Antiretroviral Adherence in a Resource-poor Setting

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Adherence is key to successful antiretroviral therapy (ART). Many countries with increased HIV prevalence and the greatest need for ART have limited health resources. Recent assumptions that the adherence required for successful ART will not be achieved in resource-poor settings have led to calls for caution in expanded access programs. New studies from Africa refute this, showing excellent adherence and virologic outcomes. Major factors contributing to adherence or nonadherence are whether the drug is accessed for free or is self-funded, patient preparedness for use of ART, stigmatization related to being HIV-positive, and ease of use of regimen.

Introduction

Adherence to antiretroviral therapy (ART) has been repeatedly shown to be the key to successful virologic outcomes in both resource-poor and developed countries [1–6]. The greatest need for ART exists in countries with an increased prevalence of HIV. Many of these countries (eg, Africa, South America, or Asia) are limited in the health resources they can provide to an individual. Over the past few years, there has been a general assumption that the high levels of adherence required for successful therapy will not be achieved in such resource-poor settings, and a number of groups have called for caution in expanded access programs [7–9]. One major concern is that with expanded ART access, resistant strains of HIV will emerge, leading to the limitation of treatment options for the future [7,10•].

Having limited resources certainly makes scaling up ART access more challenging, but in reality, access will occur. Consequently, viral resistance will emerge, whether or not structured programs are in place [11]. People who are in need of therapy will go to some lengths to seek out ART, often buying therapy as they can afford it or seeking treatment from untrained practitioners. Poor antiretroviral prescribing practices and intermittent therapy will likely hasten the development of resistant virus. Implementing structured and regulated access to therapy, even on a large scale, should reduce this risk. Already many African countries—including South Africa, Senegal, Uganda, Cote d'Ivoire, and Malawi—have commenced government programs and other large observational cohorts, with published data showing high adherence or good virologic outcomes in some cases. [5,12•,13–16]. Community-based antiretroviral delivery has been successful in rural Haiti, and Brazil's large government ART program shows declining mortality from AIDS from 1996 until the present [17–19]. Only a subset of the studies published on ART delivery in resource-poor areas contain data relating to adherence.

Studies Measuring Cohort Adherence to Therapy

Table 1 lists 15 studies from resource-poor countries appearing in the recent literature. These papers detail adherence to ART in a number of diverse public sector health care facilities. Nine describe observational cohorts, and six describe a clinical trial setting. Often ART is supplied free through various government or non-governmental organization access programs, but in some cases, people are purchasing their own therapy. Adherence is comparable with similar cohorts in developed countries. The virologic response corroborates the adherence findings in the majority of cases. In addition, Table 2 lists three studies that describe specific adherence interventions in Africa.

Methods of measuring adherence

A number of methods are used to measure adherence. Such measures are usually classified as subjective (in the opinion of the patient) and objective (data recorded independently of the patient).

Subjective assessments include recall questionnaires: These are the most widely used tools to collect adherence data (Table 1), with the dosing recall expected from the patient varying from those missed in the past 3 days to the past month [12•,13,17,20–24]. Success of the measure varies according to the method of collecting the information. More open, accurate responses may be expected where a separate research team interviews the patient and the results are not reported to the clinical team [25]. Using the clinical team to administer the questionnaire may result in an overinflated estimate of individual adherence. In the Gugulethu site in Cape Town, the clinic counselors, who

Table 1. Studies from resource-poor countries that measure adherence

Author, year	Country	Adherence*	% VL < 400†	Measure(s)	N	Duration	ARV access, program type
Oyugi *et al.*, 2004 [12•]	Uganda	91%–94%	76.5	Self report (3-day recall), 30-day visual analogue scale, electronic medication monitoring, unannounced home pill count	34	3 months	Self-funded ART, clinical trial.
Orrell *et al.*, 2003 [5]	South Africa	87%–92%	70.9	Clinic-based pill count	289	12 months	Free ART, clinical trials.
Nachega *et al.*, 2004 [21]	South Africa	> 90% for 97% of cohort	75 (includes 33% cohort on dual therapy)	Self report (30-day recall)	66	Cross-section (median 18 months)	Mixed free and self-funded ART. Observational cohort and clinical trials.
Lanièce *et al.*, 2003 [13]	Senegal	91%	Not given	Self report (30-day recall, pill count (pharmacy)	158	Cross-section (median 21 months)	Self-funded ART, observational cohort
Byakika-Tusiime *et al.*, 2005 [20]	Uganda	> 95% for 68% of cohort	Not given	Structured patient interview collecting 3-day recall	304	Cross-section (mean 7–12 months)	Self-funded ART, clinical trial
Laurent *et al.*, 2005 [32••]	Senegal	88.1% > 95%	61.8	Self report (30-day recall)	176	36 months	Patient and government co-pay, observational cohort
Weiser *et al.*, 2003 [26]	Botswana	> 95% for 54% of cohort	Not given	Self report (up to 1 year), health care work interviews	109	Cross-section	Self-funded ART, observational cohort
Laurent *et al.*, 2004 [32••]	Cameroon	99%	80	Self report (7-day recall), plasma drug levels	55	6 months	Free ART, clinical trial
Remien *et al.*, 2003 [17]	Brazil	> 90% for 82% of cohort	Not given	Self report (4-day recall)	200	Cross-section, nonrandom convenience sample	Free ART, observational cohort
Boulle *et al.*, 2005	South Africa	> 95% for 92.4% of cohort	89	Self report (4-day recall). Separate research team	110	12 months	Free ART, observational cohort
Brigido *et al.*, 2001 [6]	Brazil	~95% for 60% of cohort	58 if good adherence > 93; 43 with ≤93	Structured patient questionnaire (30-day recall)	168	50 months	Free ART, observational cohort
Weidle *et al.*, 2002 [27]	Uganda	> 95% for 88% of cohort	~45	Self report (since last visit)	221	Cross-section	Self-funded ART, observational cohort
Eley *et al.*, 2004 [31]	South Africa	> 85%	75	Pediatric syrup returns	17	12 months	Free ART, observational cohort
Landmon *et al.*, 2003 [28]	Senegal	> 95% for 95% of cohort	95	Self report (3-day recall), plasma drug levels	40	6 months	Free ART, clinical trial

* Adherence is either given as a single mean percentage value for the whole cohort or as the proportion of the cohort achieving adherence above a defined percentage.
† Triple therapy, unless otherwise stated.
ART—antiretroviral therapy; ARV—antiretroviral drugs; VL—viral load.

Table 2. Studies describing adherence interventions

Author	Country	Key factors	Intervention	*N*	Duration	Outcome	Program type
Coetzee *et al.* [14]	South Africa	Primary care setting. Continuity of care.	Clinical (WHO 3 or 4, CD4 < 200), adherence (to visits, cotrimoxazole) and social (disclosed to treatment partner, live at address) criteria met pretreatment. Three structured patient preparation sessions, on Rx support (counselors on-site, peer support groups, material support—pill box, diary, dosing schedules).	287	24 months	69.7% with viral load < 400 copies/mL	NGO-funded, observational
Orell *et al.* (Bangkok poster) [24]	South Africa	Primary care setting. Dedicated counselor visits to homes.	Three counselor-based treatment readiness sessions with assessment. Home visit pretreatment. Monthly on-treatment support groups	84	12 months	92% with viral load < 400 copies/mL	PAWC/research
Frick *et al.* [30]	Kenya	STI/family planning clinic.	Alarmed vs nonalarmed medication bottles.	140	1 month	82% with adherence > 95% in alarmed cohort vs 36% nonalarmed	Randomized, controlled trial

NGO—non-governmental organization; PAWC—province of Western Cape; STI—sexually transmitted infections; WHO—World Health Organization.

are also responsible for adherence education and home visits, administer the recall questionnaire. The median adherence is 100%. It is speculated this may be due to the patient fearing disapproval from the clinical team if they admit poor adherence [24]. A 30-day visual analogue scale of doses taken used by Oyugi *et al.* [12•] seems a faster and more efficient means of obtaining similar information to the recall questionnaire.

Objective adherence assessments included pill counts, Medication Event Monitoring System (MEMS) caps recordings and plasma drug level monitoring. Pill counts are valuable but can be time consuming in a busy clinic, especially if the medication is being redispensed after each visit, resulting in an increase in the total number of tablets returned each month. There is the innate risk of people dumping their tablets to "improve" their adherence, but this is not a dominant feature of the experience in Cape Town, nor is it in Uganda [5,12•,24]. Surprise or unannounced pill counts at home may decrease the risk of pill-dumping but would require a dedicated team of counselors to visit every client at home and may not be a practical approach to monitoring adherence on a large scale [12•,24].

There is not much experience with the use of MEMS caps in developing countries. Only Oyugi *et al.* [12•] used this method, which is accepted as one of the best means of objectively assessing adherence in the developed world but is prohibitively expensive for most resource-poor settings. Two clinical trials used plasma drug levels as a marker for adherence. Although this may be a useful procedure in selected patient subsets (eg, those failing virologically with high recorded adherence), the use of this tool to measure adherence in expanded access programs is not practical.

All measures are only an approximation of adherence in the end. The study by Oyugi *et al.* [12•] was the only one to provide a comparison across four of the above methods; they found no significant difference between the measures and excellent correlations of each of them with viral outcomes.

Recurring themes

A number of issues impacting on adherence recur throughout the papers in Table 1. The most important of these are discussed below.

Self-funding

ART contributes to poor adherence. Either inadequate regimens, such as dual nucleoside therapy, are purchased, or treatment is purchased erratically. Adherence tends to decrease as the contribution to drug costs by the individual increases. Antiretroviral agents are expensive for people in countries where the average income per year may range from $240 to $300 (eg, Senegal, Uganda) [13,20–22,26,27]. Lanièce *et al.* [13] showed a marked increase in mean adherence when drug costs fell due to the introduction of access-pricing in late 2001. Inability to pay was the most important barrier to adherence in Uganda [20,27]. Nachega *et al.* [21] showed that a large number of patients paying for their own ART were on inadequate therapy, usually dual nucleoside regimens. In Brazil, needing money for transportation to attend the clinic was a factor associated with nonadherence [6]. Adherence to antiretrovirals is good in all cohorts where drug is provided at no cost to the patient (Table 1) [5,6,17,22–25,27,28]. Weiser *et al.* [26] predicted a 20% improvement in adherence in Botswana if treatment was free.

Fear of being stigmatized

Nachega *et al.* [21] noted that fear of being stigmatized by their families or community (including fears of physical violence and/or rejection) was independently associated with poor adherence. This fear often results in nondisclosure of HIV status to families and sexual partners. From our experience of more than 1000 people on antiretrovirals at three sites in Cape Town, people who have not disclosed their HIV status do worse on therapy. They have frequent treatment interruptions, as tablets must be hidden and cannot be taken when others are present. Qualitative data from patient interviews at Médecins Sans Frontières (MSF) clinics in Khayelitsha, Cape Town confirms this (Des Michaels, personal communication). Weiser *et al.* [26] noted a tendency to better adherence with disclosure of HIV status to others (odds ratio, 3.55; confidence interval, 0.91–13.92). People tend to want to reduce contact with the clinic, both because visiting a clinic may be costly (in terms of both money and time), and there is a risk of being seen by others and potentially having their HIV-status exposed [13,26]. Clinic-based directly observed therapies (DOT), requiring daily clinic visits, would be a disadvantage for this reason.

It is widely expected that the ongoing encouragement of disclosure of HIV-status among a community with an ART program may in time result in an increased uptake of voluntary counseling and testing (VCT) and a subsequent reduction in stigma and discrimination as more people learn their status [29].

Ease of regimen

Lanièce *et al.* [13] showed that efavirenz-based regimens (twice daily dosing, smaller tablet burden) were better adhered to than indinavir-based therapy (3 times a day dosing, larger tablet burden); and a generic fixed-dose combination (1 tablet, twice daily) showed superb adherence in the Cameroon [22]. Generics are beneficial if they are easy to take, are cheaper, and are of high quality [22]. Pill burden is often, but not always, found to be a significantly contributing factor to adherence [5,20]. Logic dictates an easy regimen would be preferable and more easily tolerated, at least for first line regimens. Dosing schedule usually is important. Orrell *et al.* [5] showed a reduction in adherence with increased doses per day, as did Nachega *et al.* [21].

Between 8% and 17% of some cohorts cited adverse events as a contributing factor to poor adherence [6,20,25–27]. All medication side effects, however minor, should be actively managed.

Continuity of care

Coetzee *et al.* [14] suggests that having smaller patient-centered clinics, with manageable patient numbers, will improve adherence as the patient will see the same team at each visit. One of the successes of delivering antiretrovirals in Gugulethu, Cape Town has been the low counselor to patient ratio. A counselor assigned to a patient at their first clinic visit remains their first point of contact with the clinic. Qualitatively, this has been key to patient retention and adherence on this program [24].

Maintaining small clinics will be challenging in the African-context with large numbers of people requiring therapy. The increasing use of lay peer counselors, often HIV-positive themselves, to maintain the low staff to patient ratio (of 1:50) is an attractive option; although high staff numbers will be required, the relatively low cost of employment of such lay staff ($300 a month) makes this feasible. In addition, expanded access ART programs become a source of employment for the local communities.

Patient preparedness

The use of a multidisciplinary team to prepare patient for treatment is considered key to long-term success in a number of ART programs [6,14,18,24]. Lay peer counselors provide invaluable insight to the clinical team and carry much of the burden of patient education. There is a shift away from the paternal medical view of "do what the doctor says" to one where the patient takes responsibility for their health and well-being. Thorough education about HIV disease and of the risks and benefits of therapy should occur prior to starting therapy and preferably in the patient's home language [5]. Issues of disclosure should be discussed at length. Two Cape Town programs have shown great success with this approach [14,24], and education is a key part of the Haiti government antiretroviral program [18]. Patients should have a belief in the efficacy of ART and be aware of the need for near perfect adherence. Skepticism about ART may result in poor adherence [6].

Ongoing adherence support

Forgetfulness is a common reason for nonadherence [6,20,23,25]. People are more likely to forget their ART with a disruption of their living pattern, such as being away from home, either at weekends or due to traveling for work [20,21,26] Adherence also seems to decrease temporally [13,14]. Ongoing adherence counseling is needed at each visit from clinical, dispensing, or counseling staff. On-treatment support groups may be valuable. Material support in the form of treatment diaries or pillboxes is important in reminding people to take their doses. These items need not be costly and can be made at the clinic or at home. Alarmed pill bottles improved adherence in a cohort of women in Mombasa [30].

A treatment partner, as used by the MSF program (a family member or friend who "buddies" with the patient on treatment), may be a valuable adjunct to long-term adherence [3,25]. The rural ART delivery program in Haiti successfully uses trained community workers to deliver DOT to each patient at home [18]. In our experience, clinic-based DOT is not necessary to achieve adherence to therapy in the first instance [5,24] and may not be practical in some situations (eg, rural areas) due to large distances that would need to be traveled. In addition, fears of exposure or stigma result from frequent clinic visits [13,31]. Using a treatment partner or community-based DOT would be preferable, particularly as a focused intervention for those who had proven themselves to be poor at adhering to ART.

Conclusions

Adherence to therapy itself is no worse a problem in the described resource poor cohorts than developed countries. Resource-poor countries are not uniform and many health care settings will adequately support ART therapy already [17]. Programmatic emphasis on adherence, as well as laboratory and clinical support from the outset is crucial. The approach to adherence support should be multifactorial [11].

Delivery of ART should be free or of minimal cost. Generic fixed-dose combinations may play a valuable role in reducing cost and creating an easy treatment regimen, providing quality can be assured [21]. A sustainable drug supply is critical.

Therapy, even in the very ill, should not precede comprehensive patient treatment-readiness education. Disclosure of HIV-status to a loved one prior to commencing ART should be actively, but sensitively, encouraged.

The multidisciplinary team delivering ART needs to identify a means of measuring adherence that is practical in their setting. Either a clinic-based pill count or a self-report questionnaire (or 30-day visual analogue scale [12•]) is available and easy to use in resource-poor settings. Increasing viral loads may be used as a late surrogate marker for poor adherence, if they are available. Adherence should be actively encouraged by all members of the team at every encounter with the patient.

A plan for adherence improvement should be implemented if poor adherence is identified. This may include a repeat of the patient-preparedness process, the use of material support (pillbox, diary card), increased support-group visits, and/or the use of a treatment partner or buddy to encourage dosing or even directly observe the dose at home. Surprise home pill counts by a member of the ART team and clinic-based DOTs could be reserved for those hardened in non-adherence.

Expanding access to antiretroviral therapy to the people needing treatment across the resource-poor areas of the world remains a daunting prospect. Although the data from these initial cohorts is extremely positive, there remains an anxiety that the clinical and political pressure to enroll large numbers of people onto ART programs may adversely influence the quality of the service rendered. Both new and existing ART programs need to maintain a

focus on adherence and create systems and structures that withstand the process of expansion.

The days of using the fear of poor adherence in poor countries as an excuse for not implementing ART programs are over. The problem lies not with the people living with HIV, who have repeatedly proved their ability to adhere, but with the financial and political will of the global community to learn from these first studies and to embark on the process of establishing sustainable programs of access to antiretroviral therapy for all.

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