HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2019 August 28.

Published in final edited form as:

AIDS. 2005 August 12; 19(12): 1243–1249. doi:10.1097/01.aids.0000180094.04652.3b.

No room for complacency about adherence to antiretroviral therapy in sub-Saharan Africa

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Abstract

Medication adherence is essential to successful treatment of HIV/AIDS. Maintaining high adherence will likely prove a major challenge in Africa —just as it has in developed nations. Despite early reports suggesting that adherence would not pose a major barrier to treatment success, more recent research shows that adherence rates in Africa are quite variable and often poor. Given the large number of patients whose disease will progress if adherence is suboptimal, research is urgently needed to determine patient-level behavioral barriers to adherence and the most effective and appropriate methods for assessing adherence in African cohorts.

Keywords

antiretroviral therapy; HAART; HIV/AIDS; adherence; Africa; PEPFAR; Global Fund; behavioral research

Introduction

While highly active combination antiretroviral therapy (HAART) dramatically reduces morbidity and mortality due to AIDS [1,2], these benefits critically depend on patients achieving and maintaining high levels of medication adherence. Missing more than 5–10% of doses is linked to incomplete suppression of viral replication, declining CD4 cell counts [3-5] clinical progression to AIDS or death [3,6-8], and the development and spread of antiretroviral drug-resistant HIV [9-13]. Just as human behavior is the key to preventing HIV infection, behavior is arguably the most important determinant of successful treatment outcomes [3,5-8,14,15].

The unprecedented multilateral support through the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, TB and Malaria (GFATM) are necessary to alleviate structural barriers to treatment in low resource countries and to expand access to essential drugs. However, even if all structural barriers to HAART are removed, HAART programs can still fail if they do not adequately address behavioral factors influencing adherence. Notwithstanding several encouraging reports on African populations [5,16,17], recent reports show that HAART adherence and clinical success rates vary widely

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across sub-Saharan programs, and offer no justification for complacency at this stage in our response to the global HIV/AIDS pandemic.

The challenge of measuring adherence

Medication adherence research from developed nations makes clear how difficult adherence is to measure accurately. In the absence of directly observed therapy, levels of adherence can only be estimated by use of surrogate measures. Commonly used methods include pill counts, pharmacy refill records, drug level monitoring, electronic drug monitors (EDM), and various selfreporting tools, such as questionnaires and visual analog scales. Each method has clear advantages and disadvantages (Table 1).

Knowledge of the comparative accuracy of different surrogate measures is based mainly on research conducted in developed countries over the past decade. Arnsten *et al.* reported mean HAART adherence rates of 79% by self-report but only 53% by EDM. Moreover, patients whose EDM data indicated high adherence (above 90%) were far more likely to achieve undetectable viral load (UDVL) than patients self-reporting the same level of adherence [18]. Liu *et al.* concurrently compared several measures against patient UDVL rates [19]. Mean adherence using EDM was 63% versus 83% for pill count and 93% for self-report. However, among patients who failed to achieve UDVL at 8 weeks, mean adherence was 87% for self-report, 74% for pill count, but only 59% for EDM. In both these studies, the poor association between self-report or pill counts and UDVL – compared with the relationship between EDM and UDVL – implied that they greatly overestimated true adherence. Similarly, a recently validated self-report instrument achieved 72% sensitivity and 91% specificity for detecting good (above 90%) adherence using EDM as the reference standard [20]. A simple interpretation of this finding is that skepticism is warranted when patients report high adherence, though patients should generally be believed when reporting poor adherence.

Trials of directly observed HAART provide additional evidence of the accuracy of EDM. Since adherence can be known precisely, the link between adherence levels and UDVL can be established with a high degree of confidence. One trial studied the effectiveness of azidothymidine/lamivudine/abacavir among HIV infected prisoners. Mean adherence was 94% with 85% of inmates achieving UDVL [21]. These results are remarkably similar to the relationship between UDVL and EDM-rated adherence: Paterson *et al.* observed UDVL in 80% of those with above 95% adherence, [3] while Arnsten *et al.* found UDVL in 78% of those with above 90% adherence [18].

These observations allow us to construct an approximate hierarchy of adherence measures, with physician assessment and self-report being least accurate, pill counts intermediate, and EDM the most accurate surrogate adherence marker. At least in developed country cohorts, self-report and pill count appear to greatly exaggerate actual adherence rates. Whether this hierarchy holds true for resource-poor country populations is currently unknown.

What is known about HAART adherence in Africa?

One of the earliest reports found high (above 90%) mean self-reported adherence and relatively high proportions (71%) achieving UDVL [5]. This attracted much attention in the scientific and lay press given earlier concerns about the feasibility of HAART in Africa [22]. Notably, the New York Times responded with a headline reading 'Africans Outdo US Patients in Following AIDS Therapy' [23]. However, the study's patients may not have represented a generalizable example as all were concurrently enrolled in ongoing randomized controlled trials, and would have benefited from the structural supports provided by the trial. Moreover, the analysis excluded the adherence data for 52 subjects (16% of the total) who abandoned HAART before completing 48 weeks of follow up. Average adherence for the overall group would certainly have been lower had these subjects been included.

That said, several more recent reports of African HAART programs, most of which were not part of clinical trials, also reported high levels of adherence. In general, most relied on self-reported adherence, followed small numbers of patients for short periods, or were cross-sectional analyses and thus could not comment on sustained adherence rates (see Table 2).

However, a growing number of programs have now reported mediocre or poor adherence, and in the few studies that reported longitudinal data, declining adherence over time (Table 2). In Senegal, Laurent *et al.* noted that over 95% of their patients had adherence exceeding 80% after 1 month on therapy, but 18 months later only 80% of patients remained above that level. Concurrently, the proportion of their patients with UDVL fell from 79.6 to 59.3% [24]. In Cameroon, Akam reported that mean self-reported adherence was initially only 68% and declined further over time [25].

Few studies compared multiple surrogate measures in parallel. Oyugi *et al.* measured adherence via self-report, pill count, visual analog score, and EDM, and found adherence levels at 24 weeks of 85, 86, 88, and 82%, respectively, implying a high degree of concordance between the various measures, and leading to speculation that the relationship between EDM and self-reported adherence in African cohorts might be tighter than was seen in US studies [26]. However, these rates only applied to the 46% (32/70) of their participants who completed 24 weeks of observation, and the investigators only reported aggregate UDVL rates. In contrast, Omes *et al.* reported highly discordant levels of adherence between two forms of self-report: questionnaire and visual analog scale [27]. Neither study provided data on which surrogate marker best predicted UDVL, therefore precluding conclusions about their relative accuracy. In studies that did report both UDVL and measured adherence, the association was frequently poor. Eholié *et al.* in Côte d'Ivoire reported that 52% of their patients were poorly adherent, and that HIV was often detectable even among those reporting over 90% adherence [28]. A report from Durban, South African was perhaps most striking: with 100% of patients self-reporting 100% adherence, only 57% actually achieved UDVL [29] — a result highly reminiscent of US studies showing a significant disconnect between self-reported adherence and clinical success [18,19].

Where do we go from here?

Several observations emerge. First, reports that generalize about ‘adherence rates in Africa’ should be interpreted cautiously. A safer conclusion would be that adherence is proving to be highly challenging in African cohorts — just as it has for patients living in North America or Europe. We also question whether publication bias might lead results from less successful programs to go un-reported. Second, given growing doubts about the accuracy of self-reported adherence, some programs which appear to be successful may, in fact, be less so. Our interpretation of the limited data, notably those studies showing high self-reported adherence but low attainment of UDVL, [29,30] is that self-report is proving to be as unreliable a measure of adherence in Africa as it has elsewhere [18,19]. Third, external multinational funds should be allocated to supporting and studying adherence, and should not stop merely at the provision of test kits, basic training, and medications. Fourth, assuming successful models of adherence support can be found, it is uncertain whether they can be sustained with the often-limited support available from the public sector in many sub-Saharan countries. Notably, three of the lowest performing programs all appeared to have received little external technical or financial support through collaborations with foreign investigators or aid agencies. In contrast, the well-supported Médecins Sans Frontières (MSF) programs all included comprehensive adherence support mechanisms, and were among the most successful in terms of high reported adherence, low default rates, and high proportions of patients with UDVL. It would be extremely valuable to learn what aspects of MSF’s adherence structures could be adapted cost-effectively and at scale in other settings.

These reports also help focus the research agenda for coming years. First and foremost, qualitative research into the behavioral reasons for patient non-adherence is urgently needed. The African adherence studies to date have all limited their scope to reporting adherence rates and occasionally population-level risk factors for non-adherence. Unfortunately, while epidemiologic studies are helpful at identifying ‘Who is non-adherent?’ they provide less insight into the more pressing question of ‘Why?’ a given patient chooses to adhere or not. Similarly, once a sufficient level of adherence is achieved, what are the behavioral factors that foster sustained adherence? Second, for programmatic evaluation, it is important to determine the most accurate and cost-effective approach to measuring adherence in African populations. To provide a common point of comparison between studies and populations, we feel strongly that the relative accuracy of surrogate adherence measures should always be indexed against an external clinical gold standard. UDVL may be best suited for this role, though rising rates of resistance and other factors could lead to an underestimation of adherence rates over time. Another option would be drug level monitoring, though operationalizing this would no doubt prove enormously challenging.

We have learned much over the past decades about treating HIV infection in developed settings. However, because of the demanding and unforgiving nature of the disease and our dependence on human behavior to take these highly effective medications, it is essential that we both truly understand the local complexities of adherence behavior and can respond to it effectively. It is important that the scope of programs funded by large multinational programs (PEPFAR, GFATM) support investigation of these issues within the context of existing and future programs.

Acknowledgements

C.J. Gill notes that support for his work on this paper was provided through NIH/NIAID K23 AI62208 01. Additional support was provided through the US Agency for International Development. Neither funder played any role in this article's design or had any input into its content, which does not necessarily reflect their views.

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Table 1.

Summary of methods for assessing adherence.

Method	Advantages	Disadvantages	Direction of potential bias	Comments
Physician's assessment	Simple Cheap Requires no structured tool	Subjective Inaccurate Adherence estimates may affect/be affected by physician-patient relationship	No particular bias	*De facto* manner in which adherence is usually assessed Inaccurate both for predicting adherence and non-adherence [31-33] One study noted that physicians correctly rated their patients' adherence 40% of the time [3]
Patient self-report	Simple Cheap Allows qualitative assessment of adherence	Subjective Inaccurate Accuracy can be affected by: poor patient recall, failure to recognize mistimed doses, dose missed over holidays/ weekends as non-adherence, lack of patient candor	Overestimates adherence	Currently the most widely-used adherence measure More accurate for predicting non-adherence than high adherence [20] Encompasses a variety of techniques, including unstructured interviews, visual analog scales, and standardized questionnaires One study found that patients recalled only 41% of documented visits, while 28% recalled visits that never occurred [34] One study found that of patients who denied missing any protease inhibitor doses, 50% had undetectable levels [35]
Pill counts	Simple Cheap Objective	Accuracy can be affected by: throwing away remaining pills prior to seeing provider (pill dumping), inability to confirm who took pills, no information on timing of doses	Overestimates adherence	Frequently used in research alone or in combination with to patient self-report
Pharmacy refill records	Objective	Requires that patients bring in bottles Accuracy can be affected by: inability to confirm who took pills, inability to confirm timing of doses taken Requires capacity to maintain records and track patients over time	Overestimates adherence	Evidence has linked high refill rates with improved outcomes [36] Frequently used in research in addition to patient self-report
Drug level monitoring	Objective	Expensive Technically difficult (requires laboratory, testing capacity) Invasive (requires blood draws) Accuracy can be affected by: limited time frame of test effectiveness (3–4 days), inability to confirm timing of doses taken Requires baseline PK profile of population under study for accurate interpretation of results	Can overestimate or underestimate depending on: patient behavior immediately preceding test genetic variations in drug metabolism	One study found that patients with low ratios of observed to predicted concentrations of efavirenz were less likely to have UDVL [37]
Electronic drug monitoring	Objective Provides data on timing of doses taken Permits monitoring over long periods	Expensive Requires training, computer, operator, and specialized pill bottles Intrusive (patients may resent being monitored) Accuracy can be affected by: inability to confirm who took pills Incompatible with pill trays	Underestimates adherence (patients may take out multiple doses at a time for later use)	EDM more accurately predicts UDVL than self-report or pill count [19]

UDVL, Undetectable viral load; PK, Pharmacokinetic; EDM, electronic drug monitor.

Table 2.

Recent reports on highly active antiretroviral therapy programs in sub-Saharan Africa.

Country	Lead author	External support	Cohort size	Study design	Surrogate markers	Reported adherence rates	Duration of Observation	Comments
Programmes without apparent external supports								
Cote d'Ivoire	Eholie [28]	NA	308	CS, PL	SR	48% with > 90% ADH	22 months per patient	Mean VL was 2.9 $\log_{10}$ copies/ml for patients with >90% ADH
Cameroon	Akam [25]	NA	333	PL	Not stated	Mean ADH was 68%	≥ 12 months per patient	Declining adherence note over time
Botswana	Nwokike [38]	NA	176	CS	SR, PC	Mean ADH was 83%	Not stated	Author concluded that ADH was 'sub-optimal'
Programs with known external supports								
Burkina Faso	Traore [39]	Author or co-author	80	CS	SR	30% 'completely adherent'; 70% 'non-adherent'	NA	Counseling helped 75% of previously 'non-adherent' to improve adherence
Uganda	Byakika-Tusime [40]	Author or co-author	304	CS	SR	67% with > 95% ADH; 71% with > 80% ADH	NA	60% three-drug ART; 30% two-drug ART; 10% monotherapy
South Africa	Brown [29]	Author or co-author	50	CS	SR	76% with 100% ADH; 8% with ≤ 50% ADH	NA	Mean UDVL was 55%; 57% UDVL for patients claiming 100% ADH
South Africa	Ferris [41]	Author or co-author	74	CS	SR	Mean ADH was 91%; 77% with ≥ 95% ADH	NA	97% with UDVL if ≥ 95% adherence; 65% with UDVL if <95% adherence
Nigeria	Daniel [42]	Author or co-author	53	CS	SR	79% with ≥ 95% ADH	NA	Final mean CD4 cell count was 262 × 10^6 cells/l
Senegal	Laurent [24]	Author or co-author	58	PL	SR	98% with ≥ 80% ADH at month 1; 81% with ≥ 80% ADH by month 18	18 months	Progressive decline in adherence and proportion of patients with UDVL
Uganda	Shihab [30]	Author or co-author	137	CS	SR	82% with 100% ADH	NA	66% achieved UDVL
South Africa	Darder [17]	MSF	539	PL	SR	88% with > 95% ADH at 1 month; 89% at 3 months; 88% at 12 months	12 months	UDVL levels correlated with adherence levels
Uganda	Oyugi [26]	Author or co-author	70	PL	SR, VAS, PC, EDM	PC ADH, 86%; SR ADH, 85%; VAS ADH, 88%; EDM ADH, 82%	24 weeks	Overall 78% with UDVL Only 32/70 patients completed 24 weeks of observation
Rwanda	Omes [27]	Author or co-author	95	CT	SR, TDM, VAS	SR, 95% with 100% ADH; VAS, 87% with 100% ADH; TDM, 85% in therapeutic range, 15% detectable	Not stated	>90% reported side effects

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Country	Lead author	External support	Cohort size	Study design	Surrogate markers	Reported adherence rates	Duration of Observation	Comments
Uganda	Muganzi [16]	MSF	530	PL	SR, PC	98% with > 95% ADH	Not stated	1.3% defaulted from HAART program; 10.2% died
DRC	Tu [43]	MSF	30	PL	SR, PC	100% with 100% ADH at 3 months	3 months	Mean increase in CD4 cell count, 153×10^6 cells/l
Mozambique	Gialloreti [44]	Author or co-author	82	PL	Not stated	ADH was ‘very high’	Not stated	71% achieved UDVL

ADH, Adherence; ART, antiretroviral therapy; CS, cross sectional; CT, clinical trial; DRC, Democratic Republic of Congo; EDM, electronic drug monitor; MSF, Médecins Sans Frontières; NA, not applicable; PC, pill count; PL, prospective longitudinal; SR, self report; TDM, Therapeutic Drug Monitoring; UDVL, undetectable viral load; VAS, visual analog scale; VL, viral load.