A Systematic Review of Antiretroviral Therapy Program Outcomes in Sub-Saharan Africa and Haiti

By

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Research Questions:

1. Do antiretroviral treatment programs for the treatment of HIV-infection reduce AIDS-related mortality and improve immunovirologic markers in HIV-infected adults in Haiti and the countries of sub-Saharan Africa?

2. What factors contribute to the improvement of health outcomes in antiretroviral treatment programs for HIV-infected individuals in sub-Saharan Africa and Haiti?

"Don't believe it when they tell me there ain't no cure
The rich stay healthy and the sick stay poor"
--U2

Background

Burden of suffering

Human immunodeficiency virus (HIV), the infectious agent of acquired immune deficiency syndrome (AIDS), currently infects forty million people throughout the world, and in 2000, surpassed TB to kill more people each year than does any other infectious agent. Three million individuals died of HIV/AIDS in 2003, and ninety percent of those deaths occurred among people living in the world’s poorest countries where few if any resources exist to combat the disease. Furthermore, in 2003, an estimated five million individuals were newly infected with HIV.
Though the pandemic spans the globe, it disproportionately infects, affects, and entrenches itself in the populations of the poorest regions on the planet. Seventy percent of the world’s infected individuals live in sub-Saharan Africa alone, where HIV infects an estimated twenty-seven million adults and children—more infected individuals than in all the other countries of the world combined. Sub-Saharan Africa has the highest adult HIV-prevalence of any region in the world at eight percent, with HIV infecting over thirty percent of the adult populations of Botswana, Lesotho, Swaziland, and Zimbabwe. In the Caribbean, the world’s second hardest hit region, HIV infects 2.2 percent of the adult population, and in Haiti, the poorest country in the Caribbean and the Western hemisphere, adult HIV prevalence estimates range from 5.5 to 6.1%. Not only does HIV/AIDS inflict a significant amount of morbidity and mortality, the disease exerts a tremendous economic, social, and political burden upon resource-poor countries. The HIV/AIDS pandemic threatens to destroy the societies, economies, infrastructures, and national and regional security of many nations. Acquired immune deficiency syndrome-related deaths disrupt family structures and seriously reduce entire work forces including those of agricultural workers, health professionals, and teachers. Of the fourteen million children orphaned by the AIDS-related death of their parents, eleven million live in sub-Saharan Africa. Human immunodeficiency virus infection acts synergistically with other diseases to overwhelm the already inadequate and overburdened medical facilities in developing countries. The stigma associated with HIV/AIDS constitutes an additional socio-cultural burden to be born by infected
individuals and their families. Many HIV-infected individuals report abuse by family and neighbors.

**Disparities in access to antiretroviral medications between wealthy and poor countries**

In the U.S. and Europe, HIV infects and kills only a fraction of the number it does in poorer nations. The U.S. and other industrialized Western countries thus might be said to be “resistant” to HIV/AIDS and better equipped to defend themselves against the virus once infected. The effectiveness of antiretroviral therapy (ART) for the treatment of HIV/AIDS in the industrialized world is well-established. The introduction of highly active antiretroviral therapy (HAART) in 1997 sharply decreased AIDS-related mortality, morbidity, and hospitalizations in wealthier industrialized countries. While HAART has become the standard of care for HIV-infected patients in wealthier nations, international health experts have traditionally considered ART to be unfeasible in developing countries. Haiti and the countries of sub-Saharan Africa represent, by almost any standard, the poorest areas of the world.

According to the World Health Organization (WHO), six million people living in the world’s poorest countries are in desperate need of antiretroviral (ARV) medications, though only 300,000 of those in need currently receive them. Despite widespread use in wealthy nations, ART in developing countries remains a novel concept, first entertained seriously only in 1998 at the 12th World AIDS conference in Geneva. As a result, we know little about the use of antiretroviral therapy in developing countries, especially those in sub-Saharan
Africa and Haiti. The inequitable distribution of antiretroviral medications persists and perpetuates the disparate dichotomy that exists between wealthy and poor nations.

**Prevention efforts not sufficient**

Current international HIV/AIDS strategies in developing countries focus primarily on preventing HIV infection rather than preventing the progression of HIV disease in those already infected. The annually increasing numbers of newly infected individuals suggests this approach is inadequate.

A whole consists not of the sum of its parts.\textsuperscript{20,21} Many infectious disease experts argue that health workers and officials need to link prevention efforts with care, including the provision of antiretroviral therapy to those already infected with HIV.\textsuperscript{1,6,8,22} Preventive and curative medicine likely act synergistically to produce better health outcomes.

The medical anthropologist George Foster in 1952 found that people in resource-poor countries are interested in prevention only after their first priority, treatment of illness, is satisfied.\textsuperscript{23} Some HIV/AIDS activists in many sub-Saharan African countries are becoming increasingly hostile toward international health agencies that provide only prevention without treatment for those already infected with HIV.\textsuperscript{1} They want HIV medications for those who have AIDS, not just condoms and prevention messages for those not yet infected.

Treatment may also decrease transmission by reducing viral load, as a high viral load is associated with increased HIV infectiousness.\textsuperscript{24-26} Managing
HIV disease with treatment may therefore constitute a means of secondary prevention that is not well emphasized in developing countries.

**Obstacles to providing antiretrovirals in resource-poor settings**

Objection to providing ART in developing countries centers around the following obstacles: the high cost of medications relative to national health budgets in resource-poor settings, lack of health infrastructure to provide treatment and follow-up, concerns about possible lack of adherence to treatment, the risk of perpetuating inequalities between the rich and poor, and the emergence of viral resistance.27

Recent sharp drops in the price of ART medications, however, now render ART increasingly practical, at least on financial grounds. Generic manufacturers in India, China, and other countries now produce and sell antiretroviral medications at substantially lower prices. The availability of inexpensive medications, however, will likely affect only the few in resource-poor settings who have regular access to medical services.6

If faced with the extremely high HIV prevalence of poorer countries, many wealthier nations might also experience the disintegrations of their public health services, as well. Some estimate that for every one dollar spent for antiretroviral medications, three dollars are necessary for health infrastructure. Inexpensive antiretroviral regimens to decrease vertical transmission of HIV are still not available to many in Africa, despite their cheap price, because of the lack of health care infrastructure and the presence of political complacency.6
Managing HIV infection requires not only access to ART medications, but adherence to potentially complicated dosing regimens, as well. Farmer, *et al.*\(^8\) point to tuberculosis (TB) as an example of a chronic infection well-managed in resource-poor settings. Like HIV/AIDS, multi-drug resistant TB (MDR-TB) is managed with multiple medications on a long-term basis. The success of managing TB with the provision of directly observed treatment (DOT) by health workers or trained community members may serve as a model for HIV treatment with ART in sub-Saharan Africa and other parts of Haiti.

**Can ART interventions work in Haiti and sub-Saharan Africa?**

A number of unanswered questions exist regarding the establishment and expansion of ART programs in resource-poor countries such as sub-Saharan Africa and Haiti:

- Do these countries have the capacity to establish and maintain programs to treat large numbers of HIV-infected patients?
- In successful ART programs, what factors contribute to improved health outcomes for HIV-positive individuals in these countries?
- As interest in providing ARV therapy increases in developing countries, what should new programs look like to effectively provide ARV therapy?

This paper is a systematic review of existing programs that provide ART in sub-Saharan Africa and Haiti. It proposes to report the health outcomes of ART provision in those areas and to identify factors that contribute to the failures and successes of those programs. Primary health outcomes used to assess
program effectiveness include AIDS-related mortality and the surrogate immunovirologic markers of CD4+ cell count and viral load. Findings from this study will be useful to ascertain the effectiveness of ART programs in developing countries, and to determine if programs are successful enough to warrant a shift in international health policy focus from HIV prevention-only strategies to prevention plus treatment.

Methods

Criteria for selecting studies for this review:

The principle investigator performs a systematic search of the literature to select studies, with the inclusion considerations being study design, geographic location, study participant characteristics, type of intervention, and health outcomes.

Study Designs: Study designs must be randomized controlled trials (RCT), prospective cohort studies, retrospective cohort studies, or case series published between January 1996 and April 2004. The study must enroll at a minimum twenty participants. Although randomized controlled interventions are ideal to determine effectiveness, few published studies likely exist that use an experimental RCT study design, owing to ethical considerations.

Geographic Location: Studies must be conducted in Haiti or a country of sub-Saharan Africa (Botswana, Namibia, Mozambique, Zimbabwe, Zambia, Angola, Malawi, Tanzania, Congo, Zaire, Kenya, Gabon, Guinea, Cameroon,
Uganda, Nigeria, Benin, Togo, Ghana, Cote d’Ivoire, Liberia, Sierra Leone, Senegal, Mali, or South Africa).

Study Participants: Participants must be adults (defined as 13 years or older, as used in the CDC classification, which includes adolescents\(^28\)) who are infected with HIV, and may or may not have an AIDS diagnosis or AIDS-related symptomatology. Studies with both male and female participants will be considered, though studies that include pregnant female participants treated with ART only to prevent transmission of HIV from mother to infant will be excluded. Criteria for HIV infection and AIDS include those specified by the CDC (1993-revised)\(^28\) or by WHO classification (Clinical Stage 4).\(^29\)

Intervention: Studies must provide an intervention of ART, either a single drug or multi-drug regimen, to HIV-positive, non-pregnant adults for the treatment of HIV/AIDS. The intervention can be either directly observed therapy (DOT) or non-DOT.

Health Outcomes: Principal health outcomes include probability of survival; the proportion of patients achieving an undetectable HIV-ribonucleic acid (RNA) level (viral load), e.g. viral load less than 50 viral copies/ml; mean change in CD4+ cell count relative to baseline; and change in HIV-RNA levels relative to baseline. Secondary health-related outcomes include clinical outcomes such as adverse drug events, adherence, and any quality of life indicators the studies report. The review will report adverse advents as either minor or major. Major events will be those severe enough to require change or discontinuation of treatment.
Search strategy for identification of studies

To identify relevant articles, the principal investigator searched the MEDLINE database via PUBMED, restricting the search to published articles from January 1996 through April 2004. The MEDLINE search used the Medical Subject Headings (MeSH) "HIV" AND "DEVELOPING COUNTRIES" Limits were set for "adult" and "human." This yielded very few ART programs, and the investigator consulted a reference librarian at the Health Sciences Library at The University of North Carolina at Chapel Hill.

The revised search utilized the following search terms:

"ANTIRETROVIRAL AND (AFRICA OR BOTSWANA OR NAMIBIA OR MOZAMBIQUE OR ZIMBABWE OR ZAMBIA OR ANGOLA OR MALAWI OR TANZANIA OR CONGO OR ZAIRE OR KENYA OR GABON OR GUINEA OR CAMEROON OR UGANDA OR NIGERIA OR BENIN OR TOGO OR GHANA OR COTE D'IVOIRE OR LIBERIA OR SIERRA LEONE OR SENEGAL OR MALI OR HAITI)" The investigator set the following limits: "All Adult, Publication Date from 1996 to 2004, Human." The revised search yielded 127 articles on April 8, 2004. The investigator conducted the same search again on April 19, 2004, which yielded an additional two articles.

In addition to the PUBMED search above, the principal investigator performed a search of Cochrane Data Base of Systematic Reviews via OVID using the search term "antiretroviral," and a search using CINAHL (via EBSCOHost) with the keywords "HIV AND developing countries." These
searches yielded no additional articles. A search of the NIH, CDC, and UNAIDS websites yielded no additional studies for consideration.

Lastly, the investigator's consultation of infectious disease experts at the University of North Carolina at Chapel Hill identified an unpublished manuscript in Malawi, Africa for consideration.

**Results**

**Data abstraction**

The principal investigator examined titles and abstracts of the 127 articles identified by the PUBMED search and the additional one unpublished manuscript from Malawi and assessed them for the selection criteria specified above. Of the 127 articles identified from the search, only 27 articles initially appeared to meet the inclusion criteria, for which the investigator reviewed the full texts. Ten of these articles met the selection criteria and were included in the analysis. Two of these articles addressed the same antiretroviral program, so a total of nine ART programs in Africa and Haiti were identified—eight in Africa and one in Haiti. The most common reasons for exclusion of articles included the following: the article addressed only antiretroviral use for the prevention of maternal-fetal transmission; the article evaluated only non-retroviral care of HIV/AIDS patients; or the article represented the authors' expert opinion with no evidence-based findings.

Once the principal investigator selected articles for inclusion in the review, he abstracted relevant information from each article and placed it into evidence tables (Tables 1 and 2). Descriptions of each study are presented in
Table 1, with the variables being author, year, study location, study dates, study design, study setting, type of ART intervention, delivery method of ART, intervention duration, whether or not patients have to pay for study drugs, number in sample, percent lost to follow-up, and whether or not intention to treat analysis was carried out. Table 2 presents baseline characteristics and outcomes that were abstracted from the selected studies. Baseline data extracted include whether or not participants had taken antiretroviral medications at some time prior to the study, CD4 count, and viral load. Outcomes that were measured post-intervention included percent of patients with undetectable viral load, CD4 cell count change, viral load change, probability of survival, adherence data, and any adverse drug events.

The primary investigator combined outcome data wherever possible to calculate a weighted mean value, with the denominator consisting only of those participants for whom studies reported values.

Methodological description of selected studies

All ten of the selected studies employed non-randomized, and in most cases uncontrolled, drug trials to determine effectiveness of ART in Africa and Haiti. Kebba, et al. conducted a retrospective cohort study in Uganda comparing the effectiveness of three different ART regimens. This Uganda study did not randomize patients into treatment groups and did not include a placebo control group for comparison. The remaining studies consisted of prospective and retrospective case series designs in which the investigators or programs administered ART to participants and followed them to observe what outcomes
occurred without the use of control groups. With no comparison groups in these
descriptive studies, no basis exists to conclude that outcomes represent an
improvement over the natural course of the disease or that outcomes result from
the ART intervention itself. These studies describe the frequency of occurrence
of health outcomes associated with the ART intervention, but their study design
precludes them from providing definitive evidence for the effectiveness or
ineffectiveness of ART in Africa and Haiti. They describe initial attempts to treat
HIV positive individuals in these resource-poor regions and may generate
hypotheses to be later tested in randomized trials and ideas to be incorporated in
the planning and execution of future programs.

The studies evaluated programs in the Central Plateau of Haiti (Farmer, et.
al)\textsuperscript{1,8} and in five large sub-Saharan African cities: two studies in Abidjan, Cote
d'Ivoire (Djomand, et. al and Seyler, et al.);\textsuperscript{30,31} two in Kampala, Uganda
(Weidle, et. al. and Kebba, et al.);\textsuperscript{32,33} two in Dakar, Senegal (Landman, et al. and
Laurent, et al.);\textsuperscript{34,35} one study in Capetown, South Africa (Orrell, et al.);\textsuperscript{36} and
one in Lilongwe, Malawi (Hosseinipour, et al.).\textsuperscript{37} Each of the sub-Saharan
African studies took place in tertiary care centers, outpatient clinics, and military
hospitals, all within or near large cities. These medical centers represent the best
medical care available in their respective countries, which contrasts greatly with
the level of care available in more rural areas where health care infrastructure is
likely much more limited or non-existent. This confines the generalizability of
these study results to ART programs in larger cities with relatively well-
developed health care infrastructures. The program described by Farmer, et al. in
Haiti, however, differs from the African studies, as it operates from a small clinic in a poor, rural setting, so that its results might be more widely generalizeable to poorer areas with fewer resources.

The amount of money patients paid for ART differed greatly among studies. The South African and Haitian studies and the study by Seyler, et al. in Côte d’Ivoire completely subsidized ART medications, and the programs evaluated by Djomand, et al. in Côte d’Ivoire and by Laurent, et al., in Senegal heavily subsidized ART. The remaining studies either provided no ART subsidy or did not specify the amount patients paid. Those studies that did not provide subsidies likely selected wealthier patients for inclusion, which may bias results toward better outcomes if higher socioeconomic status acts as a confounder to contribute to improved outcomes. The results of the programs that provided ART free of charge are more widely generalizeable, as most HIV-infected patients in Africa and Haiti are poor and unable to afford antiretroviral medications without financial assistance.

**Description of study participants**

Both Ugandan studies and Landman, et al. in Senegal enrolled only patients infected with HIV-1, which limits the generalizeability of their results, as HIV-2 infection is not uncommon in Africa. Laurent, et al. in Senegal enrolled fifty patients with HIV-1 and only three patients co-infected with HIV-1 and HIV-2. The other studies did not specify HIV type. Djomand, et al. in Côte d’Ivoire; Kebba, et al. in Uganda; and both the Senegalese studies included only patients with no prior history of ART use, which renders their results readily generalizeable.
to only ART-naïve patients. Weidle, et al. in Uganda and Hosseinipour, et al. in Malawi included both ART-naïve and experienced patients, but did not breakdown outcomes by ART status. The Haitian and other Côte d’Ivoire study do not specify participant ART status.

Baseline clinical and immunovirological data show that the majority of the participants in these studies had advanced HIV-disease. CD4+ cell counts were below 200 in a majority of patients in all studies, though the Haitian study did not specify baseline CD4+ count. Mean baseline viral load exceeded 200,000 copies/ml in all studies that report values. Seyler, et al. in Côte d’Ivoire; the Senegalese studies; and Hosseinipour, et al. in Malawi enrolled a majority of patients with WHO stage 3 or 4 disease or CDC stage B or C disease, late clinical stages of HIV infection. The severity of HIV disease contributes to the generalizeability of these studies to other populations in Haiti and sub-Saharan Africa where HIV testing and counseling programs are sparse, and HIV infection is therefore commonly diagnosed at a relatively later stage than in more developed countries.

**Description of study interventions**

Study interventions included provision of a variety of antiretroviral agents, alone or in combination, to include the following drug classes: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleotide reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI). One category of drug combination employs the use of two NRTIs (2NRTI). Highly active antiretroviral therapy, another retroviral combination, was defined as the use of a NRTI with a NNRTI,
PI, or abacavir. All nine programs provided HAART as an intervention. The Côte d’Ivoire and Uganda studies also provided 2NRTI to participants. The Haitian program delivered DOT-HAART via community health workers. The Senegalese program evaluated by Landman, et al. delivered a non-DOT one pill per day HAART regimen. The other studies did not specify whether or not ART was directly observed. A central pharmacy dispensed antiretroviral medications in the Côte d’Ivoire studies; in Landman, et al. in Senegal; and in Orrell, et al. in South Africa. This allowed for tighter control over medication dispensation.

Duration of ART varied from a median of ninety-four and 152 days (HAART and 2NRTI, respectively) in Weidle, et al. in Uganda to 546 days (19.5 months) in the Laurent, et al. Senegalese study.

Orrell, et al. in South Africa reported eighty-seven percent adherence without DOT, and Landman reported ninety-five percent adherence in Senegal with once a day dosing without DOT. The study by Farmer, et al., the only study using DOT, does not report adherence, so no comparison can be made between DOT and non-DOT ART programs. Randomized control trials should be conducted, using HAART as the standard of care, to compare DOT programs versus non-DOT programs.

**Changes in health outcomes**

Despite initially high drug costs, a small pilot HIV/AIDS project in a poor rural community in Haiti provides directly observed therapy (DOT) with HAART to sixty patients with advanced HIV disease. The project serves patients in the poorest part of the poorest country in Western hemisphere and was built on an
existing TB-control infrastructure. The project initially began providing zidovudine to HIV infected pregnant women, which led to dramatic decline of vertical transmission of HIV to infants. It expanded in 1997 to provide post-exposure prophylaxis with three-drug regimen to victims of rape or professional injury. In 1998 it began to provide HAART to patients with long-standing HIV infection.\(^1,^8\)

The Haitian pilot DOT-HAART program, modeled on successful TB control efforts, provides each HIV patient with a community health worker who observes ingestion of medications, responds to patient/family concerns, and offers moral support. Support includes help with children’s school fees; free, uninterrupted access to medications; continuity of care; and monthly meetings. The initial cohort of sixty patients experienced dramatic responses to HAART. HAART-treated patients were far less likely to enter the hospital than were non-treated patients, and the HIV viral load dropped to undetectable levels in most patients. Many of these patients returned to work and to caring for their families.\(^1,^8\)

All studies that report values show an adherence, reduction in plasma viral load, and increases in plasma CD4+ cell count comparable to those of studies conducted in developed countries using similar ART regimens. Overall, participants in ART programs in Africa and Haiti took eighty-two percent of medications and experienced a weighted mean log10 viral load reduction of 1.83 after approximately one year of treatment. Sixty-five percent of all participants achieved an undetectable plasma viral load, the definition of which varied with
the sensitivity of the laboratory test from less than fifty RNA copies/ml to less than 400 copies/ml. Plasma CD4+ cell count increased by a weighted mean of $123 \times 10^6$ cells/L. Adherence and viral load suppression in these sub-Saharan African and Haitian studies compare favorably to adherence and virologic outcomes in developed countries where studies report an adherence of seventy percent and viral load suppression to undetectable levels in fifty percent of patients on similar ART regimens.34,36,38-45 Overall survival in the Haitian and African studies was eighty-percent.

Adherence was generally higher among programs that provided ART free of charge, though this trend may or may not be statistically significant. Further studies should be conducted to determine those factors that contribute to adherence in non-DOT sub-Saharan African programs. Loss to follow-up also reflects this trend. Among programs that provided ART subsidies, loss to follow-up ranged from zero percent to 1.7%. Loss to follow-up ranged from twenty-four to forty-two percent in programs that provided no subsidy. Most studies reported unscheduled treatment interruption, most often owing to pharmacy stock shortages and lack of personal resources.

The average incidence of medication-related adverse events was ten percent, and most of these events were minor, such as gastric discomfort, not necessitating a discontinuation of therapy. No study reported any drug-related deaths.

**Discussion**
Results from these studies show clinical, virological, and immunological responses to antiretroviral therapy in sub-Saharan Africa and Haiti that compare favorably with those same responses in industrialized countries, despite differences in the HIV-1 subtype distribution in Africa and the fact that many of the sub-Sahara African studies enrolled a majority of patients with advanced disease. These studies suggest that ART interventions can be implemented in sub-Saharan Africa and Haiti, and can demonstrate improvements in surrogate markers for health outcomes, such as viral load, CD4 counts, and adherence.

Financial constraint emerged as the leading cause for non-adherence. Most studies reported unscheduled treatment interruption, most often owing to disruption in the provider’s drug supply (pharmacy stock shortages) or to lack of personal resources. Programs that provided medications, monitoring, and other care free of charge to patients achieved much greater rates of adherence. Adherence likely contributes to decreased viral resistance and has been shown to correlate with better virologic suppression and immune recovery and with decreased HIV-related morbidity and mortality. In those studies in which antiretroviral supply was assured, viral resistance rarely emerged. HAART was well-tolerated, at least in the short-term, in these studies.

Many individuals in sub-Saharan Africa who can afford ART medications already use them, sometimes sporadically, as individual resources allow. As drug prices continue to fall, more and more Africans are likely to use antiretrovirals, whether or not organized programs exist to ensure their proper prescription and use. Failure to establish organized well-maintained ART programs will likely
result in indiscriminate antiretroviral use that contributes to drug toxicity, sub-optimal clinical results, and the emergence of antiretroviral-resistant viral strains.

**Secondary benefits from ART**

Improvement of health care infrastructure in Africa and Haiti to facilitate the provision of ART will likely contribute to better health outcomes in other diseases, as well. The lack of infrastructure argument, however, should not be a deterrent to developing and implementing ART interventions. Instead, further research should be undertaken to evaluate these interventions for their effectiveness in settings of limited health infrastructure, and the optimal way of doing so would be through randomized controlled trials.

Perhaps most importantly, providing HIV treatment—a biomedical attempt to ameliorate a social as well as biological problem—may have even more profound positive secondary and tertiary psychological and societal effects. Providing treatment to the millions most in need not only fills an immediate need; it evens the playing field, reduces inequality, and brings into the fold those on the fringes of society, lifting them from the lowest rungs of the societal ladder to give them hope and a future.

HIV/AIDS decreases resistance to tuberculosis (TB), and the global spread of HIV threatens TB control efforts worldwide. HIV/AIDS dramatically increased the incidence of TB in sub-Saharan Africa, where up to sixty percent of TB patients are co-infected with HIV, and each year 200,000 TB deaths are attributable to HIV co-infection. HIV now threatens control of TB in Asia, Eastern Europe, and Latin America. Treating HIV with ART could therefore
secondarily aid TB control in developing countries. In addition, TB programs provide an important entry point for the treatment of HIV/AIDS, as was the case in the program evaluated in Haiti.

Factors contributing to program success

Several factors contribute to the success of the ART programs evaluated by the studies in this review. Perhaps most important are the free provision of an uninterrupted supply of ART medications and the availability of regular medical care. If ART is available, but not made affordable for the impoverished individuals who need it, or if HIV-infected individuals have no access to regular medical care, patients will not use the available medications, or may use them improperly or sporadically, possibly leading to resistant viral strains. Falling drug prices make the free provision of ART much more feasible. Because the presence of HIV infection is readily and well defined through HIV testing, patients are unlikely to overuse free HIV treatment services.

Strong public control and support are also required for successful ART expansion.17 Strict control of ART medications and close follow-up of patients will prevent illegal and inappropriate trade in the informal market that may lead to resistance.17,27 Guidelines should be in place before administering ART to prevent drug resistance, and a program must train health care workers how to administer antiretroviral medications effectively. Using existing TB programs as delivery mechanisms for ART, as in the ART program in Haiti, may facilitate the establishment or expansion of ART programs.
Follow-up and social support by pharmacists, physicians, other medical personnel, support groups, and social or community workers may also contribute to program effectiveness. In Haiti, Haitian patients value the moral support provided to their families, and may perceive those who use this tactful approach as better health care workers. The fact that caring community members administered the intervention, as opposed to culturally insensitive physicians or nurses, might partly explain the success of the program. It is possible that Haitian communities value their autonomy and might resist taking orders from an outside doctor, so that this community-led approach is more likely to be accepted and to produce better health outcomes than would be a rigid clinic-based system such as we have in the U.S. This is one example of an AIDS treatment program providing ART in an extremely impoverished area despite the lack of a developed health infrastructure.

A once a day regimen, such as that in Senegal, allows patient confidentiality to be more easily maintained, as the patient can take the medication at bedtime without the knowledge of other family members. Ease of administration and maintenance of confidentiality will likely increase adherence to ART. Adherence in the Senegalese one pill per day program was enhanced by the regimen’s simplicity, tolerability, and uninterrupted supply.

A thorough knowledge of the culture and health care system of the region, country, or community in which the program will operate will also greatly contribute a program’s success. Programs in different regions may look different, as they should be designed and adapted to use the existing strengths of the
national or local healthcare system and other attributes of the region to include local culture and leadership. A detailed, theoretically well-conceived program designed to deliver efficacious medications may prove clinically irrelevant and ineffective on the ground owing to simple yet grave oversights, even when great effort is made to incorporate all available information into the planning process. Therefore a program plan must be flexible and amenable to change once the program is put into practice.

The presence of the four Cs-- concern, commitment, competence, and continuity-- is essential for program success.49 These may come from government, national health officials, local leaders, or program leaders. A successful program conducted in a country such as Uganda where the four Cs are present will unlikely be as successful if carried out in Botswana or South Africa where the four C's may be absent and relatively little or no attention been given to HIV as a national health care priority. The Haiti study is important in that it shows an HIV program operating in a country where the four Cs are absent. A program designer should first find out to what degree the four Cs are present in a country or region before designing and implementing an HIV program or any program. If concern, commitment, competence, or continuity is lacking, an ART program leader may be able to provide the missing component or components, but he or she will almost certainly meet resistance to create a new environment in which a program will flourish. Program leaders in Haiti appear to have stepped in to fill a four Cs gap in a small, poor region in Haiti. Many such leaders will be
necessary in a country devoid of leadership, and program designers should be aware of this before establishing any program.

For the establishment and maintenance of a program designed to treat large numbers of people, a strong national government that recognizes a problem and commits itself to solving it is indispensable. A few countries in sub-Saharan Africa, such as Uganda, may provide this favorable environment, while many may not. A small, isolated program, such as that in Haiti, will experience problems with its prevention efforts, as it cannot influence what goes on in larger cities where many rural inhabitants go to work. Local prevention efforts do little to prevent people from going to the city and bringing HIV back home.

**Barriers to overcome**

Even with recent price decreases, the price of antiretroviral medications is still a major issue for Haiti and the countries of sub-Saharan Africa with limited health care budgets. Countries must create supply and distribution networks for antiretroviral and other medications and laboratory materials to facilitate adherence. The diagnosis and treatment of opportunistic infections is deficient in many parts of Africa and Haiti. Many patients in these studies came for treatment late in the course of their disease. Frequent use of less effective lower cost 2NRTI regimens for patients with advanced stages of disease may compromise clinical response to ART. The marginal cost of a third drug required for HAART was unaffordable for many, even for the relatively wealthy patients in these studies.
The high costs of laboratory monitoring also presents a potential barrier to ART programs. As with ART, the price of laboratory testing is dropping. Former President Bill Clinton recently announced a deal he negotiated with five companies that manufacture laboratory tests. One of the companies, Becton, Dickinson & Co., reduced the cost of its CD4+ cell count from $10 to $3.19

Woefully inadequate healthcare infrastructure in Haiti and sub-Saharan Africa is a reality. Most of the studies reviewed in this paper were conducted in the best medical centers of the respective participating countries. The existing infrastructure in the surrounding areas may not support the expansion of the ART programs. The Haiti program operates in one of the poorest regions of Haiti. It builds, however, on an already successful non-government organization (NGO) TB treatment program in place for years before it began providing ART to HIV patients. Haiti and the countries in sub-Saharan Africa likely need to expand and improve their healthcare infrastructure to facilitate the provision ART or any other therapy, though the existing infrastructure supports TB therapy to some extent.

Perhaps the most formidable barriers to the provision of ART in Haiti and sub-Saharan Africa are the absence of “the four C’s:” concern, commitment, competence, and continuity. Until recently, many sub-Saharan African leaders denied or ignored HIV as a major problem in their respective countries. Until leaders acknowledge HIV/AIDS as a problem, they cannot begin to develop solutions.
Current discourse at international forums and the formation of organizations and initiatives such as UNAIDS, the Global Fund, and the 3X5 Initiative reflect an increasing concern for the millions of HIV/AIDS patients in the poorest areas of the world and a commitment to reduce the inequalities of ART availability. Remaining to be seen, however, is if the global community is competent to treat HIV/AIDS in poor areas of the world and if it can provide the continuity to ensure the success of providing ART to those most in need.

**Antiretroviral therapy only a partial fix**

Uncontrolled spread of infection marks societies with woefully deficient resources and minimal exposure to disease prevention education, though a country’s HIV epidemic could start anywhere for reasons that have nothing to do with poverty. The disease was initially spread among homosexual men in the U.S., and through the jet-set in Brazil, but no matter how HIV enters a country, HIV infection travels downhill along a common pathway of least resistance to settle among the most marginalized. The disease was initially spread among homosexual men in the U.S., and through the jet-set in Brazil, but no matter how it enters a country, it travels downhill along a common pathway of least resistance to settle among the most marginalized. HIV/AIDS tracks along social fault-lines to find the poor. Poverty and inequality are the risk factors most strongly associated with HIV infection and AIDS-related mortality.

HIV/AIDS is a dye that stains the world for the presence of poverty and inequality. Where there is HIV, there is poverty and inequality. The entrenchment and uncontrolled spread of HIV/AIDS in impoverished areas is a symptom, a surrogate marker for deeper societal and global problems that existed long before the HIV/AIDS pandemic. The pandemic merely paints the earth and
allows us to epidemiologically map the location of these more fundamental problems.

Successful HIV treatment, or even the development of an effective vaccine, solves only the surface problem. Malaria, TB, and other diseases still stain the impoverished and the marginalized. Other diseases are likely to emerge, as well. Further technological advances will have minimal impact if national and international leaders fail to address the deeper societal issues affecting disease management.

**Future Research**

Most studies examine only ART-naïve patients infected with HIV-1. Future research should concentrate on HIV-2 infected individuals and on ART-experienced patients, as well, as these patients represent a significant portion of the populations of sub-Saharan Africa. A small, limited study by Adjé-Touré, *et al.* in Côte d'Ivoire (not included in this review) of HIV-2 patients receiving ART showed nelfinavir-containing ART regimens may have little or no immunovirologic effect on patients infected with HIV-2. Further studies should identify those ART regimens effective against HIV-2.

The short duration of these studies may fail to demonstrate possible antiretroviral drug intolerance and the development of antiretroviral resistant HIV strains. Future longer-term studies may reveal drug intolerance to be an adherence issue, as it already is in industrialized nations. Therapeutic cohort studies should also study long-term survival, morbidity, immunovirological response, and drug resistance in sub-Saharan Africa and Haiti.
Farmer, et. al. advocate the use of DOT for the provision of antiretroviral drugs in resource-poor settings\textsuperscript{9}, though evidence for the superiority of DOT versus non-DOT treatment is limited.\textsuperscript{56} For example, Orrell, et. al. in South Africa reported eighty-seven percent adherence without DOT. One might argue that DOT might have resulted in even greater adherence. Randomized control trials should be conducted, using HAART as the standard of care, to compare DOT programs versus non-DOT programs. Randomized trials should also compare programs that provide different mixtures of social and financial support to determine which supplementary interventions prove most effective and feasible. Differences in the way a program is designed and administered may make larger differences in treatment outcomes than do choices of specific antiretroviral combinations, though research should continue to sort out which drug combinations provide the greatest benefit, given the prevalence of HIV-2 and many HIV-1 subtypes in sub-Saharan Africa not found in other areas of the world.

Limitations of this systematic review

Ideally two other readers would independently review the titles and abstracts of the 128 articles identified by the literature search. Those articles the independent reviewers agreed did not meet eligibility criteria would be excluded. If the initial reviewers disagreed, the investigators would carry the full text articles to the next review stage in which the investigators would review the full text articles and make a final decision about inclusion or exclusion by consensus.
The primary investigator alone selected articles for inclusion in the review and abstracted relevant information from each article and placed it into evidence tables. Ideally, two independent investigators would perform this information abstraction. One reviewer would have abstracted the relevant information and placed it into the evidence tables, and a second investigator would then check these tables and note any discrepancies, which would then be resolved by consensus. Owing to the limited resources available for the production of this systematic review, the primary investigator carried out the above review process.

Limitations of this review also include the investigator’s limited experience in Africa and Haiti and relative unfamiliarity with the history, politics, economics, health care systems, and culture of Haiti and sub-Saharan African countries.

**Conclusion**

Antiretroviral therapy programs in sub-Saharan Africa and Haiti achieved similar health outcomes as did treatment programs in wealthier Western countries. These studies suggest that ART works in African patients. The major issue is how to expand existing programs and establish new ones to get the medications to those in need. Free access to uninterrupted antiretroviral medications and regular access to a primary care provider are essential to success of any ART program in these resource-poor areas. International and national concern, commitment, competence, and continuity on the behalf of political, health, and community leaders will greatly increase the likelihood of success of the difficult undertaking to provide ART millions in need of it.
"In war it is the things which are thought impossible which most often succeed, when they are well conducted."---Eighteenth century general

Acknowledgment

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References


28. Castro KG WI, Slutsker L, Buehler JW, Jaffe HW, Berkelman RL. 1993 Revised classification for HIV infection and expanded surveillance case


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<table>
<thead>
<tr>
<th>Author, year, location</th>
<th>Study Design</th>
<th>Study Setting</th>
<th>ART Intervention (n)</th>
<th>Delivery method</th>
<th>Intervention Duration</th>
<th>Free or Patient Pays for Drugs (% subsidy)</th>
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<th>Loss to Follow-up</th>
<th>ITT</th>
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<tr>
<td>Djomand, et al. 2003 Abidjan, Côte d'Ivoire</td>
<td>Retrospective case series</td>
<td>Tertiary care Outpatient clinics</td>
<td>HAART (276) 2NRTI (204)</td>
<td>Central pharmacy</td>
<td>NS</td>
<td>50-95% subsidy</td>
<td>480</td>
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<td>Seyler, et al. 2003 Abidjan, Côte d'Ivoire</td>
<td>Prospective case series</td>
<td>Clinical research Center</td>
<td>HAART (90) 2NRTI (11)</td>
<td>Central pharmacy</td>
<td>Median (IQR) 17 months (13-30)</td>
<td>90% subsidy; then 100% for poorest after Jan 2001</td>
<td>101</td>
<td>0%</td>
<td>NS</td>
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<td>Weidle, et al. 2002 Kampala, Uganda</td>
<td>Case series</td>
<td>5 centers in/near Kampala</td>
<td>HAART (29) 2NRTI (74)</td>
<td>NS</td>
<td>Median (IQR) HAART 94d (33-278) 2NRTI 152d (28-385)</td>
<td>No subsidy</td>
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<td>Research center</td>
<td>HAART (16) 2NRTI (9)</td>
<td>NS</td>
<td>HAART: EFV 30.6 +/-5.9 wks IDV 30.8 +/-4.7 wks 2NRTI: 30 +/-9.7wks</td>
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<td>Non-DOT One pill/day Central pharmacy</td>
<td>15 months</td>
<td>NS</td>
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<td>Prospective case series</td>
<td></td>
<td>HAART (58)</td>
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<td>University HIV HIV clinics</td>
<td>HAART (244) 2NRTI (45)</td>
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<td>100% subsidy</td>
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<td>0%</td>
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<td>Hosseinipour, et al., 2004 Lilongwe, Malawi</td>
<td>Retrospective case series</td>
<td>Lilongwe Central Hospital</td>
<td>HAART (625)</td>
<td>NS</td>
<td>Median (IQR) ART: 201 d (49-337)</td>
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<td>625</td>
<td>42%</td>
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<td>Farmer, et al., 2001 Central Plateau, Haiti</td>
<td>Case series</td>
<td>Rural clinic</td>
<td>HAART (60)</td>
<td>DOT-HAART by community health worker</td>
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NS = not specified
ITT = intent to treat
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<tr>
<th>Author, year, location</th>
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<th>Baseline ART status</th>
<th>Base CD4 (x10^6/L)</th>
<th>Baseline Viral Load (copies/mL)</th>
<th>Mean log10 change VL</th>
<th>CD4 chg Probability of Survival</th>
<th>Adherence Drug Events</th>
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<tr>
<td>Djomand, et al., 2003</td>
<td>480</td>
<td>ART-naive 100%</td>
<td>&lt;200 n=331 &gt;200 n=127 missing=22</td>
<td>50% at 1 yr (&lt;200 copies/ml)</td>
<td>↓1.9 at 1 yr.</td>
<td>0.84 1yr</td>
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<td>NS</td>
<td>&lt;50 n=21 &gt;50 n=73 missing=7</td>
<td>51% at 1 yr</td>
<td>NS</td>
<td>↑115 1 yr</td>
<td>By base CD4</td>
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<td>Weidle, et al., 2002</td>
<td>103</td>
<td>HAART: 57% naïve 2NRTI: 65% naïve</td>
<td>Median HAART 78 2NRTI 55</td>
<td>HAART: 39% 1yr 2NRTI: 24% 1yr (&lt;400 copies/ml)</td>
<td>At 1 year: HAART: ↓1.5 2NRTI: ↓0.3</td>
<td>0.74 1 yr</td>
<td>6 mo. 0.77 1 yr. 0.67</td>
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<td>Kebba, et al., 2002</td>
<td>25</td>
<td>ART-naive 100%</td>
<td>Mean 164 5.4 (+/- 0.4)</td>
<td>70% at 1 year 77% at 15 months (&lt;50 copies/ml)</td>
<td>↓3.4 at 15 mo</td>
<td>199 NS</td>
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<td>40</td>
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<td>58</td>
<td>ART-naive 100%</td>
<td>Median 109 50 (28-117)</td>
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<td>↓2.3 at 12 mo</td>
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<td>625</td>
<td>47% naïve</td>
<td>Median 70 55</td>
<td>86% (time NS)</td>
<td>NS</td>
<td>NS</td>
<td>NS Major: 25</td>
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<td>NS</td>
<td>86% (time NS)</td>
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<tr>
<td>Total (n)</td>
<td>1781</td>
<td>37% naïve</td>
<td>65%* (935)</td>
<td>1.83* (681)</td>
<td>123 (1244) 0.82* (735)</td>
<td>83%* (432)</td>
<td>10%</td>
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NS= not specified
EFV = efavirenz
IDV = indinavir

*calculated from data closest to one year, weighted for number of participants with values.