carinii* pneumonia, cryptosporidiosis and herpes simplex virus[42,43,44,45,46]. In Latin America, fungal diseases, *Pneumocysitis carinii* pneumonia, tuberculosis, herpes simplex virus, Kaposi's sarcoma, and cytomegalovirus (CMV) are important AIDS related conditions[47,48,49,50]. Many OIs such as thrush and toxoplasmosis are readily treatable with low cost therapies or preventable with prophylaxis[51]. However, some OIs, like the fungal infection cryptococcal meningitis, require much more expensive and less effective therapy and may require life long prophylaxis to prevent recurrence[52]. Opportunistic viral infections require expensive therapy and frequently recur without continued prophylaxis.

It is likely that some, if not most, of the variation in the prevalence of OIs is due to variation in the capacity for detection of organisms with laboratory tests[37]. OIs that are less common or difficult to diagnose may not be tested for at all in resource-poor countries. However, there are differences in disease prevalence and the rural/urban disease ratios that influence the frequency of OIs and the prevention and care that is required. This means that, the most cost-effective care interventions for prevention and care of OI, to a considerable extent, need to be individualized to particular regional, national or community situations. The next section will identify some of the ways that the lives of HIV-positive people can be improved according to current knowledge.

INTERVENTIONS TO REDUCE MORBIDITY AND MORTALITY AMONG HIV POSITIVE PEOPLE:

Effectiveness and Cost-effectiveness

There are essentially four intervention strategies for HIV/AIDS care – treating the viral infection itself, prophylaxis of opportunistic infections, treatment of specific conditions and general care and support. All possible interventions are intended to improve the quality and quantity of life for people with HIV and they do so to differing degrees. There is a clear need to know what interventions provide the greatest increase in the quality or quantity of life for the least cost. One way of doing so is to use comparisons of cost-effectiveness to make evidence-based decisions that are appropriate to the specific community.

There are unique challenges to carrying out CEAs for interventions dealing with HIV/AIDS care. In the literature there are very few studies of the cost-effectiveness of HIV/AIDS care interventions, although considerable data is available on costs of particular interventions and on their efficacy. This in part because the outcome measures are difficult – measuring increases in survival requires long term follow up, which goes beyond the scope of most therapeutic trials. Although studies focused on the prophylaxis or treatment of opportunistic infections can measure "cases averted" or "cases cured", this may not provide data on the effect on longevity. Furthermore, the experience with antiretrovirals (ARV) in developing countries is quite short and no long-term studies are available to determine their effect on survival. Also given that there are currently no curative interventions for HIV infection, the outcome measures used necessarily must deal with improving quality of life as well as promoting longevity. This is problematic in making comparisons in that small increases in longevity may be very valuable in the young and productive group of people who are primarily those infected with HIV, particularly if there are families to support. Adding even short periods of high functioning, quality life on a large scale may be of greater benefit to a society than providing great increases in longevity to an elite few. However, there are no empirical data to allow this kind of analysis. Studies of these issues would be enormously valuable in making evidenced based decisions about what interventions to promote and support.

Most work on cost effectiveness of HIV/AIDS care interventions come from industrialized countries where the most common measure of outcome has been the quality adjusted life year (QALY)[53,54,55,56,57]. Quality of life tools measure the impact of interventions on well-being and discover unmet needs. Similar tools could be adapted for

language and literacy levels in developing countries to measure the impact of interventions on the quality of life of HIV positive people, but that has not yet been done.

A further caveat to this paper is that all individuals in developing countries are not the same just as all countries are not the same. A few individuals have the income to purchase for themselves all the state of the art strategies for improving their well-being and longevity. The analysis presented here is based on either a government funded health care system or a user funded system, in which the user's ability to pay for services is severely constrained.

THE ROLE OF ANTIRETROVIRAL THERAPY

Antiretroviral Therapy for HIV Infection

Antiretroviral drugs are medications that directly inhibit HIV replication. In 1987, zidovudine (AZT) became the first widely available antiretroviral drug to show both safety and efficacy in the treatment of HIV[58,59]. However, AZT used alone (mono-therapy) did not provide long-term benefit in altering disease progression[60]. Throughout the first half of the1990's, several other mono-therapy and dual-therapy regimens became available[61,62,63]. Although many combinations resulted in improved clinical outcomes, their benefit was limited.

With the development of new nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors, Highly Active Antiretroviral Treatment (HAART) became possible in 1996 and is now considered the standard of care in industrialized countries. Several HAART regimens (made up of combinations of reverse transcriptase inhibitors and protease inhibitors) can achieve reductions in plasma HIV RNA levels to below the level of detection while increasing CD4 counts[64] and significantly prolonging life[65]. The advent of HAART was heralded as the end of AIDS by the lay media and the perception arose that AIDS had become a manageable chronic disease. This is proved to be a great oversell of the benefits of HAART in the long term and has done little to reduce the spread of HIV throughout the world. However, demand for access to HAART in middle and low-income countries, where more than 95% of HIV infected people live, has increased with the growing death

rates. Pricing of these drugs has effectively excludes most individuals (over 90%) with HIV from therapy. HAART is far too expensive for the majority of individuals or governments in low and middle-income countries. A sense of moral outrage and inequity sparked an intense debate about equity, access to care, and drug costs, which has resulted in significant reductions in the price of some drugs. Effective therapy may soon be widely available for US $1/day for drugs. This is a very significant development and will prolong many lives but the role of HAART must be kept in perspective. While drug costs are important impediments to access to HAART, there are other significant challenges to instituting and maintaining HAART in low and middle-income countries. How long the benefit of HAART is maintained is unclear currently because of the short period that these therapies have been in use. HAART regimens require complicated dosing schedules, close monitoring of HIV RNA levels and CD4 counts and frequent changes in drugs regimen for optimal effect. Strict adherence – 95% accurate and consistent use – is required for long-term viral suppression[66]. There are also noteworthy issues related to tolerance of the regimes and significant and sometimes serious adverse effects[64,67]. Finally it is unclear how HAART compares to other interventions in terms of cost effectiveness.

Although HAART has been very successful[68,69,70], it is not a cure. It reduces and prevents many opportunistic infections and prolongs lives[71,72,73,74]. However, while HAART reduces viral load to very low levels, considerable replication continues[75]. People living in even the world's richest countries continue to live with opportunistic infections and occasionally die of AIDS-related causes[76,77,78].

There have been attempts to reduce the cost and complexity of antiretroviral therapy for developing countries by using scaled down drug regimens. Less expensive, yet effective drugs could make tremendous differences to the total health expenditures of a region. Proposals to develop a DOTS equivalent for HIV therapy have been made. Certainly simplified therapy is desirable but it is not clear that it is possible.

Studies in sub-Saharan Africa examined the effectiveness of two nucleoside analog reverse transcriptase inhibitors (NARTIs)[79,80]. Unfortunately, this therapy was found to be less effective than HAART. In one study area, viral load and CD4 counts reverted back to their baseline levels within one year in the majority of patients.

The protease inhibitors saquinavir, indinavir, ritonavir, amprenavir, and nelfinavir are highly effective agents and when used in combination with reverse transcriptase inhibitors plasma viremia decreases and CD4 counts increase[81,82]. A study in the US found that amprenavir used in isolation reduced HIV RNA levels as effectively as triple-drug therapy[67]. However, when protease inhibitors are used in isolation, resistance emerges quite rapidly even with strict adherence to the therapeutic regimen[83].

The point in the course of HIV infection that HAART should be instituted is also unclear. The ARV therapy philosophy of the mid-1990's "Hit Hard and Hit Early"[84] is now a matter of debate. Furthermore, delaying treatment may be beneficial to some patients[65]. Therapy that is started in the early stages of the disease progression (before CD4 count is < 350), may risk increase the frequency of adverse effects, toxicity and the development of resistance[67].

Challenges Of ARV Therapy

While ARV therapy may provide many benefits, challenges arise for those people needing this treatment in resource-poor areas. HAART is a highly complex therapy, requiring sophisticated care providers, close adherence to the therapeutic regimen and sophisticated laboratory facilities. The extent to which these are lacking is illustrated by a recent Kenyan study, Kimani et al. showed that while physicians throughout the country were prescribing ARV and the drugs were widely available, only 30% had received any training in ARV and outside of Nairobi no laboratory facilities were available for monitoring therapy[85]. Using ARV, particularly HAART requires a sophisticated health care delivery system that is just not available to the majority of HIV-1 infected individuals in middle and low-income countries. It may be that a syndromic approach, using clinical outcomes as indicators of the success of therapy and the need for modification of treatment are possible, but a considerable body of research is needed before we will know this. The complicating factors of poor compliance, complexity of regimes, side effects, the emergence of drug resistance and the lack of infrastructure for monitoring therapy complicate the wide spread and effective use of ARV in low and middle-income countries.

People receiving HAART therapy do not always achieve the desired viral load suppression. While clinical trials have shown that HAART has reduced plasma HIV-1 RNA levels to less than 500 copies/ul in 60% to 90% of patients, in practice the rates appear to be much lower. One study in a large urban clinic sustained viral suppression was only achieved in about 40% of patients[86]. Poor outcome was associated with missed clinic appointments and inconsistent adherence. Many people who have access to the therapy have difficulty following the regimens consistently. HAART regimens can be complicated to follow as many AIDS patients have regimens consisting of as many as 40 pills daily[87,88,89] and many people with access to the therapy have difficulty following the regimens reliably. Difference in pharmacokinetics and bioavailability require that some drugs be taken with food, while others must be taken on an empty stomach. Recent advances have led to a reduction of number, size and frequency of pills in HAART [90,91]. Unfortunately, combining the anti-AIDS drugs into a single pill also limits some of the flexibility needed to find an appropriate combination for the individual patient. The importance of these factors for delivering effective therapy to a population is illustrated by a report from a US inner-city HAART project found that only 1 in 7 of HIV-infected people achieved undetectable virus levels[92]. Meanwhile, the prevalence of non-adherence in Sao Paulo, where the drugs are given free of charge, is estimated to be 31%[93]. The reasons given for poor adherence include missed appointments (OR = 5.7), low or no income (OR = 1.9 and 2.7 respectively) and low education (OR = 2). Clearly there are some major problems to contend with in ensuring adherence to ARV therapy even when available. These are described more fully in a paper by Miriam Rabkin[94] in the Commission on Macroeconomics and Health Working Group 3 report.

HAART requires close monitoring of plasma viremia, tolerability and adverse effects. Frequent changes of treatment regimens are required. A US study showed that patients on HAART are forced to change their drug regimen after 10.6 months for the first course, 8.1 months for the second course and 6.4 months for the third course[95]. Patients were more likely to achieve sustained viral suppression with the initial combination (49%) than they were with the subsequent attempts (30% and 15% respectively).

Poor adherence to HAART is often attributed to sub-optimal effect and adverse reactions[96]. Most HIV infected people receiving HAART experience some side effects. These reactions could include anything from diarrhea and headaches to cardiac and metabolic disorders[87,97]. Protease inhibitors (PIs) have been associated with exacerbating pre-existing diabetes and hypoglycemic conditions, as well as triggering new cases of diabetes mellitus[98,99].

HIV resistance to ARV is also a problem. It is not a question of whether resistance will emerge but questions of how severe the problem of resistance will be and what measures can be put in place to reduce the rate of the development of resistance and minimizing the spread of resistant strains of HIV. In the United Kingdom, 25% of new infections are with drug resistant strains. A report from Max Essex at the Kampala meeting on AIDS care indicated that a high proportion of HIV isolated from Botswana and Ethiopia.are resistant to one or more ARV. Less than optimum adherence to HAART due to unreliable availability of drugs, complicated regimens or adverse effects results in the emergence of resistant strains of HIV. Erratic treatment affects the ability of the therapy to suppress viral replication and encourages drug resistance[88,100,101]. A study in Uganda examining phenotypic resistance in 30 AIDS patients on ARV therapy found that 74% of the subjects were resistant to at least one anti-AIDS drug[102]. A similar study in Cote d'Ivoire found that 57% had resistance to at least one antiretroviral[103]. This is not only an important issue for the individual patient but also for public health. Drug resistant HIV strains are transmissible[104,105,106] making ARV treatment of subsequent individuals more difficult. Even with conservative assumptions, modeling studies[107] indicate that any effect of ARV on the transmission of HIV would be relatively short-lived.

The Cost of ARV Therapy

The drugs required for effective antiretroviral therapy are expensive. The estimated cost of providing HAART to all HIV positive people globally was US$ 65.8 billion annually in 1997[108]. Lifetime costs for HIV positive people in the US are estimated to be around US$ 200,000[109]. As a result of an international outcry about the price of ARV, steep reductions in the cost of therapy have occurred through a

combination of reductions in price and the availability of generic drugs[110]. Even with the reduced costs of $50-$100 per month, ARV remains too expensive for the majority of HIV infected individuals in the lowest income countries. This is certainly a much more realistic cost for many middle-income countries. While the reductions in drug prices are a welcome achievement, there needs to be some realistic thinking about what lower prices will do to improve access for the majority of HIV-1 infected people. As an illustration of how difficult improving access to ARV therapy through reductions in cost of the drugs consider Kenya. Kenya's GNP is $10 billion ($350 per capita). The poverty line is $30 per month and 50% of people have income below this line. Even under the best-case scenario of US$1/day, ARV would cost 100% the average monthly income of Kenyans. At the national level, the Kenyan government is also unable to afford the provision of wide spread ARV. Annual government spending on health is $87 million ($3 per capita). At currently offered costs of $100 a month, treating 25% of all HIV infected individuals in Kenya would cost $630 million or 6.3% of GNP or more than 7 times the current government spending on health[111,112]. Thus it is clear that if ARV are to be widely used in low-income countries some other payer must be found.

In countries with domestic pharmaceutical manufacturing industries, less expensive generic antiretroviral drugs can be produced. Brazil has done this. The Brazilian Government began providing ARV therapy in the 1990's with the provision of free AZT. In 1994, a Presidential Decree guaranteed free access to ARV therapy to all HIV-infected Brazilians[113]. As more therapies became available, the demand for ARV therapy increased. While 10,000 Brazilians were on ARV therapy in 1996, 87,500 had initiated treatment by April 2000. Consequently, the cost to the government has increased from an estimated US$ 34 million (0.0044% of the GNP) to US$ 332 million (0.06% of the GNP) in the same period [113,114]. However, the combination of ARV therapy and chemoprophylaxis of opportunistic infections has been able to reduce the AIDS deaths by 54% in the city of Sao Paulo since 1995[113]. How long the Brazilian government will be able to sustain this is unclear and how the infringement on patent laws of multinational pharmaceutical companies will be dealt with are important questions.

As with other countries such as Costa Rica, Thailand and Uganda, Brazil has also been able to negotiate reduced prices of antiretroviral drugs[115,116]. The end-user cost of 100 mgs of zidovudine in Brazil is about one-tenth the cost that it is in the US[115]. Due to the significant price reduction, the drug cost for the country's 85,000 HIV positive people was approximately US$339 million. UNAIDS[115] estimates that the cost was to some degree offset by the US$200 million savings in averted AIDS-related hospitalizations. Even at this reduced rate, the $US100 million increased spending over savings is about two thirds of the annual $US 141,054,756 that the countries of Sub-Saharan Africa report receiving in national and international HIV/AIDS funding[117].

The UNAIDS HIV/AIDS Drug Access Initiatives have been active in providing ARV therapy to people who would have otherwise been unable to access it. Since 1998, this initiative has been working with national governments to provide laboratory support, subsidized drugs and follow-up care to people with HIV/AIDS. The countries participating in the initial phase of this initiative are Chile, Côte d'Ivoire, Uganda, and Vietnam. The initial findings are available from Uganda.

In Uganda, after two and a half years of the programme, only 58% of the patients were still alive and on treatment[118]. Of those who died, 24% died of bacterial infections, another quarter died of cryptococcis, and 15% died of tuberculosis. Changes in therapeutic regimens were required during 15% of follow-up visits. Resistance to ARV drugs was seen in specimens from participants including 3TC (78%) and AZT (20%). The cost of the ARV drugs fluctuated during the trial due to the introduction of new drugs, the decrease in prices from pharmaceutical companies, and the change in the value of the Ugandan shilling against foreign currencies. The costs of even the simplest ARV drug regimens were well beyond the Ugandan per capita GNP (US$30). This experience suggests that even with subsidized drugs and external support for infrastructure, achieving long-term benefit with ARV will be challenging.

Although there has been much focus on the costs of antiretroviral drugs, these are not the only costs associated with therapy. There are also be a number of infrastructure costs that need to be considered before an ARV programme can be widely introduced. Firstly, reliable testing facilities must be available to confirm that people who are about to begin ARV therapy are in fact HIV positive. Testing for HIV could cost between US$3

and $10 for testing and 2-3 times that amount for appropriate pre- and post-test counseling[119]. Health care workers need to be trained in the use of ARV, something that has been ignored until now. Ideally, monitoring of CD4 counts and viral load should be carried out and the facilities for doing so just don't exist in lower income countries. It maybe that clinical monitoring is feasible or that a DOTS for HIV can be developed but the basic research has not been done. Mechanisms for transporting, storing and dispensing of drugs will also need to be created to ensure a continous supply. The importance of this is illustrated by the fact that in June 2001no antiretroviral drugs were available in Kenya because the demand for drugs resulting from lower prices was not anticipated.

Despite some of the problems mentioned above it is almost certain that ARV will become widely used in low and middle-income countries in the near future, through a combination of reduction of prices on the part of pharmaceutical companies, generic production of drugs and subsidization of costs by multilateral agencies and philanthropic organizations. It is extremely important that the impacts of these therapies on longevity, the emergence of resistance and the overall HIV and AIDS epidemics be monitored closely. We will need to know in 5 to 10 years what has been achieved with these initiatives and what the consequences have been.

The Cost-effectiveness of ARV Therapy

Even in circumstances where a country is financially able to subsidize a national ARV therapy programme, decision makers should ask themselves, "How does this intervention compare to the other possible uses of this resource?" Although studies measuring the cost-effectiveness of anti-retroviral therapy in the prevention of mother to child transmission in low to middle income countries have been published[120,121,122], it is difficult to find evidence about the CEA of ARV for long-term use**.**

Studies from North America and Europe have shown antiretroviral therapy CEAs to range from $10,000 to $30,000 per life year gained[123]. This compares favourably to such interventions as hemodialysis, renal transplant and advanced cardiac care[124] in developed countries, but would compare poorly to interventions to prevent HIV-1 infection or treat readily curable infectious diseases such as malaria or tuberculosis in

developing countries, even if the cost-effectiveness ratio were many fold lower. Obviously, it is difficult to compare the economic situations from industrialized countries to those in developing ones as wages for health care workers, cost of maintaining infrastructure etc. vary radically from place to place. However, knowing that in the West, a QALY gained from ARV therapy for someone with HIV costs from $10,000 to $30,000, demonstrates that this is expensive treatment, even by the standards of wealthy countries. It is very important that as ARV is introduced in poor and middle income countries the mechanisms for monitoring impacts and evaluating the costs are put in place.

PREVENTION OF OPPORTUNISTIC INFECTIONS

The principal cause of morbidity and mortality in HIV-1 infection are opportunistic infections. OIs are associated with mortality, independent of CD4 count and their occurrence may accelerate disease progression[125]. It is thus possible that prevention of these infections not only directly increase survival but also affect HIV-1 disease progression. Many of the most frequent opportunistic infections can be readily prevented and there is a large literature on their efficacy and cost-effectiveness from North America and Europe. There has been little work on prophylaxis of opportunistic infections in developing countries with the notable exceptions tuberculosis and bacterial infections.

Prophylaxis of Tuberculosis and Other Mycobacterial Infections

About one third of the global population is estimated to be infected with M*ycobacterium tuberculosis*[41]. Tuberculosis is the most common life-threatening OI in sub-Saharan Africa[126] in people with HIV infection. People with HIV in Latin America and Asia are also at high risk of TB infection[37]. Among those who are HIV positive in India, Thailand, and Mexico, 68%, 31% and 30% respectively are concurrently infected with tuberculosis[42].

Tuberculosis and HIV epidemics go together for two reasons. HIV positive people fail to contain a primary infection due to immunodeficiency or they may have

reactivation of a latent infection[127]. From a public health perspective, there are obvious repercussions to having simultaneous uncontrolled HIV and TB epidemics. Not only is there a much higher level of morbidity and infectivity in the vulnerable HIV positive population, but HIV uninfected care providers, family members, and communities are also at risk of tuberculosis.

Bacillus Calmette-Guérin vaccine (BCG) has no preventative effect on the reactivation of disease in people who already are infected with tuberculosis[128]. There does appear to be a slightly protective effect in people who are not yet infected with tuberculosis, regardless of their HIV status. BCG is credited with reducing the risk of disseminated tuberculosis. However, while a study in Columbia showed that BCG seems to be protective against extrapulmonary tuberculosis among HIV negative individuals, it was not protective for those with HIV[129]. BCG is not recommended for people with symptomatic HIV disease because of concern about the effects of the live bacteria in immune suppressed hosts[130].

The effectiveness of isoniazid (INH) prophylaxis in prevention of tuberculosis in HIV-1 infected people show conflicting results[131]. The difference in results is related to the fraction of new cases of tuberculosis that are reactivation as opposed to new infections. Where there are a large number of new infections, the prophylactic effect is limited to the period that the drug is administered, which severely compromises cost-effectiveness. However, where a large proportion of infections are reactivation, INH prophylaxis is certainly cost-effective[132]. A study in Uganda testing the effects of a 6-month daily INH regimen estimated that they were able to save $US24.16 per person when secondary infection costs were considered[132]. An economic analysis that modeled the benefits and costs of providing INH preventive therapy for TB in HIV-infected persons in Zambia did not find cost-savings for the general population. Much of the benefit derived from prevention of secondary cases of tuberculosis and modeling suggested that the benefits would exceed the costs by a significant margin if it were given to people such as teachers, prisoners, and healthcare workers who were at the greatest risk of infecting many others[133]. Middle-income countries such as Thailand and South Africa appear to have higher costs (US$261.88 per tuberculosis episode and $890.50 per patient cured respectively)[134]. Studies to determine how much longevity or quality of life

is gained by prevention of tuberculosis have yet to be performed. One long-term study of the effect of tuberculosis prophylaxis on overall mortality showed no survival benefit in individuals randomized to received prophylaxis compared to individuals receiving placebo, even though there were reductions in the incidence of tuberculosis and tuberculosis was associated with an increased mortality[135]. This result may have occurred because most of the people in the placebo arm received delayed prophylaxis, but the study still raises questions about the long-term benefit of prophylaxis of tuberculosis in HIV-1infected individuals. However, on balance it would seem reasonable that in countries with a high prevalence of tuberculosis all HIV-1 infected individuals with CD4 counts of less than 400 should receive six months of INH prophylaxis, particularly if they are tuberculin skin test positive. Further information and discussion on this subject can be found in the Working Group Five paper on tuberculosis and HIV.

Nontuberculous mycobacterial infections are a common opportunistic infection in North America and Europe but have not received much attention in low and middle-income countries. While they occur[136], their overall importance as a cause of morbidity and mortality in developing countries is unclear. This may be either because this infection is not a problem, or that it occurs as a preterminal event, or that the diagnostic capacity for the infections is lacking. Prophylaxis for these infections cost US$ 25,000 per quality adjusted life year gain in North America[137]. There are no data from developing countries, but this cost is unlikely to compare favourably to other measures.

Bacterial Infections

In sub-Saharan Africa, bacterial diseases such as *Streptococcus pneumoniae*, non-typhoid salmonella, and shigella cause a great deal of morbidity and mortality in HIV infected individuals[35,138,139]. These infections occur at an early stage in HIV-1 disease and their prevention or treatment likely results in substantial increases in longevity. Many of these infections can readily be prevented with inexpensive antimicrobial prophylaxis. Two randomized clinical trials in West Africa assessed the effects of daily prophylaxis with co-trimoxazole on adverse events and mortality[140,141]. The treatment groups showed substantial reductions in adverse events and mortality in HIV-1 infected individuals that seem to be primarily related to an effect on prevention of common

bacterial infections. In one of these studies, a 46% reduction in risk of mortality and reductions in episodes of septicemia in people with HIV-1 infection who had already experienced tuberculosis was observed[140]. receive co-trimoxazole prophylaxis daily. Anglaret et al[141] reported a 57% reduction in the risk of severe adverse outcomes in HIV-1 infected subjects randomized to daily co-trimoxazole prophylaxis. The cost of the prophylaxis was US $ 1.50 monthly[140] or US$17.50 per year[141]. Although a formal cost-effectiveness analysis has not been reported and the long-term effect on survival is not known, this prophylactic regimen is almost certainly highly cost-effective. Although there was no discernable gradation of beneficial effect with stage of HIV-1 disease in the study reported by Anglaret et al[141], it is uncertain at this time as to the optimal point in HIV-1 disease for beginning co-trimoxazole prophylaxis. In the absence of evidence it would seem prudent to begin prophylaxis when CD4 counts are below 400. In spite of the high cost-effectiveness and the potential benefit of this intervention, the scale of its implementation is small. This is one intervention that could be implemented fairly readily at scale (ie. little infrastructure or training needed) that could yield a significantly increased longevity and improved the quality of life. However, enthusiasm for implementing this regimen has recently been put into question by the results of another trials of co-trimoxazole prophylaxis from Senegal where no survival benefit and no effect on the occurrence of severe clinical events was found in HIV-1 infected subjects with CD4 counts below 400/ul and placebo recipients[142]. It is very important that the conflicting results of these three prophylaxis trials be explained through further analysis and that further research on this approach is conducted.

There has also been interest in the prevention of pneumococcal infection by vaccination. A trial in Uganda assessed the efficacy of vaccination against S*treptococcus pneumoniae* for people with HIV[143]. Unfortunately, the 23-valent pneumococcal polysaccharide vaccination was shown to be ineffective in this population.

Prophylaxis of Parasitic Infections

While *Pneumocystis carinii* pneumonia (PCP) is one of the leading causes of AIDS-related deaths in industrialized countries, it has been generally regarded as uncommon among HIV-infected individuals in Africa. However, studies in South Africa

and Malawi found that PCP was present in about 10%-15% of the HIV positive children studied[144,145]. A further study in Zimbabwe found that 33% of HIV-positive adults measured were co-infected with PCP[146]. In contrast to these findings, an autopsy study from Abidjan found that only 4% of cadavers of HIV positive individuals had PCP[36]. It was hypothesized that the reason for the low prevalence of PCP (and CMV and lymphoma) in Cote d'Ivoire was that most patients had succumbed to other infections before they reached the stage of disease when PCP is most frequent.

For over a decade, the value of PCP prevention has been recognized in industrialized countries. Patients who receive either trimethoprim-sulfamethoxazole (co-trimoxazole) or aerosolized pentamidine prophylaxis have a statistically significantly decreased risk of new or recurrent PCP. Consistent use of either drug is associated with improved overall survival[147]. PCP prophylaxis has also been discontinued in many patients on successful HAART regimens[68].

Prophylaxis of PCP is also quite inexpensive. As noted above, a study in Cote d'Ivoire reported that a daily dose of co-trimoxazole (800 mg trimethoprim and sulfamethoxazole 160 mg) cost only US$1.50 per month. The cost of treatment for PCP was estimated to be US$8 in sub-Saharan Africa and US$270.76 in Thailand[42].

Co-trimoxazole is also the recommended prophylaxis for prevention of toxoplasmosis. This protozoan has been found to be prevalent in HIV positive patients in Burkina Faso (25.4%), Mexico (32% of those with HIV and neurological complications), and Thailand (23.2%)[148,149,150]. Extrapolation from studies in North America and Europe suggests that that prophylaxis with co-trimoxazole will improve people's health and extend life by protecting against several infections, which would add to the cost-effectiveness of co-trimoxazole prophylaxis.

Prophylaxis of Fungal Infections

Mucosal infection with *Candida albicans* is a major cause of suffering in HIV-1 infected individuals. Infections of the vagina, mouth and esophagus can be extremely debilitating, but are infrequently a direct cause of death. Once a first episode has occurred there is a substantial chance of recurrence. Prophylaxis with low cost antifungal agents such as nystatin may be effective early in the disease[151]. Once weekly

doses of flucozanole have been effective at preventing candidia in patients at advanced stages of the AIDS process[152,153], although this drug is very expensive. It is unclear as to whether there is any survival benefit to prophylaxis of candidal infection, although anecdotaly quality of life is improved. Azole drugs have also been used to reduce the frequency of cryptococcal disease in people in the later stages of the AIDS disease process[154]. This requires life long prophylaxis and is probably not practicable because of cost. In addition, drug resistance has been occurring, partly due to the widespread and long-term use of azole drugs for treating and preventing candidiasis. In terms of the practical use of antifungal prophylaxis, prophylaxis of individuals with recurrent episodes of oral or esophageal candidiasis with nystatin would be a reasonable approach until more data are available.

Prophylaxis of Viral Infections

Recurrent or persistent viral infections such as Herpes Simplex Virus type 1 and type 2, Varicella Zoster Virus and cytomegalovirus produce severe and debilitating disease in HIV-1 infected individuals. Prophylaxis with antiretroviral agents can prevent reactivations of these infections but require life long administration of the prophylaxis, unless there is improvement in immune function. There have been no studies of their cost effectiveness in low and middle-income countries and it is unclear as to whether they increase survival, although they certainly increase the quality of life. Prophylaxis is expensive and their role in the care of AIDS in developing countries is unclear at this time.

Vaccines Preventable Opportunistic Infections

There are several vaccines that protect against infections that are prevalent in HIV positive people in developing countries. However, there are still questions about the efficacy of vaccines in people at different stages of the HIV/AIDS disease process[40,155]. More research is needed to understand the possible effectiveness and cost-effectiveness of vaccines to prevent other diseases such as hepatitis B, measles or herpes simplex virus for people with HIV/AIDS.

Treatment of OIs

Variations in disease stage, co-morbidity, antiviral drug use and costs of therapy in low and middle-income countries make it difficult to generalize about the costs of treatment of OIs. In spite of this, there are examples of care initiatives that have been effective and cost effective in reducing OIs and improving the quality of life and longevity of people with HIV/AIDS.

Treatment of Tuberculosis

In situations where adherence to drug regimens may be difficult, the World Health Organization recommends the Directly Observed Treatment Shortcourse (DOTS) programme. This programme has been shown to improve the access and efficacy of TB treatment worldwide[156,157]. A study measuring the DOTS treatment outcomes in South Africa found that 97% of the HIV-infected participants who adhered to the therapy were cured[158]. Therapy of tuberculosis is highly cost-effective in AIDS, although no studies of the impact on survival have been performed (because withholding treatment is unethical) survival is almost certainly prolonged because tuberculosis begins to occur relatively early in HIV-1 disease. Therapy of tuberculosis also prevents transmission of the infection to the population and so is a public good as well. Further discussion of therapy of tuberculosis is found in the Working Group Five paper on tuberculosis.

Treatment of Bacterial Infections

As noted above, infection with common bacteria, particularly *Streptococcus pneumoniae* and non-typhoidal salmonella are major causes of mortality in HIV-1 infected individuals. These infections are readily treatable with relatively inexpensive antimicrobial agents such as penicillin and ciprofloxacin. Unfortunately, high levels of antibiotic resistance have been measured in resource poor populations[159] where testing for resistance cannot be routinely done and monitoring for adherence to therapy is difficult. For example, resistance to ampicillin (79%), co-trimoxazole (72%) and gentamicin (55%) was found in a study of HIV positive children with bacteremia in Malawi[160]. Oftentimes, HIV positive people will have recurrent bacterial infections. A

study in South Africa discovered that 69% of children who were being treated for concurrent HIV and pneumococcal bacteremia had recently received a course of antibiotics for a previous infection[139]. Prophylaxis against further episodes of infection should be considered. These infection begin to occur relatively early in the course of HIV-1 infection and so treatment yields considerable gains in high quality survival time and although formal analysis has not been performed they are almost certainly highly cost-effective. The cost of treating an episode of septicemia in Africa is estimated to be US$60[41].

Treatment of Parasitic Infections

Pneumocystis carinii pneumonia is readily treatable with co-trimoxazole. The main challenge of therapy of this infection in developing countries is making a diagnosis in the absence of laboratory support. Once and individual has experienced an episode of Pneumocystis the chances of recurrence are high and life long prophylaxis of recurrence is highly recommended. Toxoplasma encephalitis is the main other parasitic OI. Once again diagnosis of this infection is challenging in the absence of laboratory support. Toxoplasma encephalitis is associated with a high mortality[161], even in developed countries[162]. Recurrences of encephalitis are also frequent and life long suppressive therapy is indicated. Overall the effect of treating toxoplasma encephalitis on longevity are unclear.

Treatment of Fungal Infections

Candidiasis effects about 53% of HIV positive people globally[51]. This fungal infection may occur in the mouth (thrush), eyes, esophagus, digestive tract, vagina or on the skin. Candidiasis can be treated with localized medications such as oral lozenges and mouthwashes, vaginal creams or topical ointment. If used early on in the disease process, treatment of esophageal candidiasis with gentian violet can be effective. A study from Kinshasa in the early 1990's found that it was also relatively inexpensive, costing only US$0.50 per treatment course[163].

Treatment for oral thrush is estimated to cost US$2.00 in sub-Saharan Africa and US$2.48 in Thailand per episode. Esophageal thrush is much less prevalent and costs

US$10.00 in sub-Saharan Africa and US$4.96 per episode in Thailand. People with AIDS are likely to experience reoccurrence of esophageal candidiasis within12 months of treatment (regardless of which antifungal is used)[164] and the cost effectiveness of the therapy is unclear. The cost of treating cryptococcal disease which is prevalent throughout the world, is estimated to be US$1,741.40[42]. There are high occurrence rates of this infection and maintenance therapy with expensive antifungal drugs is required[165]. The cost-effectiveness of therapy has not been assessed.

Penicillium marneffei has recently become a serious threat to HIV-positive people in South East Asia and the southern part of China[166]. Most patients in a study in Thailand responded to treatment of this potentially lethal fungal infection with amphotericin B followed by itraconazole[167]. Cost for treatment of penicilliosis is estimated to be US$697.40[42]. Maintenance of *Penicillium marneffei* with itraconazole has also been shown to be required for this infection. While over 50 percent of patients normally relapse after the initial treatment within six months, none of the patients that were given prophylactic itraconazole had a relapse within one year[168]. Cost effectiveness analysis has yet to be performed.

Treatment of Viral Infections

Varicella-zoster virus, the Herpes simplex viruses and Cytomegalovirus all can produce severely debilitating and sometime life threatening infections in people with HIV-1 infection. Varicella-zoster virus reactivations occur early in the course of HIV-1 infection and are usually self-limited and can be managed symptomatically. However, a case could be made for treatment with antiviral drugs such a acyclovir if the infection is life threatening or threatens vision, since the therapy is short term and the chances of several years of relatively healthy life after an episode of zoster are excellent. Severe oral or genital reactivations of Herpes simplex virus infection are difficult to manage and while they respond to antiviral therapy there is a high frequency of recurrence and maintenance therapy is required unless there is improvement in immune function. Cytomegalovirus retinitis occurs at very advanced stages of AIDS. Therapy with extremely expensive drugs such as ganciclovir can be effective but its cost-effectiveness is very questionable.

PALLIATIVE CARE FOR THE TERMINALLY ILL

As there is no cure for HIV disease, it could be argued that all care for people with AIDS is palliative[169]. The goal of AIDS palliative care is to slow the course of the opportunistic infections, preserve a high level of quality of life, and prepare for a peaceful death. Alleviating pain, relieving other symptoms, training carers and providing spiritual and psychological support are interventions that can assist individuals and families through the difficult final stages of the disease. They ease and dignify the end of life.

Symptom Relief

Many different kinds of pain are encountered in the HIV/AIDS disease processes, particularly in the advanced stages. Pain in people with AIDS is normally associated with an underlying infection[170]. Other sources of pain may be ulcers, headaches, inflammation and skin problems. Obviously, if the underlying causes of pain could be managed the pain would be alleviated. However, diagnosing and treating the underlying cause may be difficult in some settings and may require costly therapies, that are simply not available. In this case simple pain management, although not ideal, provides some a welcome relief.

The location and severity of the pain dictate which treatments are appropriate. Medications such as aspirin or acetaminophen are useful for mild pain. These drugs are estimated to cost about $1.12 per episode[42]. More severe pain may be treated with codeine or morphine. These more potent drugs are expected to cost about US$14.00 per episode. Unfortunately, many analgesics that are used for palliative care in industrialized countries are not legally available in resource-poor countries due to strict international controls on narcotics[42].

Fever is one of the most prevalent symptoms experienced by people with AIDS[171] and may also be a sign of underlying opportunistic infections. Acetaminophen, drinking fluids and bathing in tepid water can alleviate discomfort and adverse effects caused by increased body temperature. The estimated cost of treating an episode of fever is US$0.60[42].

Diarrhea lasting longer than one month occurs in an estimated 50% of people with AIDS in Africa[37]. Episodes of diarrhea may be associated with parasites or enteric viruses[172] or a side effect of a medication. Whenever possible, the underlying cause should be identified and treated. However, in studies from several East African countries, the cause for a significant number of episodes of diarrhea in HIV-positive patients was unclear[173,174,175]. Effective symptomatic treatment of diarrhea include taking medications such as kaopectate to decrease the frequency and amount of stools. More importantly, liquids and nutritious foods are needed to replenish the lost fluids and nutrients. Diarrheal treatment is estimated to cost US$13.00 per episode[42].

Nausea and vomiting are prevalent in people with AIDS and can contribute to anorexia and weight loss. The underlying cause such as reactions to medications, infections or tumors[170] should be identified and treated. Temporarily, antiemetics or ginger can be used to control the vomiting. Fluids should be encouraged to keep the patient hydrated. Cost of treatment for an episode of nausea is estimated to be US$1.75 per episode[42].

Approximately 90% of people with HIV have some form of skin condition[170]. These problems may include infections, drug reactions, scabies, pressure sores or cancers. Skin often becomes dry in the late stages of AIDS due to persistent diarrhea, vomiting and malabsorption. Anti-pruritic agents such as calamine lotion and antihistamines such as chloropheniramine tablets can be used to ease itchy skin rashes. The cost of treating an episode of skin rash is estimated to be US$2.00[42].

Respiratory problems are prevalent in people with AIDS in developing countries due to the frequent occurrence of tuberculosis, PCP and bacterial pneumonia. Cough and shortness of breath are often alleviated with treatment of the underlying infections. Symptoms may be relieved with cough suppressants, hot vapors or analgesics[170]. Seating the patient in an upright position may also allow them to breathe easier.

As the disease process advances, many people with AIDS will experience cachexia, a general weakness due to malnutrition, diarrhea, and immune system activation. Improved nutrition and treatment of diarrhea can help to limit the effects of wasting and prevent cachexia[176].

Improving Nutrition and Hydration

Even in industrialized countries, people with HIV often have micronutrient deficiencies. Adequate nutrition and hydration are associated with better outcomes in HIV positive patients in people who use injection drugs in the United States[177]. Many people in developing countries have generally poor nutrition, but the problem can be intensified with HIV due to oral and esophageal infections, nausea, diarrhea and economic vulnerability.

The association of nutritional deficiencies and AIDS has prompted several studies of the effect of nutritional supplementation on AIDS. Iron, vitamins A and E, selenium and zinc supplementation have all been assessed as possible treatments for people with HIV. A study in Zambia found that while low serum concentrations of vitamins A and E were accurate predictors of early death, supplementation of multivitamins did not influence morbidity or mortality[178]. Conversely, a study in Tanzania found that providing vitamin A supplements to children with pneumonia reduced mortality by more than half [179]. Increasing caloric intake has also been hypothesized as an intervention for people with HIV/AIDS. A study in Switzerland found that providing oral arginine and fatty acids to people with HIV increased their body weight but did not improve their CD4 counts, viremia or any immunological parameter measured[180]. A US study found that caloric supplements did not increase the average weight in people with HIV beyond that offered by vitamin and mineral supplements[181]. Thus while it seems sensible to maintain good nutrition the evidence that specific interventions, apart from vitamin A supplementation in HIV infected children with pneumonia, have a significant impact is mixed.

Support of Care Givers

As AIDS progresses, the need for demanding physical care increases. Diarrhea, nausea, nutritional needs and loss of income put enormous pressures on families. Furthermore, families may be isolated, stigmatized, and lacking information about how to care for their ill family member in the home. Many times people attempt to admit their relative to hospital. Unfortunately, hospitals and clinics are already overburdened with

an estimated 190% bed occupancy rate in some areas[182]. The cost for one day in hospital as an inpatient is estimated to be US$7.25 per day in sub-Saharan Africa and US$ 22.44 in Thailand[42].

In an effort to alleviate the overburdening of hospitals and reduce costs, there have been many attempts to strengthen home-based care services. A Zimbabwean study estimated the cost of home-based care in urban environments to be between US$16 and US$23 per visit[183]. In rural areas, the cost increased to between US$38 and US$42. The rise in the rural area cost was attributed to travel time. As many health care workers in sub-Saharan Africa travel by foot, up to 75% of the total cost per home visit can be used up getting to the patient's home[183]. The efficacy of home-based care is unknown but it does not seem to result in significant overall cost savings. It may shift the burden of costs from the public to the private sector to some extent, depending on how health care is funded.

In home based care programs, family members who have little or no training or support provide much of the care. Community groups, religious institutions, NGOs and local health care workers are often willing to assist with care and supplies but the needs in many areas have become too great. Training community and family members to deliver simple palliative care treatments may be a cost-effective way to improve the quality of life of people with AIDS in developing countries, although there is little systematic study of this question. Development of instructional reading materials might be appropriate in areas of high literacy.

Spiritual and Psychosocial Support

As we examine interventions to improve the quality of life for people with AIDS, we must look at the needs of their whole being. Meeting the spiritual and psychological needs may be the most important components of health to the individual as they prepare for their death. Oftentimes in developing countries, people are first diagnosed as having HIV/AIDS when they are already very sick. Time from diagnosis to death may be very short.

Issues such as the HIV status of their partner(s), and children, funeral costs, and spousal land rights etc. may need to be addressed. Community groups can assist in providing information about orphan care, income generating activities and legal rights. Many people also need spiritual support as they prepare for death. Psychosocial support from counselors, religious leaders, health care staff and community members is a vital part of the essential care of people with HIV/AIDS (UNAIDS, 2000 Report on the).

Constraints to Scaling up

A number of ways of improving the quality of lives for people with HIV/AIDS in developing countries have been identified since global recognition of the epidemic in the early 1980's. Unfortunately, creating effective clinical and social programmes to meet the needs of HIV positive citizens in many countries has not happened. The reasons for this are complex and vary across the regions. However, there are certain constraints to scaling up care programmes for those with HIV that are consistent across many developing countries.

The epidemic tends to begin in populations that are marginalized and may be operating outside the law such as injection drug uses (IDUs) and female sex workers (FSWs). Governments that prioritize care and prevention in these groups may appear to be supporting the illegal activity. As the epidemic spreads to the larger population, health care systems become overwhelmed with patients who are suffering from persistent opportunistic infections[182]. In some countries such as Tanzania (4.1 doctors and 85 nurses per 100,000 people), Indonesia (16 doctors and 50 nurses per 100,000 people), and India (48 doctors and 45 nurses per 100,000 people), the ratio of health care workers to patients is very low[184].

Before people can receive care for HIV, they must know that they are HIV positive. Unfortunately many people in developing countries are not aware of their status until they are very ill[185]. Access to reliable voluntary counseling and testing is severely limited in many countries. Even when people are tested, many do not return to find out the results of the test[51]. There are a number of reasons why people are unwilling to learn their HIV status. Tests may not be accurate due to the unrefrigerated storage of reagents,

the use of kits beyond their date of expiry, and human error[186,187]. If treatment and secondary prevention mechanisms are not available and known about, many people will not see any benefit to being tested [188]. Furthermore, denial of the existence of HIV will also add to the resistance to HIV testing.

Once someone knows that they are HIV positive and seeks care, they may find that the appropriate drugs are out of reach financially. Although the benefits of drugs like cotrimoxazole, INH and ARVs are recognized, access to even the most inexpensive of them is far from universal. The reasons for this may include breaks in the distribution systems, poor storage, short dating, and cost[51]. In addition to the costs of drugs there are significant costs to accessing the health care systems in many countries. Health care systems have been going through major adjustments over the past decade[189]. The patient's portion of cost of care has risen in many places as governments have initiated cost sharing programmes. Care of any kind may be associated with a user fee causing the poorest people to delay or forgo treatment[190]. The time and money spent on travel and time of work and necessary blood tests etc are also substantial**Error! Bookmark not defined.**.

In time the emergence of resistance of HIV to ARV and bacterial opportunistic infections to antibiotics will limit the effectiveness of the drugs. This will be exacerbated by poor adherence to therapy or interruptions in treatment due to unavailability of drugs[100,160,191].

Conclusion

Many of the needs of HIV-positive people in low to middle income countries are not being met. There is now much that can be done to increase the life span of HIV infected individuals and improve its quality. The costs for these measures, as discussed in this paper, ranges from US$0.50 for treatment of oral thrush to up to US$ 1,200 for HAART. Although the issue of availability of ARV has received much attention, basic drugs for treatment or prevention of opportunistic infections are often not available. Of course knowing the cost is meaningless unless they have an important impact on the quality of life or its length. We need systematic evaluation of the impact of these different interventions value so that the most those interventions have on the quality of

life is known. It may be helpful to compare the impact between interventions such as co-trimoxazole and HAART, or even improved nutrition and sanitation and HAART. Priorities within countries must be based on the ability to sustain lasting benefit to the population. ARV is the gold standard for HIV care and should be implemented in areas where reliable drug distribution and monitoring can be carried out, and where it makes economic sense. In regions where there is the capacity to deliver these complex regimens and the cost yields rational benefits, they should be offered. However, where the economic and logistical reality does not allow for such treatments, holistic approaches to providing care and prevention must be designed in strategic and compassionate ways to meet the needs that are important to the individual and family.

The whole issue of better access to therapy for people with HIV and AIDS also needs to viewed in the context of the entirety of health problems in poor and middle income countries. There are many life-saving treatments that are not available in developing countries for a variety of reasons. Chemotherapy for cancer, dialysis, and cataract surgery are beyond the reach of many people living in resource poor areas. At the same time, many people do not have access to clean water, food, treatment for malaria, respiratory and diarrheal diseases. Realistic priorities must be set to avert the largest amount of suffering and death in low and middle-income countries of the world.

Finally, the pressing issue of how best to care for the many millions of HIV infected people in low and middles income countries must not divert resources and effort from prevention of new HIV infections. We must continue to push for the widespread implementation of effective interventions, work on developing new strategies for interruption of HIV transmission and redouble efforts to develop HIV vaccines.

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