Antiretroviral therapy adherence and retention in care in middle-income and low-income countries: current status of knowledge and research priorities

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Purpose of review

Adherence to combination antiretroviral therapy (cART) is one of the most important contributing factors to positive clinical outcomes in patients with HIV, and long-term retention of patients in low-income and middle-income countries is emerging as an important issue in rapidly expanding cART programs. This review presents recent developments in both treatment adherence and retention of patients in low-income and middle-income countries.

Recent findings

Adherence is among the most modifiable variables in treatment, but there still is no 'gold standard' measurement. Best estimates demonstrate that adherence in resource-limited settings is equal or superior to that in resource-rich settings, possibly due to focused efforts on support groups and community acceptance of adherence behaviors. However, long-term data show that sustained efforts to ensure high cART adherence and evidence of intervention effects are critical, but that resource-intensive interventions are not warranted in settings where cART adherence is high. Furthermore, well conducted evaluation of culturally sensitive interventions to maximize pre-cART and post-cART initiation retention is badly needed in low-income and middle-income settings.

Summary

Further research is needed to identify risk factors and to improve adherence and retention among children, adolescents, and adults through use of social networks or emerging technologies for patients at risk for poor adherence.

Keywords

adherence, combination antiretroviral therapy, HIV/AIDS, low-income and middle-income countries, retention

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Introduction

Since approximately 1996 in wealthy settings and early 2000s in poorer settings, combination antiretroviral therapy (cART) has transformed HIV infection into a treatable and chronic condition for individuals with access to treatment [1–4]. However, only about 30% of people in low-income and middle-income nations have access to needed treatment. This is a significant concern for global control of HIV because 95% of HIV-infected individuals live in these settings. Although coverage still needs to increase in developing countries, substantial improvements seen since 2004 are encouraging [5••].

Sustaining expansion of cART access in countries with limited resources will depend on local infrastructure and available resources, which are critical for delivering cART and providing healthcare and for monitoring treatment adherence, one of the most important predictors of treatment effectiveness. Research has shown that adherence is a major predictor of viral suppression of HIV replication [6–10,11•], emergence of ART class-specific drug resistance [12,13], disease progression [14], and death [15–17].

Furthermore, although adherence in developing countries is often equal to or higher than that in developed countries [18–20], recent studies have shown that adherence may wane over time [21•]. In all settings, maintaining high treatment adherence for a lifelong condition is a considerable challenge [22]. In low-income and middle-income countries, retention in treatment programs is also an emergent issue [23]. Recent studies have identified barriers to adherence in these settings [24,25,26•], and various others have examined effectiveness of culturally appropriate interventions to improve

adherence in these settings. This review focuses on the current status of knowledge about adherence and retention in low-income and middle-income countries and discusses the clinical and research implications.

Adherence to combination antiretroviral therapy

Treatment adherence is defined as the extent to which a person correctly takes prescribed medication. Early unboosted protease inhibitor-based cART regimens required about more than 95% adherence to be consistently effective [27], but today's nonnucleoside reverse transcriptase inhibitors (NNRTIs) and boosted protease inhibitor-based cART can achieve virologic suppression at moderate adherence (70–90%), although optimal outcomes can require maximum adherence [9,10,11•].

There is no gold standard to measure adherence. Commonly used methods include pill counts, electronic monitoring, therapeutic drug levels, pharmacy records, and self-report, each of which has advantages and disadvantages depending on the setting [11•,28] (Table 1). Currently, in resource-limited settings, self-report or pharmacy refills are most commonly used [11•,28]. Recently, Bisson *et al.* [29••] reported that pharmacy refill-based adherence levels outperformed CD4 cell count changes in the first year following cART initiation for patients in Cape Town, South Africa, enrolled in the private sector Aid for AIDS disease management program [30•]. There is a need for validation of novel, feasible, and cost-efficient adherence monitoring tools capable of capturing real-time adherence behavior, which are useful in both resource-limited and resource-rich settings and useful for routine application in clinical care and research studies [29••,30•].

Reported cART adherence levels in resource-limited settings are excellent and encouraging [18–20], but should not reduce maintenance efforts, given that HIV treatment is lifelong [22]. Emerging evidence indicates that initially high adherence may wane over time [21•]. Nonetheless, a few studies with relatively longer patient follow-up are beginning to be reported and are confirming sustained high levels of adherence. For example, in a study from Cape Town, South Africa, Nachega *et al.* [31] reported data on cART adherence assessed by pill count showing a median adherence level of more than 95% at all time points during 2-year follow-up.

Barriers to combination antiretroviral therapy adherence in low-income and middle-income countries

All patients face social, economic, and individual barriers to treatment adherence. In resource-limited settings, however, structural barriers are emerging as perhaps the most important barriers to cART adherence. A cohort analysis from Kampala, Uganda, found that initially excellent adherence declined over 1 year as patients experienced pharmacy stockouts, access/transportation difficulties, or simply forgot to take their medicines [32]. Monitoring and evaluation of treatment rollout programs in developing countries and clinical studies in developed settings, in which individuals still may be resource-limited, must distinguish between doses missed due to poor infrastructure and patient-specific or culture-specific problems if adherence interventions are to be appropriate. A systematic review [25] indicated that the most important and frequent factors reported to negatively impact adherence in developing countries are cost [33,34] nondisclosure to a loved one or fear of being stigmatized [20,35], alcohol abuse [35], and structural barriers, such as lack of transportation, pharmacy stockouts, among others [32]. Although structural barriers may not be a patient's fault, the virus does not care; frequent treatment interruptions could cause increased risk of poor clinical outcomes including death [32].

HIV/AIDS and directly observed treatment programs

Directly Observed Therapy for antiretroviral therapy (DOT-ART) has been contentious. DOT is used by

Table 1 Combination antiretroviral therapy adherence monitoring tools: accuracy, advantages and disadvantages

Tool	Accuracy/reliability	Detection of adherence patterns (interruptions and discontinuations)	Real-time monitoring to detect poor adherence before breakthrough viremia	Feasible in routine clinical practice	Cost-efficient
Self-report	Specific, very insensitive	Yes	No	Yes	Yes
Pharmacy refill or claim	Specific, fairly sensitive	No	Could be	Yes[a]	Yes
Pill count	Fairly specific, fairly sensitive	No[b]	No	Yes	No
Electronic pill-container caps (MEMS caps)	Specific, too sensitive	Yes	No	Yes	No
Electronic Web-enabled pill box	Specific, too sensitive	Yes	Yes	Yes	Unknown
Drug concentration	Specific, sensitive	Yes	Yes	No	No

Adapted from [29••].
[a] Feasible when patients obtain medication from a single pharmacy source.
[b] Data on interruption could be collected by patient interview during pill count.

Table 2 Directly Observed Therapy-ART studies from high-income countries

Author	*N*	Setting	Country	Study design	Duration	Viral load <400 or <50 copies/ml
Babudieri *et al.* [38]	37	Prison	Italy	Non-RCT	9 months	62 vs. 34%; $P=0.01$
Fischl *et al.* [39]	50	Prison	USA	Non-RCT	12 months	100 vs. 68%, $P<0.01$
Clarke *et al.* [40]	39	Methadone clinic	UK	Cohort	12 months	65 vs. 51%; $P<0.01$
Lucas *et al.* [41]	75	Methadone clinic	USA	Non-RCT	12 months	56 vs. 32%; $P<0.009$
Wohl *et al.* [42]	250	Community unselected	USA	Non-RCT	6 months	54 vs. 54%; $P>0.05$
Macalino *et al.* [43]	87	Community IVDU	USA	RCT	3 months	No effect in ART-naïve patients; OR for VL suppression is 2.8 (95% CI 2–7) ART-experienced patients
Altice *et al.* [44]	141	Community IVDU	USA	RCT	6 months	70.5 vs. 54.7%; $P=0.02$
Gross *et al.* [45•]	274	Community unselected	Mainly USA, Caribbean	RCT	6 months	72 vs. 78%; $P=0.19$

ART, antiretroviral therapy; CI, confidence interval; IVDU, intravenous drug users; Non-RCT, non-randomized control trial; OR, odds ratio; RCT, randomized controlled trial; VL, viral load.

most tuberculosis programs, but may not be suitable for lifelong cART [36,37]. Tables 2 and 3 summarize reported DOT-ART studies in high-income, middle-income, and low-income countries [38–53]. Randomized trials with both long-term virologic and clinical endpoints that evaluate the impact of community-based DOT-ART interventions with a patient-nominated volunteer treatment supporter (friend and/or family member) are in progress in low-income and middle-income settings.

Few studies reported from South Africa, Malawi, and Nepal have shown that DOT for tuberculosis treatment by patient-nominated community supporter may be effective and feasible [54–57]. Observational data reported by Farmer *et al.* [46] from rural Haiti using community health workers showed that DOT-ART was acceptable and associated with good clinical outcomes. A peer-delivered community randomized trial of DOT-ART in Mozambique by Pearson *et al.* [49] showed its feasibility, but lacked virologic outcomes.

Nachega *et al.* [31] have evaluated partial DOT-ART by patient-nominated treatment supporter versus self-administration in Cape Town, South Africa, and found that intervention did not affect the primary endpoint of virologic failure. Adherence assessed by pill counts was high (median >95%) and similar at 12 and 24 months for both study arms. Patients on DOT-ART had better early CD4 responses that were not sustained beyond 6 months. The authors reported a survival benefit in the DOT-ART arm that was not explained by virologic outcomes after controlling for other factors associated with death.

Several other community-based randomized trials testing DOT-ART interventions have been described. Wohl *et al.* [42] in the United States studied a mixed treatment-naïve and treatment-experienced population without selection for risk factors for nonadherence in whom community workers administered DOT-ART for 6 months, whereas the ACTG A5073 study by Gross *et al.* [45•] evaluated DOT-ART strategies delivered by a health professional (pharmacist, nurse, etc.) in unselected ART-naïve populations in the United States, Caribbean, and one site in South Africa. Both of these studies found that DOT did not confer a significant advantage in virologic suppression or adherence. Macalino *et al.* [43] compared community-based once-daily DOT delivered by outreach workers versus self-administered therapy in a

Table 3 Directly Observed Therapy-ART studies from middle-income and low-income countries

Author	*n*	Setting and provider	Country	Design	Duration	Viral load <400 or <50 copies/ml
Farmer *et al.* [46]	60	Community (worker)	Haiti	Case series	Not reported	91%
Jack *et al.* [47]	17	TB–HIV clinic patients	South Africa	Case series	18 months	88%
Idoko *et al.* [48]	175	Community (family/friend)	Nigeria	Cohort	12 months	91% (daily DOT), 88% (twice weekly DOT), 84% (weekly DOT) vs. 79% ($P<0.01$)
Pearson *et al.* [49]	350	Community (family/friend)	Mozambique	RCT	12 months	No VL data better mean adherence in DOT vs. self-ART
Sarna *et al.* [51]	234	Clinic (nurse)	Kenya	RCT	18 months	90 vs. 55%; week 72; $P<0.02$
Taiwo and Idoko [50]	500	Community (family/friend)	Nigeria	RCT	6 months	62 vs. 50%; week 24; $P<0.006$
Bussmann *et al.* [52]	350	Community (family/friend)	Botswana	RCT	24 months	No effect; low virologic failure rate
Gandhi *et al.* [53]	119	Community TB–HIV patients (family/friend)	South Africa	Case series	12 months	88%
Nachega *et al.* [31]	274	Community (family/friend)	South Africa	RCT	24 months	73 vs. 70% at 12 months ($P=0.42$); 56 vs. 52% ($P=0.62$) at 24 months

ART, antiretroviral therapy; DOT, Directly Observed Therapy; RCT, randomized controlled trial; TB, tuberculosis; VL, viral load.

randomized trial of 87 active substance users followed for 3 months in the United States. Although they found a benefit, secondary analyses showed that the entire benefit was conferred upon ART-experienced patients who had failed prior antiretroviral regimens.

These trials suggest that studies of community-based DOT-ART (and perhaps other resource-intensive interventions) should focus on populations at greater risk for poorer adherence and should incorporate adherence skill-building to sustain the intervention's effect. Indeed, a recent meta-analysis of randomized controlled trials found that DOT had no benefit over self-administration in HIV-infected cART-naïve persons [58]. In a similar analysis, Amico *et al.* [59] showed that studies targeting groups with poor cART adherence had stronger effects than those targeting groups with mixed adherence levels.

Qualitative studies from South Africa have examined patient characteristics, social support networks, and relationship factors and demonstrated that patient support is very important to adherence [35]. A study from Nigeria, Tanzania, and Uganda [60•] suggested that social relationships are a particularly important mediator of sustained cART adherence in these settings. The authors argued that, in the face of extreme poverty, individuals rely heavily on social capital – 'the use of relationships to obtain benefits and achieve desired ends' – to obtain resources, such as transportation or food [60•]. Therefore, social capital provided by a trusted patient-nominated treatment supporter may contribute to survival through mechanisms beyond the impact of cART on viral replication, and does so even without DOT. According to Uchino's [61] model of potential pathways linking social support and health, social support can influence behavioral processes (healthy lifestyle choices in addition to medication adherence) and/or psychological processes (e.g., decreased depression, heightened sense of control, and self-efficacy), which, in turn, contribute to biological processes that may ultimately lead to decreased morbidity and mortality for DOT-ART patients. Many AIDS Service Organizations across Africa now heavily encourage patient participation in adherence support groups. These groups are maturing and, although initially focused on adherence, are now developing additional support infrastructure including business development and skills building.

Emerging technologies as strategies to improve adherence

Emerging technologies-based intervention strategies recently evaluated for their ability to improve adherence include counseling, pill organizers, electronic reminder, and education devices and cell phones [62]. Pill-box organizers and reminder keyrings are attractive for resource-limited settings but have not yet been evaluated [63]. Cellular telephone technology, however, may be of great utility in both developing and developed countries to provide reminders for adhering to medication schedules and keeping clinic visits. A cell phone-based strategy was originally piloted in Los Angeles (USA) [64], and a pilot has begun in South Africa [65].

The cellular phone approach is culturally relevant for telephone owners, is largely confidential (particularly if text messages are used), is not affected by distance, and can be uniquely modified to meet patients' individual education or lifestyle needs. As an example, one company in South Africa texts football (soccer) results and jokes to tuberculosis patients and, more recently, to HIV patients, rather than sending just cold, clinical reminders [66]. Lester *et al.* [67] are conducting a randomized trial in Kenya where local greetings are used as a reminder and a patient can text back requesting a telephone call if they are having difficulty. This strategy was particularly useful during stock shortages during political violence in Kenya in 2008. Chang *et al.* [68] recently reported a pragmatic cluster randomized trial assessing the effect on AIDS care of community-based peer health workers with and without a mobile phone support intervention at ART clinics in Rakai, Uganda. In this trial, health workers did not affect shorter-term cART virologic outcomes, but did appear to decrease failure rates in patients on cART for 96 weeks or more. The mobile phone support intervention did not provide any additive effect. Similar randomized trials are ongoing in other resource-limited settings such as Kenya, Democratic Republic of Congo, and Malawi.

Adherence to highly active antiretroviral therapy in children and adolescents

Children and adolescents are particularly marginalized, whether infected or affected by HIV/AIDS [69]. A recent study conducted in South Africa by Nachega *et al.* [70•] found that compared with adults, adolescents were less adherent to cART, had lower rates of virologic suppression and immunologic recovery, and had higher rates of virologic rebound after initial suppression. There is an urgent need to determine specific barriers to adherence for children and adolescents and to develop appropriate interventions [70•].

Children often are cared for by grandparents or elderly neighbors who may have their own health challenges and who are often further impoverished by the children's lack of income. The limited evidence available suggests that caregivers are highly effective at providing care for children [71–73], although measuring adherence in children is very difficult [72]. In a cross-sectional study in an urban setting in Uganda, of 170 pediatric patients

(aged 2–18 years) attending an outpatient hospital-based clinic, the vast majority (89.4%) reported more than 95% adherence [71]. A nationwide study of children and adolescents in Uganda found that almost all (94.9%) had excellent (>95%) adherence.

Association between combination antiretroviral therapy adherence and direct healthcare cost

Understanding the relationship between cART adherence and healthcare costs should help funders and program managers decide whether interventions to monitor and improve adherence are worthwhile. Cost models suggest that excellent adherence could be cost-effective in the United States [74], but few data are available from resource-limited settings.

Nachega *et al.* [75] found that in South Africa higher adherence to cART was associated with lower total monthly healthcare costs in a dose–response pattern, primarily due to significantly lower hospitalization costs for patients with higher cART adherence and despite the potentially significant cost of cART itself. The authors speculate that if cART costs continue to decline (e.g., by increasing availability of generic drugs), then the relative contribution of cART costs to total costs will decline, further accentuating cost savings in patients with higher adherence. This study did not consider indirect or social costs of adherence.

There is a critical need for research including assessment of cost-effectiveness of cART adherence in resource-limited settings as well as the impact of improving cART adherence on costs and clinical outcomes. In addition, there is critical need for studies of the efficacy and cost-effectiveness of simple, valid, and reliable interventions to improve cART adherence to assist funding and policy decisions in low-income and middle-income countries.

Adherence to combination antiretroviral therapy in current and postconflict settings

Early skepticism about providing cART to populations affected by violent conflict delayed guidance on this issue. Since 2003, Medecins Sans Frontieres (MSF) has been successfully providing cART care in conflict settings in the Democratic Republic of Congo and other countries [76]. Up to 2006, 494 patients, most in advanced stages of disease [WHO stages III (49%) or IV (34%)], had started on cART, and early outcomes were excellent, with a median CD4 gain of 163 at 6 months [interquartile range (IQR) 82–232]. Of note, excellent cART adherence, measured by pill counts and defined as more than 95% adherence at last clinic visit, was achieved by 99% of patients. Thus, it is not surprising that 12-month mortality (7.9%, IQR 3.6–12.1) and loss-to-follow up (5.4%, IQR 3.2–7.4) compare favorably to those in peaceful settings [77]. A recent evaluation of more than 1500 patients in northern Uganda who are affected by violence, predominantly due to the Lord's Resistance Army, found that excellent adherence was reported by 92.2% of patients and that better adherence was significantly associated with increased survival [78•].

These programs demonstrate that cART can be successfully provided in conflict or postconflict settings and should provide encouragement to humanitarian agencies currently unwilling to provide care for chronic diseases in such settings [76,77].

Pre-antiretroviral therapy attrition and retention in rollout combination antiretroviral therapy programs

Although early skepticism about likely adherence levels in Africa was adequately rebuffed by 2006, pre-ART attrition and long-term retention of patients in care programs in low-income and middle-income countries is emerging as an important issue in rapidly expanding cART programs.

Of 4570 patients followed up for at least 1 year in the Free State province of South Africa, 53.2% died. Eighty-seven percent of the patients who died had not received cART [79•]. In a study from Durban, South Africa, 82 cART eligible patients (16.4%) were lost before ART initiation. Of those, 28 (34.1%) had died [80•]. In Uganda, of the 4321 HIV-infected patients screened, 2483 were eligible for cART. Of those, 637 (26%) did not complete screening and did not start ART (mostly men). At about 1 year median follow-up, 181 (28%) had died. Seventy of 158 (44%) patients seen at follow-up said they had not started ART because they could not afford transport [81•]. In a 5-year HIV care program (2003–2007) in the Sihanouk Hospital Center of HOPE, Phnom Penh, Cambodia, Thai *et al.* [82•] reported a combined endpoint of mortality and loss to follow-up of 48.7% after 1 year in patients who were waiting for cART and this was significantly higher than that in patients on cART (log–rank $P < 0.001$).

Using data on 5491 adult patients starting cART in 15 treatment programs in Africa, Asia, and South America with at least 12 months of follow-up, the ART-LINC collaboration has investigated risk factors for no follow-up after treatment initiation and loss to follow-up or death in the first 6 months of cART initiation [83••]. Overall, 211 patients (3.8%) had no follow-up, 880 (16.0%) were lost to follow-up, and 141 (2.6%) were known to have died in the first 6 months. The probability

of no follow-up was higher in 2003–2004 than in 2000 or earlier [odds ratio (OR) 5.06; 95% confidence interval (CI) 1.28–20.0], as was loss to follow-up (hazard ratio 7.62; 95% CI 4.55–12.8) but not recorded death (hazard ratio 1.02; 95% CI 0.44–2.36). Lower baseline CD4 cell count was associated with a higher probability of no follow-up, loss to follow-up, and death. Compared with free treatment, fee-for-service programs were associated with a higher probability of no follow-up (OR 3.71; 95% CI 0.97–16.05) and higher mortality (hazard ratio 4.64; 95% CI 1.11–19.41). Possible explanation for poor retention during widespread scale-up of cART is that patients switch to a free clinic or one nearer to their homes. However, it is important that future studies try to identify these reasons.

MSF has recently reported encouraging results on 3595 adults enrolled over 5 years in a program in Cape Town, South Africa. Of these, 254 (7%) were lost to follow-up and 375 (10%) were known to have died during the observation period. The risk of death decreased rapidly during the first year on cART and remained constant thereafter, whereas the risk of being lost to follow-up decreased gradually over time [84]. However, as total annual consultations increased from 4157 in 2001 to 34 825 in 2005, without an increase in clinics providing care, the proportion lost to follow-up after 6 months on cART increased from 0 to 3.0%, underscoring the need for decentralization of services. After 5 years, 72% (95% CI 68–76) of all patients remained in care, 18% had died, and 13% were lost to follow-up. Younger age, history of prophylactic treatment at childbirth, and less than 6–12 months since cART initiation were associated with loss to follow-up.

The above pre-ART and post-ART attrition reports underscore the need for better patient-tracking procedures, better understanding of loss to follow-up, and earlier initiation of cART to reduce mortality. Therefore, well conducted evaluations of interventions to improve pre-ART and post-ART retention in low-income settings are badly needed.

Conclusion

In conclusion, although adherence is often high in low-income and middle-income countries, waning adherence over time and frequent loss of patients from monitoring programs during scale-up are emerging, interconnected, and poorly studied problems. Children, adolescents, and populations at increased risk for poor adherence should be the focus of thorough, well conducted studies to identify barriers to adherence, to develop appropriate interventions to maximize adherence and retention, and to evaluate the clinical effectiveness and cost impact of these interventions.

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