HIV/AIDS Care and Treatment in sub-Saharan Africa

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Abstract

Antiretroviral (ARV) drugs have become the cornerstone of care and treatment for AIDS in North America, Brazil, and Europe. Twenty years into the epidemic, and more than 10 years after the introduction of ARV's, effective global treatment of AIDS, particularly in sub-Saharan Africa where the epidemic is most concentrated, is an extraordinary challenge. Guidelines and experience in anti-microbial prophylaxis, prescription and monitoring of ARV's in resource-rich countries should inform the efforts to scale-up AIDS care and treatment in Africa. Here, we review the considerable experience of ARV treatment acquired largely in the Americas and Europe, and the fledgling clinical trials and observational studies in Africa. Implementation of safe, effective, and equitable access to ARV's in Africa should be cognizant of the guidelines for ARV treatment in the Northern countries. Careful observation and operational research to accrue more African data, and evaluate regional and local solutions to this daunting challenge, will identify new approaches to scaling-up of ARV treatment.

Key words

Africa. Antiretroviral therapy. Drug resistance.

Introduction

The HIV/AIDS epidemic in sub-Saharan Africa has reached catastrophic proportions. AIDS has become the leading cause of death among adults and children in many sub-Saharan African countries. In 2001, 2.2 million Africans died of AIDS-related illnesses and 3.5 million Africans were newly infected with the virus. Seven countries reported HIV prevalence rates over 20% in the year 2002[1]. Although there have been encouraging reports of decreased rates of infection among women in Uganda, Zambia, South Africa, and certain parts of Ethiopia, prevalence rates in most sub-Saharan African countries continue to rise[2].

Mortality and morbidity rates may be attributed to common opportunistic infections associated with immunodeficiency, most prominently a sharp increase in disease due to *Mycobacterium tuberculosis* (TB)[3]. In the absence of prophylaxis against opportunistic infections and antiretroviral therapy (ART), adults and children with advanced AIDS rarely survive more than two years[4,5]. The vast majority of those infected in sub-Saharan Africa are unable to access diagnostic tests, adequate prevention, or HIV/AIDS care. High rates of HIV infection are accompanied by sustained transmission. There are far-reaching social and demographic ramifications for severely affected countries, including orphaned children (who in some nations exceed one million in number[1]), decreased skilled labor[6], and political and economic instability[7,8]. Each of

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these elements creates further strains on health systems, dramatically lowering life expectancies.

There are clear barriers to the implementation of effective AIDS care and treatment in sub-Saharan African nations[9], including limited numbers of trained personnel, inadequate or nonexistent laboratory, clinical, and administrative infrastructure, alongside the daunting costs and logistics of providing and monitoring prophylactic and ARV drugs. Some have argued, on the basis of cost-effectiveness, that prevention measures should be the focus of international efforts on HIV in resource-limited countries[10]. Thus, resources have been directed towards population-based prevention interventions. However, there are compelling moral, economic, and practical arguments for the introduction of active treatment programs[11]. The United Nations General Assembly Special Session (UNGASS) resolutions in 2001, led by Secretary General Kofi Annan, called for global funding for AIDS, TB and malaria, and included a substantial treatment component[12]. Recent commitments by the United States government of $2 billion dollars per year for treatment in sub-Saharan Africa are aimed at providing treatment to nearly two million people in Africa and the Caribbean[13]. These programs alone are expected to increase by more than 100-fold the number of people who will have access to treatment.

The large burden of disease posed by the AIDS epidemic in Africa requires a multisectoral and multidisciplinary approach. Many social programs to increase HIV/AIDS awareness and influence behavior change are active in most sub-Saharan African countries. Diagnostic capacity and prevention measures to reduce transfusion-associated and iatrogenic disease transmission are increasingly being addressed. Antiretroviral therapies to prevent mother-to-child transmission have gained widespread acceptance. Providing single-dose or short-course ART lowers mother-to-child transmission of HIV infection by 50% and has in theory been embraced by most parties, but is not widely practiced[14-18]. While barrier methods and behavior modification are key elements in decreasing the risk of horizontal transmission of HIV, data which support lower infectivity associated with lower plasma HIV viral load provide a rationale for ART as a plausible additional preventive method to reduce horizontal transmission[19]. Regardless of policy decisions, the increasing availability of low-cost ARV's and antimicrobials, and the demand generated by millions of patients, will result in an enormous increase in ARV use. While the optimal use of ARV's in HIV infection, particularly in Africa, has not been systematically addressed, incorporating the experience of more than five years of highly active antiretroviral therapy (HAART) in developed countries may inform the complex task of providing care to those infected, as well as reducing the propagation and impact of the epidemic.

In this review, data from studies in Africa, and evolving guidelines for the use of antiretroviral therapy in non-pregnant adults, are considered. With new drugs and growing experience, guidelines are annually reformulated in the US and Europe and, recently, the World Health Organization (WHO) has developed guidelines for "scaling-up antiretroviral therapy in resource-limited countries"[20]. The recommendations in evolution address questions which remain, for the clinician, patient, and policy maker, the fundamental issues in ARV treatment: when to start ARV's, which combinations to use, when to change therapy, and how to monitor patients.

Natural history of HIV in Africa and effect of chemoprophylaxis

Several cohort studies have looked at the natural history of HIV infection in different African countries. While some studies have suggested a more rapid progression of disease in the sub-Saharan African context[4,21,22], other studies have found survival after seroconversion to be comparable to that seen in developed countries prior to the wide-spread use of HAART[23]. Certain AIDS-defining illnesses, such as wasting syndrome, esophageal candidiasis and Kaposi's sarcoma, are associated with more rapid progression to death (3-4 month survival) compared to others such as chronic herpes simplex virus infections or extrapulmonary tuberculosis[23].

The role of viral subtype as well as variable genetic host factors have also been entertained as factors contributing to variable rates of disease progression[24]. However, there is little reliable data that directly compares disease progression between Africans and non-Africans infected with different subtypes of HIV-1. In one well-characterized sex-worker cohort in Senegal, there is evidence of more rapid progression of disease in those infected with subtypes C or D compared to those infected with subtype-A infection, with over an eightfold risk of developing AIDS in those with non-subtype-A infection[25]. Another study in Uganda similarly found more rapid progression of disease in those infected with subtype-D virus compared to those infected with subtype-A virus[24]. Some *in vitro* studies have shown variable responses and mutation patterns to antiretroviral drugs between B and non-B HIV-1 virus[26], but small studies in London and Denmark have not found differences in pathogenesis or response to HAART between African and non-African patients infected with B and non-B HIV-1 virus early in the course of treatment[27-29]. The study in London did find that, after initial virologic suppression, there was a tenfold increase in viral load among Africans with virologic failure. However, African patients in the London study had a statistically significant lower CD4+ lymphocyte count compared to their European counterparts at the initiation of ART (140 vs 240 CD4+ lymphocyte count per mm[3]), but showed equivalent increases in CD4+ lymphocyte count on treatment. The authors additionally surmise that adherence to therapy may have contributed to the divergence of virologic response to HAART. Treatment of a cohort of patients with B and non-B HIV-1 virus with HAART in Belgium also showed a similar virologic response; but among patients with non-B virus, particularly in subtype A and circulating recombinant forms (CRF's) which included subtype A, there was a significantly lower CD4+ lymphocyte recovery

compared to patients with subtype-B virus (an increase in median CD4+ lymphocyte count per mm cu of 161 vs 235 at 24 months, p < 0.02)[30].

The natural history of HIV/AIDS can be altered by the use of prophylactic medications, and interventions to prevent commonly occurring opportunistic infections have become the standard of care in Western countries. Studies from Ivory Coast have demonstrated the clinical benefit of cotrimoxazole chemoprophylaxis in HIV-1 infected patients, including in patients with CD4+ lymphocyte counts >200 per cu mm, as well as in patients with HIV/TB co-infection[31,32]. Such findings prompted the recommendations made by the WHO/UNAIDS secretariat to initiate cotrimoxazole chemoprophylaxis in patients with symptomatic HIV (WHO clinical stage 2-4), asymptomatic patients with CD4+ lymphocyte cell counts <500 per cu mm, and pregnant women after the first trimester of pregnancy[33]. While this has somewhat become the yardstick against which alternate practices are measured, a Senegalese pilot study that randomized subjects with CD4+ lymphocyte counts <400 per cu mm to receive single-strength cotrimoxazole or placebo was not able to demonstrate a survival benefit, though the study was discontinued prematurely based on the findings from Ivory Coast[34]. The use of cotrimoxazole in those with advanced disease makes theoretical sense, while the fact that some of the illnesses prevented by use of this agent commonly occur at CD4+ lymphocyte counts greater than 200 per cu mm makes its earlier administration somewhat attractive[35]. The potential benefits of early chemoprophylaxis with cotrimoxazole need to be weighed against the possible emergence of microbial resistance to this useful, affordable, and typically widely-available agent. The optimal use of cotrimoxazole prophylaxis will need to be determined on a regional basis.

The use of isoniazid (INH) chemoprophylaxis in patients with latent tuberculosis infection (LTBI) can also help prevent the morbidity and mortality associated with active tuberculosis infection, the most common co-infection that has associated high morbidity and mortality[3,36]. However, the duration of therapy needed in areas where tuberculosis infection is endemic, and where the risk of re-exposure is high, is unclear. Studies that have examined INH prophylaxis in LTBI have cited the cost of ensuring the absence of active disease as a potential limitation to widespread implementation of INH chemoprophylaxis[37]. Indeed, the impact on disease progression and drug resistance of tuberculosis with the use of INH in this setting is yet to be determined. The potential benefit of HAART in preventing development of active tuberculosis in patients with advanced HIV disease has been shown in a South African cohort[38], and increased use of HAART in resource-limited settings may have a significant impact on the incidence of active tuberculosis. Risk of relapse after initial treatment of active tuberculosis is significant, and the need and potential benefit for secondary prophylaxis after treatment of active tuberculosis is an area that requires further investigation[39].

When to initiate antiretroviral therapy

The goals of pharmacotherapy for individuals with HIV disease are reduction in virus replication, immune restoration, and the prevention of opportunistic infections associated with immunodeficiency. The population goals of AIDS treatment include reduction in mortality, health care costs, morbidity, and the transmission (incidence) of HIV infection. Based on the potential for cumulative toxicities, and the observation that a substantial percentage of patients fail their first ARV therapy secondary to development of resistance to one or more drugs, there has been a shift towards a more conservative stance in the initiation of ART. Issues of medication-related toxicity, inconvenience, presence of untreated opportunistic infections, and the potential for emergence of drug resistance, should all be factored into the decision of when to initiate antiretroviral therapy[40].

Among HIV infected adults, the risk of clinical progression and mortality is directly related to both CD4 cell count and viral load[41,42], with the same laboratory markers being useful in anticipating progression in the setting of ART[43]. In the US and Europe, where HAART is readily accessible, accelerated progression to the development of AIDS-defining illnesses is seen if HAART is initiated after the CD4+ lymphocyte cell falls below 200 per mm[3] rather than if HAART is initiated at a CD4+ lymphocyte count between 200-350 per mm[3]; no survival benefit is derived by initiating HAART at CD4+ lymphocyte counts >350 per ml[44-48]. Initiation of HAART after development of an AIDS-defining illness, or with a plasma HIV-1 RNA level >50,000-100,000 copies/ml, is also associated with a worse prognosis[44,47]. Along with the baseline CD4+ lymphocyte count and viral load at the initiation of therapy, key ingredients that have also been found to affect survival include the combinations of ART used, adherence, and demographic and socioeconomic differences that affect ability to access care[45,49,50]. Despite immunologic benefit with delayed onset of AIDS-defining illnesses in those treated with HAART, the significant numbers of those who require treatment interruption due to drug intolerance and side effects (35% in the Swiss cohort) underscores the importance of appropriate follow-up and monitoring in patients who are initiated on HAART[46].

The widest experience of chronic antiretroviral therapy originates from resource-rich settings, and treatment guidelines from the US, Britain, Brazil, and the WHO, are contrasted in table 1[20,51-53]. Sophisticated tools such as CD4+ lymphocyte cell counts and HIV-1 plasma RNA levels are unlikely to be accessible to most patients in resource-limited settings. The WHO guidelines offer guidance regarding therapy based on both clinical grounds as well as on laboratory values using the WHO staging system for HIV infection and disease[20,54], recorded in table 2. In areas where CD4+ lymphocyte-count testing is available, the recommendations are that therapy be initiated in those with WHO Stage IV (regardless of the CD4 cell count), and in those with stage I, II, or

Table 1. When to initiate therapy: antiretroviral treatment recommendations based on laboratory and clinical markers of HIV-1 infection

Country/Organization	CD4+ lymphocyte count per mm^3	Viral load (HIV-RNA copies/ml)	Total lymphocyte count	Clinical symptoms / Other
WHO (2002)[3]	<200		<1200 + WHO stage II or III	Symptomatic HIV or WHO clinical Stage II-IV
US DHHS/ CDC	<350	>55,000	NA	Symptomatic HIV
International AIDS Society – USA Panel	<200 >200 with rapidly declining CD4 count (>100/yr) and <350[1]	>50,000	NA	Willingness to adhere to therapy
British HIV Association	<200 <350 – consider treatment >350 – defer treatment regardless of viral load, if asymptomatic	>55,000 (except if CD4 count >350/mm^3 and asymptomatic)	NA	
Brazil – Ministry of Health	<350 >350 <500 – initiate Rx if VL >30,000	>100,000[2]		HIV-associated clinical manifestations

[1]Some practitioners use CD4+ lymphocyte count <350 per mm^3 as 'threshold' to initiate treatment
[2]If concurrent high CD4+ lymphocyte count (>500 per mm^3), consider close monitoring and initiate ARV when there is a rapid decrease in the CD4+ lymphocyte count
[3]A revised draft version (2003) of the WHO treatment guidelines is currently available for public consultation at the following web address http://www.who.int/hiv/pub/prev_care/draft/en/

III, with a CD4 cell count <200 per mm^3. Where CD4 cell-count testing is not available, the suggestion is to start ART in those with symptoms, and in those with a total lymphocyte count (TLC) <1200 per mm^3. If adjunctive laboratory testing is not available, treatment of those without symptoms is deferred[20].

Several studies have examined the validity of the WHO clinical staging system as a prognostic indicator[22,55]. Though different diagnoses in the later WHO clinical stages have variable risks of death, in those with advanced disease the decision to initiate ART is not affected by these differences, as the presence of clinical stage III or IV defining illnesses would warrant initiation of HAART. Combining the TLC as a laboratory adjunct to clinical staging may improve the prognostic of clinical evaluation, but was not found to be associated with mortality in a predictable manner[22,55]. Substitution of TLC as a marker for CD4+ lymphocyte count can be problematic due to the limited sensitivity of this test[56]. When US guidelines (CD4 and HIV-RNA) were compared to WHO clinical stage supplemented with adjunctive, simple markers for disease risk such as hemoglobin, total lymphocyte count, and body mass index (BMI) in an Ethiopian cohort, application of the WHO guidelines would have led to half the number of people being treated with ART[57]. It is hard to determine whether this represents 'undertreatment' using the WHO guidelines, or 'overtreatment' when applying guidelines from resource-rich areas of the world.

Another study in an Ethiopian cohort found that 17% of patients in WHO clinical stage I had CD4+ lymphocyte cell counts <200 per mm^3 (and hence were eligible for receipt of antiretroviral therapy by laboratory criteria) despite presenting without symptoms[58]. However, imminent risk of disease progression with one or more AIDS-related symptoms may be greater at these lower CD4+ lymphocyte counts, and symptomatic patients are more likely to seek medical treatment[60,61]. Because the numbers 'eligible' for therapy using surrogate-marker guidelines far exceeds the available resources, it is likely that patients with clinical illness and HIV-related symptoms will be the first to seek treatment, and that treatment programs will largely be driven by demand from patients with clinical illness. Increased voluntary counseling and testing is likely to result in diagnosis of HIV infection at earlier stages of disease, potentially increasing the pool of patients who will require treatment[59]. Expanding treatment policies in Africa will need to balance treatment access and monitoring with limited resources in diverse economic and health-care settings. Antiretroviral treatment will initially be limited to those with the greatest risk of immediate mortality (WHO clinical stage III or IV), who are nonetheless ambulatory and have family support to participate in follow-up and monitoring that are critical to successful pharmacotherapy.

What ART should be initiated?

Through the efforts of 'ethical' or 'innovator' pharmaceutical companies (those with patent rights for licensed drugs) and the growing production of generic medications, the cost of ART has been significantly reduced[9]. The costs, availability, and regulatory approval of ARV's in individual countries are in rapid flux, but an increasing number of branded and generic ARV's are becoming acces-

Table 2. WHO staging system for HIV infection and disease in adults and adolescents

Clinical stage I
 1. Asymptomatic
 2. Persistent generalized lymphadenopathy
Performance scale 1: asymptomatic, normal activity

Clinical stage II
 3. Weight loss, <10% of body weight
 4. Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
 5. Herpes zoster within the last five years
 6. Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)
And/or performance scale 2: symptomatic, normal activity

Clinical stage III
 7. Weight loss, >10% of body weight
 8. Unexplained chronic diarrhea, >1 month
 9. Unexplained prolonged fever (intermittent or constant), >1 month
10. Oral candidiasis (thrush)
11. Oral hairy leukoplakia
12. Pulmonary tuberculosis within the past year
13. Severe bacterial infections (i.e. pneumonia, pyomyositis)
And/or performance scale 3: bedridden <50% of the day during the last month

Clinical stage IV
14. HIV wasting syndrome, as defined by the Centers for Disease Control and Prevention[1]
15. *Pneumocystis carinii* pneumonia
16. Toxoplasmosis of the brain
17. Cryptosporidiosis with diarrhea > 1 month
18. Cryptococcosis, extrapulmonary
19. Cytomegalovirus disease of an organ other than liver, spleen or lymph nodes
20. Herpes simplex virus infection, mucocutaneous > 1 month, or visceral any duration
21. Progressive multifocal leukoencephalopathy
22. Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis)
23. Candidiasis of the esophagus, trachea, bronchi, or lungs
24. Atypical mycobacteriosis, disseminated
25. Non-typhoid *Salmonella* septicemia
26. Extrapulmonary tuberculosis
27. Lymphoma
28. Kaposi's sarcoma
29. HIV encephalopathy, as defined by the Centers for Disease Control and Prevention[2]
And/or performance scale 4: bedridden >50% of the day during the last month

[1]HIV wasting syndrome: weight loss of >10% of body weight, plus either unexplained chronic diarrhea (>1 month) or chronic weakness and unexplained prolonged fever (>1 month)
[2]HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings

sible. Given the significant cost differential between generic and patented medications, the use of generic medications is likely to be an integral part of treatment programs in sub-Saharan African countries. Though concerns regarding the equivalence of generic medications to patented antiretroviral medications exist, rigorous studies looking at *in vivo* activity of generic medications compared to patented drugs have not yet been performed.

The first treatment regimen has the highest likelihood of success[62], and thus, the choice of the first antiretroviral regimen is of utmost importance. There are currently 20 commercially available antiretroviral medications. Of these, 12 are on the WHO Essential Drug List, and 13 are incorporated in the 2002 WHO guidelines for ART[20]. The basic regimen that is suggested for HIV infection in non-pregnant adults (and excluding HIV-1 group O and HIV-2, which are inherently resistant to NNRTI's[63]) is a three-drug regimen that includes dual nucleoside reverse transcriptase inhibitors (NRTI's) with one of three options: 1) a third NRTI, abacavir (ABC); 2) a protease inhibitor (PI) with or without low-dose ritonavir as a second PI to 'boost' PI levels, or 3) an NNRTI, except in settings where HIV-2 and group O viruses are prevalent. Based on ease of administration and relative tolerability, the preferred 'backbone' NRTI combination is zidovudine (AZT) with epivir (3TC), especially as this is available as a fixed-dose combination. Alternative dual-NRTI backbone regimens include stavudine (d4T) + 3TC, AZT + didanosine (DDI), and DDI + 3TC. The recently licensed nucleoside emtribacine (FTC) and the nucleotide tenofovir are effective, once daily, and will, in time, become available in combination form[64].

Full-dose combinations (where multiple drugs are included in one pill) and limiting pill-burden can improve adherence, a key element in successful treatment[50,58]. The combination of AZT + 3TC + ABC is available in combination form, and its use as a triple-nucleoside-based HAART allows for preservation of susceptibility to other classes of antiretrovirals in case of failure of this drug regimen. However, this triple-nucleoside regimen may be less potent than regimens containing an NNRTI[65,66]. Recent data in treatment-naive patients, comparing the efficacy of abacavir to efavirenz or efavirenz + abacavir with a nucleoside backbone of AZT/3TC in all three arms, showed earlier virologic failure (rebound viremia to >200 copies/ml >16 weeks after randomization) in the abacavir treatment arm (21% in the abacavir arm vs 10% in the pooled efavirenz-based regimen); at 48 weeks, 74% of the abacavir treatment arm had a viral load <200 copies/ml compared to 89% in the pooled efavirenz group[67]. The success rate with either the abacavir- or efavirenz-based regimens in this study is quite high, but the seeming superiority of the efavirenz-based treatment has prompted some to reconsider the initial use of this triple-nucleoside regimen. In addition to hypersensitivity reactions that can be seen with ABC use, documented side effects of NRTI's include anemia and neutropenia, lactic acidosis, neuropathy, and myopathy.

Of the protease inhibitors, nelfinavir can be given twice daily without ritonavir pharmaco-enhancement (boosting), but other PI's require low-dose ritonavir boosting to decrease the dosing to once or twice daily rather than three times a day. This leads to concerns about the large-scale use of ritonavir-boosted regimens, given the requirement for refrig-

eration of ritonavir to maintain stability beyond thirty days. Ritonavir-boosted indinavir, saquinavir, and the combination agent lopinavir/ritonavir (available in a combined form as Kaletra) with the two nucleosides Zerit (D4T) and epivir (3TC) are superior to nelfinavir in lowering plasma HIV-RNA below 400 copies/ml, making boosted PI's an attractive option[69,70]. Recent data from Ivory Coast, albeit in small numbers, suggest a poor virologic response of HIV-2 to HAART with nelfinavir, compared to more favorable results seen with the use of indinavir[71]. The long-term side effects with this class of medications include metabolic abnormalities such as hyperglycemia, hyperlipidemia, and lipodystrophies. Gastrointestinal disturbance and some degree of diarrhea are also common. Indinavir is specifically associated with nephrolithiasis, which may be exacerbated by heat and lack of continued access to hydration. The most recently FDA-approved PI, atazanavir (ATV), provides a once-daily dosing regimen with a lower risk of development of drug-associated hyperlipidemia, although this drug is associated with hyperbilirubinemia and jaundice[72]. ATV is one of the few recently licensed drugs in which pivotal studies were performed, in part, in Africa, providing a basis for assurance of effectiveness in non-subtype B viral infections.

Efavirenz is a potent once-daily NNRTI, which with a two-NRTI backbone is as effective in virologic suppression as a PI-based regimen using nelfinavir or indinavir[68,73,74]. Efavirenz is a potential teratogen, and can decrease the efficacy of oral contraceptive medications and so should be administered with caution to women with childbearing potential. Nevirapine is a NNRTI with similar efficacy to efavirenz, is safe during pregnancy, but has shown a higher incidence of side effects that include rash and hepatotoxicity[75]. Nevirapine is likely to be used widely in resource-limited settings as a generic formulation combined with two-NRTI's (NVP + d4T + 3TC), providing HAART with a very low pill-burden.

Many patients with AIDS present with TB[3], and the issue of co-administration of anti-tuberculous medications and HAART is challenging. Managing drug interactions and toxicities in ill patients receiving three antiretrovirals, cotrimoxazole, and three anti-tuberculous drugs, may be difficult. Levels of most protease inhibitors are decreased by co-administration of rifampin, and rifabutin is substituted in the setting of PI use in resource-rich settings, with improved survival[76]. However, this is not a widely-affordable option. If a PI is chosen in the setting of HIV and TB co-infection, there is limited data showing that saquinavir with ritonavir boosting can overcome rifampin-induced sub-therapeutic levels[77]. Though rifampin has also been shown to decrease NNRTI levels, a study evaluating the use of rifampicin with an efavirenz-based HAART regimen in India was able to demonstrate effective treatment of HIV/TB co-infection, with a higher increase in CD4+ count in the co-infected group than in the patients being treated for HIV alone[78]. Nevirapine levels are decreased when co-administered with rifampin; however, successful treatment of HIV/TB co-infection has been demonstrated in practice, albeit in small numbers of patients[79,80]. Because of the side effects of nevirapine, which include hepatotoxicity and rash, efavirenz may be preferred over nevirapine as an NNRTI during treatment of HIV/TB co-infection. Overall, in stable patients with CD4+ lymphocyte counts >100 per cu mm, most practitioners defer ART until completion of at least the first 'intensive' stage of anti-tuberculous treatment[81], avoiding the co-administration of seven drugs (including cotrimoxazole). Trials to identify the optimal sequence versus simultaneous use of ART in the setting of acute opportunistic infections (OI's), including but not limited to TB, are critical given that many individuals present late in disease with OI's, which are also indications for treatment with ART[3].

Antiretroviral therapy – the sub-Saharan African experience

Is HAART as efficacious in non-B subtype virus infection in sub-Saharan Africa as it is in subtype B virus that predominates in the West? Several studies in Africa have reported short-term findings suggesting clinical and laboratory biomarker-based efficacy of HAART, including a gratifying response in those with advanced disease and CD4+ counts <200 cells per mm^3 at the initiation of therapy[32,82-86]. An all too common scenario in both Africa and the North is that of incomplete virologic suppression despite appropriate HAART. However, even with virologic failure, there is immunologic benefit, and increased CD4+ lymphocyte counts are associated with therapy, though the durability of this effect is not yet known[87,88].

Studies suggest that techniques used to monitor resistance in sub-type B can likely be used to assess emergence of resistance in non-B subtype virus once treatment is initiated[89,90]. The development of resistance in 40-57% of patients to at least one agent, reported from Ivory Coast, is likely a reflection of mono and dual therapy with NRTI's[87,90]. The estimated prevalence of resistant virus amongst those treated through the UNAIDS HIV Drug Access Initiative in Uganda was 36% for those receiving HAART, and 56% for those receiving dual therapy with two-NRTI's[88]. However, resistance data from a Senegalese cohort initiated on HAART under a government sponsored program showed a lower rate of development of resistance amongst ART-naive patients (11.8%) compared to 41.7% in those who were ART-experienced; the ART-experienced group showed higher rates of resistance after receiving dual therapy (60%) than those who had always received HAART (28.6%)[91]. Given the high risk of developing resistant virus in the setting of less potent antiretroviral therapy, and the relatively limited options for sequential triple therapies in most resource-limited settings, the initiation of treatment with a HAART (three drug) regimen is important. Initial ARV regimens should be well tolerated, have a relatively low pill burden, ease of administration, and have a high barrier to resistance in the event of less-than-perfect adherence to therapy.

Once-daily treatment regimens may have advantages in resource-limited settings. EFV/DDI/3TC was administered once daily to 40 HIV-1 infected patients in Senegal with a median CD4+ lymphocyte count of 162 per mm³ (range 48-347 per mm³), and a median plasma HIV-RNA $\log_{10}$ of 6 (range 4.5-6)[92]. This regime decreased plasma HIV-RNA level to <500 copies/ml in 95% of patients at six months, <50 copies/ml in 78% of patients at six months, and 69% continued to have virologic suppression to <50 copies/ml after 15 months therapy. Overall, a mean reduction in plasma HIV-RNA viral load of –3.4 ± 0.8 $\log_{10}$ was achieved, with a mean increase in CD4+ count of 199 ± 101 cells/mm³. Though the ARV's used in this trial were patent medications supplied by the pharmaceutical companies, this once-daily regimen is available in generic form as a blister pack containing each individual drug for simple administration. Trials evaluating a variety of once-daily regimens are currently underway, and will provide further insight into this attractive option.

Structured treatment interruptions (STI's) may reduce cumulative toxicities and will decrease the cost of drug per individual. Although STI in several small cohorts with undetectable plasma HIV RNA levels on HAART had a transient negative impact on CD4+ lymphocyte counts in two out of three studies, patients achieved virologic suppression and CD4+ lymphocyte count responses with repeated cycles of HAART[93-95]. Strategies of pulsed therapy have not been systematically studied in comparison to continuous treatment. Highly-experienced patients with multi-drug failures who underwent a STI while having detectable virus did not have favorable clinical, virologic, or immunologic outcomes[96]. On the other hand, treatment simplification switching from a PI-based regimen, after virologic suppression, to a triple-NRTI-based regimen has resulted in sustained virologic and immunologic benefit[97]. Further studies to explore the safety of treatment interruption, pulsed therapies, and simplification, are needed.

Monitoring therapy

In resource-rich areas, repeated measurement of plasma HIV-RNA and plasma viremia is used as the primary surrogate marker for efficacy of anti-viral medications. Failure to attain suppression of HIV-RNA to low levels, or a sustained increase in viral load after a period of successful suppression, indicates virologic failure. Repeated detection of HIV-RNA at levels >500 copies/ml is widely used as an indication to alter the ARV regimen[43,52,98]. However, the routine measurement of plasma HIV-RNA in Africa is unlikely, and its use will initially be limited to centralized tertiary-care units and urban areas. Simple measures such as maximizing adherence and social support contribute to enhanced virologic and immunologic outcomes[50]. In addition, clinical markers that may provide evidence for the efficacy of HAART include weight gain, resolution of mucosal and dermatological manifestations of HIV, and decreased incidence of opportunistic infections, but

further studies of alternative low-cost monitoring systems are needed. Information generated from resistance testing (viral sequencing) will be relevant to surveillance of the evolution of virus and the response to national programs, but is unlikely to play a role in individualized therapies in the short-term.

Immune restoration is assessed through measurement of the CD4+ lymphocyte cell count. Increase of CD4+ cell count has been shown to be an independent predictor of survival, and an increase of 50 per mm³ at the first visit following initiation of HAART is associated with a decreased likelihood of progression to AIDS[47]. Again, the cost and technology required to implement similar monitoring in resource-limited settings is currently limited and alternative, less expensive options are being explored[99]. Though substitution of TLC as a marker for CD4+ lymphocyte count can be problematic due to the limited sensitivity of this test[56], the WHO recommends the use of the TLC as a cheaper and less technologically challenging alternative in areas where CD4+ cell count testing is not available to decide when to initiate ART. Measuring TLC after initiation of HAART may provide an alternative to CD4+ cell count testing to monitor immune restoration on therapy[100].

Laboratory monitoring to identify ART-associated toxicities is performed on a routine basis in resource-rich areas. Though the cost and inconvenience of routine laboratory monitoring of hematologic, liver, and kidney function, as well as metabolic disturbances such as glucose intolerance and hyperlipidemia, is prohibitive in resource-limited settings, alternative syndromic management and monitoring of those on HAART has not yet been systematically explored[101].

Delivery systems

A challenge to treatment access in resource-limited settings is the relative lack of infrastructure and support mechanisms that are typically integral parts of pharmaceutical distribution and medical monitoring in resource-rich areas. An estimated 50,000 people with HIV/AIDS are currently receiving antiretroviral therapy in Africa, with scale-up to three million envisioned by the WHO[102]. HIV/AIDS treatment in Africa is provided by the private sector, governments, international agencies, private corporations, faith-based organizations (mission hospitals) or non-governmental organizations (NGO's). Public subsidies, such as those in the UNAIDS sponsored Drug Access Initiative (DAI), NGO's such as Médecins sans Frontières, and mission hospitals, provide access to ARV's and adjunctive therapies. However, the majority of those who require treatment are not able to afford it[103]. Brazil, a middle-income country, guarantees treatment to all HIV infected nationals, and has demonstrated successful implementation of therapy with an increase in survival after initiation of government mandated and supported treatment initiatives[104]. South Africa, one of the few countries in sub-Saharan Africa with the necessary resources, has recently endorsed the use

of antiretroviral therapy for HIV-infected individuals, breaking away from its prior stance which mainly only supported prevention measures[105].

One proposed mechanism to deliver HAART through the public sector is to implement directly observed therapy (DOT) programs, either in parallel or joined to tuberculosis treatment initiatives. This approach may augment sustained political commitment, ensure administration of appropriate therapy, guarantee drug procurement and distribution of quality drugs, and allow for monitoring of treatment outcomes[106-108]. This needs to be balanced against the possibility of overwhelming the capacity of existing tuberculosis treatment programs, leading some to advocate for adoption of the principles of directly observed tuberculosis treatment into a separate HIV/AIDS treatment plan[106].

Models of community-based care posit that broad participation of local people in community-based organizations is needed to facilitate broad and sustained access to ART. There are potential benefits to this approach. Delivery of treatment by community-based organizations may 1) reach marginalized and remote populations; 2) decrease stigma by including those sensitive to the cultural context of people living with HIV/AIDS (PLWHA); 3) provide local social support networks to improve adherence and care, especially to those in late stages of disease; (iv) empower and involve local community members to disseminate information, and thus enhance prevention. Examples of such treatment models include AIDS Empowerment and Treatment International (AIDSETI)[109] and Médecins sans Frontières[110], transnational organizations that provide ART in resource-limited countries. The paradigm of people affected by, or infected with HIV, playing leadership roles and coordinating support from national/governmental AIDS programs is based on the successful role of community activists and advocacy groups in AIDS treatment in the North. A similar community-driven model of health care delivery has been shown to be effective in South Africa[111], and scaling up of such community-based delivery mechanisms is likely as efforts to increase HIV treatment initiatives in resource-limited settings continue.

Conclusion

The experience of ARV treatment in North America, Brazil, and Europe provides a powerful motivation to implement similar treatment on a broad scale in Africa, where the scale and devastation wrought by HIV is greatest. While there are clear barriers to scaling-up AIDS care and treatment, the fundamental requirements for successful antiretroviral therapy are known and feasible in Africa. Low cost, sensitive and specific markers can identify those who require and are most likely to benefit from treatment. It is possible to provide access and maintain adherence to simple, effective drug combinations, where safe administration may be guided by simple clinical monitoring. The mobilization of political will and economic resources has begun, providing an opportunity to implement

treatment. However, in most of Africa the provision of health care is the responsibility of central government and Ministries of Health. Systematic distribution of drugs and training to use them has led to partnership's between the WHO and national programs, and implementing of 'best practices' supported by donor funds and expertise. There is now the opportunity, in confronting the most devastating global epidemic known, to enlist public health and scientific resources to apply the lessons learned from the first decades of the epidemic in the North.

Countries, health care systems, clinicians, and patients in Africa will identify barriers, limitations, and problems in implementing treatment of AIDS. A critical role for global medical and scientific communities is the development of effective basic, transnational and operational research to identify and implement creative and effective solutions. The mobilization of a global effort to stem the devastation of the AIDS epidemic in Africa should not be impeded by uncertainties about effectiveness; this has been demonstrated. Ten years of experience in antiretroviral therapy in the North provides an impetus to act now to provide access to essential and life saving medicines, lest "the perfect is the enemy of the good."

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