Antiretroviral therapy adherence in resource-limited and resource-rich settings: current status of knowledge and research priorities

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Adherence to highly active antiretroviral therapy is one of the most important factors contributing to treatment efficacy. Although it is one of the most modifiable variables in treatment, it is also among the most difficult to measure accurately. Best estimates of adherence demonstrate that adherence in resource-limited settings is equal or superior to resource-rich settings. Although adherence can be adequate in any setting, it is clear that this is no time for complacency regarding adherence to treatment for HIV infection – whether in developing or developed settings. Emerging evidence indicates that as the duration of treatment increases, adherence may decrease. As a result, there is a pressing need for culturally appropriate and effective interventions for increasing and sustaining adherence in all settings. In this manuscript, we mention a few and review one strategy that has been advocated to improve adherence to TB treatment: directly observed therapy. Few studies have incorporated directly observed therapy for HIV treatment, but preliminary evidence shows compelling, albeit inconclusive, findings. Directly observed therapy does not seem to improve adherence in populations with pre-existing high adherence rates. Further research is urgently needed to improve adherence among children, adolescents and adults through community and family support social networks or by using cellular telephone technology in both resource-limited and resource-rich settings.

Keywords: adherence, AIDS, antiretroviral therapy, developed countries, developing countries, HAART, HIV infection

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Until a few years ago, HIV infection almost always led to an early death from AIDS. However, since the advent of highly active antiretroviral therapy (HAART) the disease has been transformed into a treatable and chronic condition in developed countries. For individuals with access to HAART, a treatment cocktail combining three or more antiretroviral drugs, the risk of opportunistic infection and death has plummeted [1–4]. The use of HAART has additional public-health benefits, reducing vertical [5,6] and, possibly, horizontal transmission [7].

Although HAART has had a major impact on HIV infection in developed countries, its public-health impact in developing nations has been limited, even though 95% of the 36 million HIV-infected individuals in the world live in low-income countries. It is estimated that in December 2006, close to 2015,000 people living with HIV/AIDS (1.8–2.2 million) were receiving treatment in low- and middle-income countries. In sub-Saharan Africa, close to 1.3 million are receiving antiretroviral therapy for a coverage of 28% of the infected population, whereas 3 years ago only 100,000 were on treatment for a coverage of only 2%. While antiretroviral therapy coverage still needs to increase in developing countries, the rate of increase in antiretroviral access over just a few years is encouraging [101].

The benefits of HAART's in managing HIV-infected patients are clearly dramatic and life-prolonging, but the costs, feasibility and lack of effective delivery methods remain formidable barriers to the effective and sustainable scale-up of treatment in developing countries [8]. Owing to these barriers, routine use of HAART in sub-Saharan Africa and Asia was considered to be impossible until just a few years ago.

The effort to bring anti-HIV therapies to developing countries is evolving and continues to be a major theme for the public-health community, pharmaceutical companies and governmental and nongovernmental organizations. AIDS researchers in sub-Saharan Africa have been working to demonstrate the feasibility of both treatment of HIV and prevention of transmission in this setting. Activists are working diligently to make antiretroviral drugs more accessible through a variety of means, while international initiatives to increase access to HAART in sub-Saharan Africa and other resource-poor settings include discounts and marketplace competition for AIDS drugs. Examples of this include the 'Accelerating Access' initiative from major pharmaceutical companies in collaboration with United Nations and AIDS, and offers of reduced pricing and simplified dosing (fixed-dose formulations) from generic drug

makers including Cipla and Ranbaxy of India. These and other efforts have been supported in part by the US President's Emergency Plan for AIDS Relief and the United Nations Global Fund to Fight AIDS, TB and Malaria. Promising results from some of the first studies on the feasibility and early outcomes of providing HAART to large populations in resource-limited settings clearly support the effectiveness of treatment in developing countries [9,10]. Furthermore, a multicountry analysis of cohorts in low-income settings, including Africa, has demonstrated the clinical and public-health effectiveness of HAART in Africa, and also found that delayed access to HAART is a strong predictor of mortality compared with earlier access to HAART for patients in more-developed countries. This analysis also found that access to free treatment was strongly associated with survival (hazard ratio [HR]: 0.23; 95% confidence interval [CI]: 0.08–0.61) [11]. Given the economic realities of Africa, and indeed all low-income countries, free treatment has to be a priority for the international donor response.

However, expanding or scaling-up HAART access in countries with limited resources will depend on the local infrastructure and available resources. These aspects are important not just for delivering HAART and providing healthcare, but in monitoring treatment adherence, one of the most important predictors of therapeutic effectiveness in both developed and developing countries. Indeed, researchers have shown that adherence to HAART is a major predictor of viral suppression of HIV replication [12–14], emergence of drug resistance [15–17], disease progression [18] and death [19–21].

Although adherence is increasingly recognized as a critical factor in treatment effectiveness, there is an urgent need for the development and implementation of simplified, standardized treatment and monitoring algorithms that will facilitate roll-out and scale-up of programs and enable counseling and follow-up of patients, as recently recommended by WHO guidelines [101]. Required aspects of infrastructure include not only mechanisms to obtain and dispense drugs, but also to teach patients about adverse side effects and adherence and lifestyle modifications to improve treatment effectiveness.

We would be remiss to discuss treatment strategies in resource-poor settings throughout Africa and much of Asia without highlighting the greatest healthcare challenge in these settings – access to adequately trained health staff. In these regions, the physician:patient ratio is very low, ranging from 1:1000 in South Africa to 1:92,000 in Malawi, for example. Given the pressing need for delivery of care to patients with HIV/AIDS, ministries of health in these regions are using innovative approaches to delivering care, from community-based carers – non-academically educated community members who care for patients by noting common symptom patterns and helping them maintain adherence – to clinical officers, who are clinicians trained to the level of physicians but without university-recognized qualifications. The latter strategy encourages the development of a sustainable treatment infrastructure by limiting urban and overseas migration while filling the healthcare gap in less-developed countries [22–24].

Adherence to HAART

Adherence to therapy can be defined as the extent to which a person who has been prescribed a therapeutic regimen correctly takes his or her medication. Improving and evaluating HIV medication adherence has been an area for convergence of biological, clinical, behavioral and social disciplines, and each has been critically important in helping achieve the stunning therapeutic benefit for antiretroviral therapy for individuals and populations with HIV [25]. It is important to emphasize the role of medication adherence to patients if they are to obtain the full benefit of HAART, prevent the development of drug resistance and maintain suppression of viral replication. Although maximal adherence is desired, the definition of 'sufficient' adherence is changing. The old unboosted protease inhibitor-based HAART regimens required more than 95% adherence to be effective [13], but accumulating data show that therapy using today's non-nucleoside reverse transcriptase inhibitors (NNRTIs) may suppress HIV even at moderate adherence levels (70–90%), although maximum adherence is associated with optimal outcomes [26,27].

Although adherence is of critical importance, only recently have adherence measures been examined empirically [28–30], and almost exclusively in developed settings. While some HAART-adherence measurement tools are more objective than others, to date there is no established gold standard to measure adherence, in part because each measure has advantages and disadvantages in specific settings [31]. The common methods used include pill counts, electronic monitoring, therapeutic drug levels, pharmacy

records and self-report measures [32,33]. In resource-limited settings, most adherence evaluations use self-report or pharmacy refills [34]. Studies of adherence measures typically rely on limited assessment of criterion-related forms of validity, such as predictive or concurrent validity. In most cases, validation of an adherence measure is based on how well the measure predicts virologic outcomes [29]. While this is of central importance, accurate prediction of virologic outcome provides only limited information about what is actually being measured in terms of adherence behavior. Furthermore, some have argued that virologic failure is an inadequate indicator of nonadherence, as several other factors (e.g., viral mutations, HIV viral load at initiation of therapy, potency of the therapy prescribed, individual differences in absorption and interactions) also mediate virologic outcomes [32,35]. Measurement tools can be defined by content validity, that is, how well the measurement items represent the entire universe of items or domain being assessed, and by construct validity, or how well a measure reflects some underlying construct or latent variable. Studies evaluating content and construct validity are rare [33], and to our knowledge have only been evaluated in one small study from a sub-Saharan African setting, Uganda, by Oyugi *et al.* [36].

Poor adherence to therapy has consequences from an individual and a public-health perspective. These can include development of viral resistance, medication failure, disease progression and death for the individual, as well as the spread of drug-resistant disease to others [13,37]. Many factors underlie poor adherence to HAART, including pill size and number, dosage frequency, forgetfulness, lack of patient motivation/knowledge, lifestyle or cultural factors, route and complexity of administration and comorbidities, such as psychiatric illness, drug abuse and drug toxicity [13,38–40].

However, while there are many potential barriers to adherence, these barriers can be addressed and should not be reason to fail to provide HAART in any setting. Historically, there were expectations of poor adherence among patients in Africa. This sentiment had been expressed at high levels of international agency decision making [41] regarding HIV treatment programs, and arguably contributed to the delay in antiretroviral roll-out in Africa [42]. Yet, until our group assessed adherence in Africa using meta-analysis techniques, decision making regarding adherence levels in this population had been based on anecdote and personal beliefs rather than evidence. In fact, our meta-analysis, published to coincide with the International AIDS Society conference in 2006, found that on average, 77% (95% CI: 68–85%) of African HAART patients met the criteria for good clinical adherence, compared with just 55% (95% CI: 49–62%) of North American patients [34]. In our study, we examined levels of adherence measured in a variety of ways, including pill counts, Medication Event Monitoring System and self-report. Our finding has had important implications for international assistance regarding improved access to HAART and was referred to by former US President Bill Clinton at the 2006 International AIDS Society Conference as the 'nail in the coffin' of discrimination in drug access [103].

Among pilot research projects evaluating antiretroviral therapy adherence rates in resource-poor settings, a study completed in Cape Town, South Africa, found a median adherence rate of 93.5% over a 48-week period using patient pill returns as a measure of adherence [43]. Another study in Soweto, South Africa, noted patient self-reports of adherence for the previous month to be more than 95% for most patients (88% of participants) [44]. These preliminary ART adherence rates in sub-Saharan Africa are quite encouraging, but should not be reason for complacency given the very long timeline of HIV treatment. Among their limitations, most of the studies reported to date had a short follow-up period, used self-reported adherence, were from highly selected populations involving clinical trials and/or tertiary treatment centers and suffered from potential reporting bias [45,46]. It is also important to note that studies with longer-term follow-up are beginning to be reported and they are reporting declines in adherence rates as duration of treatment increases [47]. A recent analysis of a cohort from Kampala, Uganda, has found that initially excellent clinical adherence decreased over a 1-year period as patients experienced adverse events, stock-outs or access difficulties or forgot to take their medicines [48]. Doses missed owing to reasons of infrastructure, such as pharmacies stock-out or transportation difficulties, must be distinguished from those missed owing to patient- or culture-specific problems when monitoring and evaluating treatment roll-out programs in developing countries and when conducting clinical studies in developed settings, where individuals may still have limited resources.

Barriers to HAART adherence

Patients in the developed and developing world face many barriers to adherence to antiretroviral therapy, including social, economic and individual barriers. Many of these barriers are similar to those contributing to patients' failure to seek testing and treatment for HIV infection in the first place. For example, many people decline HIV testing because they believe the infection to be untreatable, they fear stigmatization by their family or community or they don't understand how the virus is transmitted. These social barriers also affect patients' adherence. In our evaluation of adherence levels, we also examined reasons for poor adherence and possible motivators to improve adherence, using a systematic review [49]. To date, the most important and prevalent factors that have been reported to negatively impact adherence in sub-Saharan Africa are: cost [44,49–51]; nondisclosure to a loved one or fear of being stigmatized [44,52]; alcohol abuse [49]; and difficult drug regimens [50,53]. Studies report that the majority of patients receiving antiretroviral treatment have told family or friends their HIV status [54,55], and that those who have not disclosed appear to do worse on therapy [44,52]. Patients who have not disclosed their HIV status must hide their pills and must not take their pills in the presence of others, so as not to reveal their secret. Encouraging voluntary HIV-status disclosure in a community with access to antiretroviral therapy may help improve use of voluntary counseling and testing for HIV, decrease HIV-related stigma and improve adherence.

Improving adherence through directly observed treatment programs

It is important to address the barriers to maximum adherence and to develop and apply interventions to improve adherence levels. One of the most controversial components of providing care in poor settings is use of the TB clinic-based directly observed therapy DOT model for delivery of HAART [56–58]. However, a community-based approach of DOT for both HIV and TB is particularly attractive for a number of reasons:

- A successful global infrastructure has already been established for DOT-based TB treatment programs;
- Significant overlap exists between those infected with TB and AIDS in sub-Saharan Africa and other limited-resource settings, since TB is the major opportunistic infection of HIV infection;
- Community workers or close family members can effectively deliver and observe therapy;
- Tight control of DOT-based drug dispensing hinders development of an underground market in antiretroviral drugs.

DOT-HAART programs ensure that the HIV-infected patient is taking medications regularly, and this should promote the best clinical outcomes and minimize the risk of drug resistance.

Several pilot DOT-HAART programs have been successfully undertaken in the USA involving DOT for HIV infection. In a study carried out by Kirkland *et al.* [59] of treatment-naive AIDS patients at the Miami AIDS Clinical Trials Unit (FL, USA), viral suppression rates for self-medicated study participants in an inmate population were compared with those for HIV-infected prisoners treated in the Department of Corrections under DOT-HAART. After 80 weeks of follow-up, 95% of the DOT-HAART prisoners had HIV RNA levels of less than 400 copies/ml, compared with 75% of the incarcerated participants in the self-administered therapy group. In a recent randomized, controlled trial by Altice and colleagues [60], the biological outcomes of a 6-month community intervention of directly administered antiretroviral therapy (DAART) were compared with those of self-administered therapy among HIV-infected drug users. Patients randomized to receive DAART received supervised therapy 5 days per week from workers in a mobile healthcare van. A significantly greater proportion (70.5 vs 54.7%; $p = 0.02$) of the DAART group achieved the primary outcome, which was either a reduction in HIV-1 RNA level greater than or equal to 1.0 $\log_{10}$ copies/ml or an HIV-1 RNA level of less than or equal to 400 copies/ml at 6 months. Patients receiving DAART also had a significantly greater mean reduction in HIV-1 RNA level (-1.16 $\log_{10}$ copies/ml vs -0.29 $\log_{10}$ copies/ml; $p = 0.03$) and mean increase in $CD4^+$ T-lymphocyte count (+58.8 cells/µl vs -24.0 cells/µl; $p = 0.002$) than patients who self-administered their medication.

As research into effective adherence interventions continues to intensify in resource-rich countries, additional questions face researchers and clinicians in resource-limited countries. Infrastructure, poverty and clinical conditions will likely continue to be formidable barriers to patient adherence in such settings. However, the availability of a large pool of potential peer

educators and traditions of community- and home-based care may provide resources not common in industrialized countries. In communities where HIV prevalence rates average 30%, where unemployment rates are high and where most HIV services are public and centralized, DOT programs based out of home, school or work may be culturally acceptable and potentially inexpensive. In several developing countries such as Bangladesh, Nepal, South Africa and Brazil, TB-DOT using a patient-nominated supervisor from the family or community has been shown to be effective and feasible [61–64].

One concern that could be raised regarding the routine implementation of DOT-HAART is that choosing a family member as supervisor could raise issues about confidentiality or stigmatization. However, based on preliminary data in Soweto, at least 90% of HIV-infected patients reported that they had already disclosed their HIV status to at least one member of their family [44]. Farmer and colleagues reported their experience in rural Haiti with a small (n = 60) DOT-HAART pilot project at Clinic Bon Sauveur [65]. In this nonrandomized trial, the treatment was directly observed therapy given once or twice per day by community health workers (accompagnateurs, many of whom are HIV-infected themselves). While only partial and incomplete virologic data have been reported to date, patients enrolled have had a clinical response characterized by weight gain and abatement of AIDS-related symptoms, and the medications have been well tolerated. Using a mixed-methods approach to describe the process of implementing a modified DOT program (mDOT) for an ongoing randomized, controlled trial in Beira, Mozambique, Pearson and colleagues conducted interviews with clinic staff and mDOT peers, and participants provided information on design elements, problems with implementation, satisfaction and benefits [66]. Acceptability and feasibility measures were obtained from the trial. Most (81%; n = 350) eligible persons agreed to participate, and of those randomized to mDOT (n = 174), 95% reported that their time with peers was beneficial. On average, participants kept 93% of the 30 required daily mDOT visits. Key components of the intervention's success included using peers who were well accepted by clinic staff, having adequate training and retention of peers, adapting daily visit requirements to participants' work schedules and physical conditions, and reimbursing costs of transportation. This study identified aspects of mDOT that are effective and can be adopted by other clinics treating HIV patients.

These DOT-HAART programs, both in developed and developing countries, are encouraging and should be considered even as other tools and interventions are developed to address barriers to adherence in resource-rich and -limited countries. However, it is still not clear whether DOT is helpful in populations with already adequate adherence. Indeed, few of the studies that found an intervention effect of DOT were conducted in selected patients with severe adherence barriers. For example, in a study conducted by Wohl *et al.*, a large, well-designed, randomized trial of DOT versus case-managed versus self-administered therapy, no differences were observed because all populations had sufficiently high levels of adherence [58]. Presumably the same would be true for resource-limited settings where antiretroviral adherence is likely higher than in the Wohl study. Indeed, in a ongoing, open-label, randomized clinical trial in Botswana, the combination of an NNRTI with either zidovudine/lamivudine or stavudine plus lamivudine resulted in high overall immunologic and virologic response in previously untreated HIV-infected patients in both the self-administered versus DOT-HAART group [67]. Results from other ongoing community DOT-HAART studies in South Africa and Uganda are expected soon.

Of note, in a meta-analysis, Simoni and colleagues found that randomized trials of interventions for HAART adherence showed that HIV-infected patients who receive an intervention were 1.5-times more likely to report excellent adherence and 1.25-times more likely to have an undetectable viral load than patients in the control group [68]. There is a clear and urgent need to test and expand HAART-enhancing adherence interventions in different populations and cultures, including for HIV-infected persons in developing countries. The safety and effectiveness trials for new treatments or new treatment combinations will require simple, affordable and safe regimens, as well as effective ways to improve and monitor treatment adherence. Our knowledge about adherence to HAART among HIV-infected patients in ever-growing HAART rollout programs is still limited. Large-scale pilot programs, coupled with scientifically sound and rigorous clinical trials, are essential to speed the provision of HAART in developing countries and to improve future research- and evidence-based treatment strategies in such settings.

Emerging technologies as strategies to improve adherence

Simple, effective and culturally relevant tools to improve adherence are needed so that patients will use them regularly, rather than finding them so interruptive as to discontinue their use. Recent strategies that have been evaluated include counseling, pill-organizers, reminder systems and education [69,70]. Although some of these interventions have efficacy, many of the human-resource-intensive strategies have limited utility beyond that of mDOT. Strategies such as pill-box organizers and reminder keyrings are an attractive option in resource-limited settings, but have not yet been evaluated.

One intervention that has surprising utility in the developing and developed world is the use of cellular telephone technology as a reminder system for adhering to medication schedules and keeping clinic visits. Although much of southern Africa suffers from tremendous poverty, the popularity of cellular phone technology would surprise many readers, and the quality of telephone systems in southern Africa surpasses much of the USA. A cell-phone-based strategy was originally piloted in Los Angeles (CA, USA) [71], and a recent pilot has begun in South Africa [72]. Although this intervention will need to be evaluated in appropriately designed randomized trials [104], there are intuitively attractive components to this approach. It is culturally relevant for telephone owners, it is largely confidential (if text messages are used), distance is not an issue and it can be uniquely modified to meet the education or lifestyle needs of the patient. As an example, one company in South Africa (SimPill) texts football results and jokes to TB patients and, more recently, to HIV patients, rather than sending the cold, clinical reminder that might initially be used [73]. We eagerly await its evaluation in even more resource-limited settings such as Democratic Republic of Congo or Malawi.

Adherence to HAART in adolescents & children

Children and adolescents are a particularly marginalized group, both those infected or affected by HIV/AIDS. This population has largely been ignored in the discussion of adherence [74,75], but a review of the available studies has recently been published [76]. For HAART treatment, children are defined as those aged under 14 years. In most of sub-Saharan Africa, drug formulations for the treatment of HIV/AIDS are targeted to adults and children's doses do not exist. First-line treatment for almost all patients in African countries is the triple combination generic therapy Triomune® (Cipla, India). Triomune is composed of stavudine (d4T), lamivudine (3TC) and nevirapine. A generic first-line pediatric formulation (Pedimmune®) has become available in a minority of African countries. For very young children, Triomune's individual drugs are available in syrup form. However, this creates difficulties for caregivers as they must measure appropriate doses of the three individual syrups. Adult pill doses create clinically important challenges for pediatric dosing as pediatric patients (greater than 25 kg; aged approximately 7 years) must receive half-doses, and therefore the pills must be split using a pill-splitter or a knife. It is currently unknown whether the distribution of the three drugs is equal throughout the pill, which could result in inconsistent dosing, although patients will end up with a full tablet by the end of day.

Adherence of pediatric populations may also be challenged beyond the logistics of dosing, because the Triomune formulation is associated with important adverse effects and drug resistance. Of the Triomune combination, d4T commonly causes peripheral neuropathy and, over time, lipodystrophy, while nevirapine causes hepatic toxicity. Both nevirapine and d4T have important risk profiles for drug resistance. While resistance to d4T develops over time, nevirapine resistance can occur rapidly, resulting in potential resistance to efavirenz as well. It is worth noting that efavirenz should not be used in children aged under 3 years (or weighing 10 kg). [105] Furthermore, the WHO recently withdrew recommendation for the 40-mg versions of stavudine-containing fixed-dose combinations (because of its above-average toxicity) and the increased drive/advocacy to use either zidovudine (AZT) or tenofovir as the thymidine analog in first-line regimens instead of d4T [106].

HIV-positive children in Africa are often orphaned, requiring families or communities to step in to care for them. Often, the children are cared for by grandparents or elderly neighbors who may have their own health challenges and are often impoverished because they have no income from their own children. Little is known about the effectiveness of caregivers providing care for children, although our own experience and the limited evidence suggest it is high [74,75,77]. In a recent cross-sectional study in urban Uganda, of 170 pediatric patients (aged 2–18 years) attending an outpatient

hospital-based clinic, the majority (89.4%) reported more than 95% adherence [75]. The proportion was even greater when assessed by pill counts (94%), but much lower when assessed by the more objective strategy of unannounced home-based pill counts. In a sensitivity analysis, when the primary caregiver was the only one who knew the child's serostatus, the child was three-times more likely to be nonadherent ($p = 0.02$; OR: 3.34; 95% CI: 1.14–9.82) than when the child's status was also known by others. Similar results have been found in qualitative studies of children and caregivers [74].

Cost–effectiveness of HAART adherence interventions

Previous studies have shown that HAART is cost effective for HIV-infected patients in both resource-rich [78] and resource-limited settings [79,80]. As HAART programs scale up to cover larger patient populations, the resources available for monitoring and maintaining adherence on a per-patient basis may diminish. Thus, a distinct need exists to evaluate the cost–effectiveness of potential interventions aimed at maintaining or enhancing medication adherence in large, representative populations of HIV-infected patients in resource-limited settings. Various interventions to improve adherence to antiretroviral therapy have been studied, including individual electronic reminders, behavioral training, nursing interventions and directly observed therapy. The efficacy of these interventions in improving virologic suppression, as tested in many different settings, has ranged from 0 to 35%. Unfortunately, most existing models for cost–effectiveness analysis of HAART-related interventions are based on data from the developed world [78,81], leaving African decision makers without a relevant framework for evaluation of potential adherence interventions.

Conclusion

Although adherence to antiretroviral treatment in Africa is not as poor as once predicted, it is critical to identify opportunities to maximize adherence as treatment programs are scaled-up in large populations. There are important challenges to identifying new and effective adherence interventions. For any intervention to be useful, it must be both simple and acceptable. Our previous review of patient concerns and facilitators to adherence identified a tremendous paucity of formative research to inform the development of new interventions. There is a pressing need for qualitative research, both individual in-depth interviews that can identify patient-specific concerns, as well as focus groups that can assist in identifying community-representative issues. While such research may seem rather nonspecific to epidemiologists, it is only through listening to individuals and communities that we will identify relevant new interventions. Individual, structural and social barriers such as alcohol abuse, HIV-status nondisclosure and stigma, as well as treatment interruptions due to transport costs and drug stock outages, are being identified as important challenges to adherence. Good adherence is a critical contributor to good clinical and public-health outcomes in the fight against HIV infection worldwide.

Future perspective

Although HAART is available in many resource-limited settings, it is still accessible to just a small fraction of the people who need it. In resource-limited settings, HAART has not yet made HIV infection the chronic condition it often is now in developed countries. A critical next step in fighting HIV in the developing world is, of course, continuing to improve availability of and access to HAART for all populations who need it. To optimize the benefit of drugs for those who do gain access to them, it will continue to be important to recognize and address the individual, social, economic and structural barriers in various communities that decrease adherence and increase the risk of drug resistance, treatment failure and death.

Currently, adherence levels in most reported studies in the developing world are higher than adherence levels typically reported in the developed world. However, as HAART programs are scaled-up and rolled-out in resource-limited areas, it may be difficult to make sure these additional patients take their medications as required, potentially leading to declining adherence rates as HAART availability increases. While it is clear that this possibility should not slow scale-up efforts, it is an important variable in these programs and should be addressed.

There is a pressing need for research into children's and orphaned children's behavior patterns regarding drug access, pharmacology and patient behaviors. If this generation of pediatric HIV/AIDS patients is to reach adulthood, we need to develop simple formulations and to design interventions to help this particularly marginalized group attain or sustain good adherence and continued access to drug supplies.

Over the next 5–10 years, we advocate for continued expansion of antiretroviral availability in sub-Saharan Africa and in other resource-limited settings. Success will be owing in large part to the ongoing commitment of various governments, the US President's Emergency Plan for AIDS Relief Fund, the UN Global Fund Against AIDS, TB and Malaria, and others to expand and to continue to provide funding and international collaboration. These efforts need to be scaled-up, coordinated and sustained with wide access to generic antiretroviral drugs free of charge across sub-Saharan Africa and in other resource-limited settings. Indeed, financial stability and a sustainable drug supply are critical to prevent structural barriers (drug costs and pharmacy stock-outs), which seem to account for much of the patient non-adherence in several countries of sub-Saharan Africa, for example.

We also advocate that the next 5 years bring more high-quality qualitative and quantitative evaluation and eventually validation of a variety of possible interventions, such as those described above, to overcome barriers to seeking HIV testing and treatment and to adherence. Randomized trials of interventions to improve adherence are a pressing necessity. Interventions should be designed to target specific patient groups at high risk of nonadherence, such as alcohol abusers, nondisclosers and so on. It is only through knowing the effectiveness of interventions that we can adequately ration resources. Furthermore, broadening access and implementation of evidence-based interventions to address barriers to seeking and adhering to antiretroviral treatment should have an important impact on the HIV epidemic. With a great deal of work and some

Executive summary

- Antiretroviral therapy is still reaching only a minority of people in need, but there is now wide recognition that expectations of poor adherence to treatment in resource-limited settings were correct, and that such expectations should not preclude populations from access to highly active antiretroviral therapy (HAART).

Adherence to highly active antiretroviral therapy

- Although there has been early success with regards to adherence levels in developing countries, it is important that it not lead to complacency, since longer-term studies have shown a decline in adherence levels with longer treatment.
- A variety of adherence measures have been studied in various populations, but because each has advantages and disadvantages, no gold standard has emerged.

Barriers to highly active antiretroviral therapy adherence

- Individual, social and economic barriers to adherence to treatment in developing countries and elsewhere can be addressed, and culturally appropriate interventions should be developed and tested in the specific patient population.
- Social and economic barriers to treatment adherence in sub-Saharan Africa and other settings include nondisclosure of HIV status, fear of stigma from disclosure, stigmatization because of HIV status, lack of money for food or transportation to clinic appointments, and alcohol and, quite likely, substance abuse.

Improving adherence through directly observed therapy programs

- Lessons can be learned from experience with other infectious disease treatment programs, including from the experience of directly observed therapy for TB treatment adherence.
- Studies in the USA and elsewhere have shown that directly observed therapy might be applied to HAART through use of third-party observers.
- Directly observed therapy does not appear to significantly improve adherence in populations with high adherence already, and so may prove to be an effective strategy for a limited subgroup of patients with pre-identified poorer adherence, rather than for all new patients.

Emerging technologies as strategies to improve adherence

- Although first reported as an adherence-boosting strategy in the USA, cellular phone technology is a surprisingly applicable tool for reminding patients of dosing schedules and clinic appointments, even in some developing countries.

Adherence to highly active antiretroviral therapy in adolescents & children

- Children remain a particular challenge in designing adherence strategies given our limited knowledge of drug dispersion, patient behaviors and access to appropriate formulations.

Conclusion

- Improving adherence is a critical aspect of HIV treatment in both developed and developing countries and will require targeted interventions to achieve maximal adherence.

luck, the combination of these advances may lead to the stabilization and even decline of HIV-related morbidity and mortality throughout much of sub-Saharan Africa and the developing world.

We have documented that current adherence levels are higher in studies reported from sub-Saharan Africa than they are in many developed countries. Although current HAART regimens appear to be able to offer effective suppression of HIV, even at lower adherence levels than the older protease inhibitor-based regimens, it is still of concern that in settings generally thought of as resource-rich, adherence should be lower than 70% on average. Therefore, we also advocate for the application of interventions and tools used to monitor and improve adherence in developing countries to address low adherence in developed countries. Directly observed therapy and use of community or family support structures might be applied to developed settings and have in fact been shown to improve adherence and outcome in such settings. Furthermore, culturally appropriate interventions should also be developed and tested in developed countries.

Adherence to treatment is one of the few modifiable variables once a patient presents for HIV treatment. For people infected with HIV, it is critical that improving adherence to therapy be a priority second only to increasing access to treatment.

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