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Editorial

When and How Should we be Measuring Adherence to Antiretroviral Therapy in Resource-Limited Settings?

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Introduction

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The primary goal of treatment with antiretroviral therapy (ART) is to prevent HIV-related morbidity and mortality. The effectiveness of ART has been clearly demonstrated, as have the positive relationships between adherence to ART and viral suppression, increased CD4 cell count, positive clinical outcomes, [1], [2] and reduced mortality. [3] More recently it has been shown to be associated with reduced risk of transmission to uninfected partners [4]. High levels of adherence are critical for successful treatment. Accordingly, for ART programs to achieve their population level goals, individual adherence must be monitored accurately and frequently and prompt action must be taken when poor adherence is identified. [1], [4], [6]

While the issue of adherence has been extensively studied, as the ART adherence research agenda matures, several issues around ART adherence remain critically important for further investigation including: (i) how to accurately measure adherence, (ii) how often to measure adherence in order to improve treatment outcomes, (iii) what modifiable factors are predictive of poor adherence and are targets for intervention, and (iv) what interventions will be most effective at improving treatment adherence?[7] Each of these questions requires careful consideration as we move into the next phase of the ART roll-out where sustaining gains already made will be just as important as expanding access.

For HIV treatment, a high level of adherence equates to taking at least 80%, and possibly as high as 95%, of the correct medication, in the correct quantities, at the correct time. [1], [8], [9], [10], [11] While reasonably easy to define, adherence to therapy is notoriously difficult to measure accurately [7] and to date, there has been no clear consensus on the ideal way to measure it in resource-limited settings. [12], [13]

In order to act as quickly as possible for patients with poor adherence, clinicians working with patients taking ART could benefit greatly from a simple, inexpensive, reliable method for detecting the prevalence of poor adherence. [13] Such a measure would ideally be low cost, brief and non-intrusive so that it could be used many times over the course of treatment. [14] It should be reliable and acceptable to respondents while also being sensitive enough to measure change. It would also be beneficial to establish the causes of non-adherence so that adherence services could be tailored to support specific patient needs. [14] Several approaches to monitoring adherence, including self-report, pill counts and lab monitoring are currently in use and meet each of these criteria to varying degrees, but none meets them all.

Self-report is the most commonly used method for measuring adherence in routine clinic settings. It has been shown to be reasonably well associated with viral suppression. [15], [16] Self-report data is easy to collect, inexpensive and flexible (questionnaires suit different language abilities) and can distinguish between non-adherence that is intentional (where the patient chooses not to take medicine, for example when they start to feel better or if it makes them feel worse) and unintentional (when the patient forgets about taking their medicine) [17]. This last point is important as non-adherence can be the result of several different underlying causes, each of which requires different interventions. [7], [14] Despite its usefulness, self-report data tends to over-estimate adherence,[18], [19], [20] and typically only reflects short-term adherence. Future efforts around self-report must improve the sensitivity and specificity of the approach and address whether questionnaires to assess adherence remain valid when translated and modified for different populations (i.e. different ages, sexes, socioeconomic and educational backgrounds) and countries.

The visual-analogue scale, Likert item (rating scale), pills identification test (PIT) and medication possession ratio, briefly described below in Table 1, provide estimates of ART adherence which correlate reasonably well with HIV viral suppression. [21] These simple adherence measures are inexpensive and easy to administer. However, they require validation and adjustment prior to implementation in the routine clinical setting. On their own, surrogate non-computerized methods such as pill-counts or Simplified Medication Adherence Questionnaires (SMAQ) all have strengths, but they also have drawbacks and limitations (Table 1). The same is true of computerized methods such as computer-assisted self-administered interviews [22], electronic pill monitoring (micro-electronic monitoring), appointment keeping/missed visits, medication possession ratio, prescription refill days or dispensing records. Advanced technology, high cost and logistical requirements have precluded the wider application of some of these methods in sub-Saharan Africa. [23] An effective adherence program for resource-limited settings may, therefore, require the combination or "triangulation" of a number of inexpensive surrogate and non-surrogate markers. [14] These inexpensive and easy to administer markers may be incorporated into electronic patient management systems to flag patients at risk for virological failure due to poor adherence. However, rigorous evaluation of these methods under routine clinical settings has yet to be conducted.

Laboratory markers provide another approach to assessing treatment adherence. Viral load is perhaps the best and most reliable indicator of poor adherence (through detection of circulating virus and treatment failure) but is expensive and not easily accessible or available in many resource-limited settings. [24] As viral load is rarely accessible in resource-limited settings there is a need to identify affordable and accessible laboratory markers that correlate well with adherence, preferably one like CD4 count which is used as part of routine care. [25] Although a rise in CD4 cell count on ART is more evident in patients with >95% adherence, it has been shown to be a poor predictor of treatment failure. [26] Other markers of adherence, including mean cell volume for patients on zidovudine or stavudine, serum lactate for patients on stavudine and serum lipid levels for patients on protease inhibitors have been investigated to measure adherence in the routine clinical setting. [27], [28], [29], [30] While each has shown promise, many of the markers that might be used to monitor

adherence are not routinely collected. In addition, questions still remain about the cost, accessibility and reliability of these methods in resource-limited settings.

It remains to be seen whether any low cost laboratory based monitoring strategy will be effective in routine care. It will likely be necessary to develop new low cost laboratory-based monitoring tools to measure adherence affordably, accurately and reliably in the routine clinic setting.

After sorting out how to measure adherence, the next important question is how often to assess it. Much of the data on the usefulness of adherence measures come from research studies that have measured adherence monthly [30]. The World Health Organization (WHO) recommends continued adherence monitoring after ART has started but does not recommend one specific method or interval [31]. Nevertheless, how often adherence is measured may be of critical importance in preserving the effectiveness of first-line ART since studies from developed countries have linked duration of treatment failure to frequency and complexity of mutation profiles [32], [33], [34]. Recent data suggest that patients should be switched within 8 weeks of virologic failure to ensure sustained virological suppression and better clinical outcomes. [35]

Data from several studies shows that possibly as much as 30% [34], [36] of subjects who experience virological failure on a first-line regimen have no HIV drug resistance mutations present, while studies have found similar results for patients failing second-line ART. [24], [37] These patients, and possibly others, could benefit from adherence interventions if poor adherence was identified earlier. Such a strategy could be effective as two South African studies showed that 40-50% of patients with at least 1 viral load above 1000 copies/ml after ART initiation resuppressed their viral load after adherence counselling [38], [39]. Early identification of poor adherence may not only result in better treatment outcomes, but could also conserve and maximize ART regimens in settings where therapeutic options are limited. Further research is needed to determine whether more frequent measurement of adherence in routine settings could preserve first-line regimens and reduce the need for expensive second-line treatment.

Table 1. Measures of adherence (*non-surrogate markers of adherence)

Method	Description	Advantages	Disadvantages
Self-report	Patient recall – either count based or estimation recall over a recent period of time (i.e. patient's assessment of pills taken in the last week out of those expected to have been taken). The recall periods could be 4 days, 1 week or 1 month	Long-standing, most common method. Simple and efficient. Short recall period of 4 days correlates with adherence rates obtained from other measures of adherence such as viral load monitoring. Easy to implement and uses existing resources	Recall-bias, time-consuming and subject to errors (over-estimation)
Simplified Medication Adherence Questionnaire (SMAQ)	Widely used tool for self-reporting. Based on Morisky scale [16]-questions are asked pertaining to perceptions and practices around medication adherence	Patients are asked to identify adherence difficulties or reasons for missing a dose (i.e. When you feel better, do you stop taking your medication?).	Recall-bias, time-consuming and subject to errors (over-estimation)
Visual-analog scale	A point on a line that shows a patient's best guess about how much (from 0 – 100%) of each drug they have taken in the past 3 or 4 weeks.	Simple to administer. Equivalent to a 3-day verbal self-report. Less time-consuming than pill-counts	Difficult to assess the validity of the questions answered. Subject to the same errors and dishonesty found with self-reporting
Pill counts	Counting the remaining doses of medication and assuming that remaining pills in excess of what is expected represent missed doses. Some studies have used announced pill counts.	Simple, cheap and objective in measuring adherence	Time consuming and prone to error. Pill dumping or pill sharing prior to clinical visit may lead to over-estimation of adherence. Does not tell you if patient took the medication, at the correct time with the appropriate dietary requirements
Pill identification test (PIT)	The PIT asks patients to examine a board displaying several pills for each antiretroviral drug and to identify which they have been taking.	Correct scores on the PIT have been shown to be associated with treatment adherence	May overestimate the impact of socioeconomic factors (i.e. poor literacy on adherence)
Likert item (rating scale)	Participants are asked to report how closely they followed their specific schedule over the last 4 days using a 5-point scale, ranging from 1 (never) to 5 (all the time)	Simple to administer. Less time-consuming than pill-counts	Subject to the same errors and dishonesty found with self-reporting
Prescription-refill days or dispensing records	Provide the dates on which antiretroviral medications are dispensed. If refills are not obtained on time, it is assumed that the patient is not taking their medication between refills or is missing doses	Analyzing dispensing records for drug distribution allows for a formal, less intrusive way of flagging non-adherence	Does not tell you if patient took the medication, at the correct time with the appropriate dietary requirements

Finally once we identify poor adherence in a patient we must think about how to intervene. A growing research agenda is developing around this topic, including ongoing education, supportive counseling, financial rewards for good adherence and intervening on modifiable barriers to adherence prior to starting ART. [37], [40] Other options for intervention include patient education and collaborative planning, adherence case management, directly observed therapy, simplified treatment regimens and adherence devices [41]. The reasons for poor adherence should dictate what approach to take and may include lack of education about the disease, stigma, non-disclosure, depression, alcohol and substance abuse, pregnancy, low literacy, lack of social support, and cultural or religious beliefs. Treatment related factors such as side effects (i.e. taking TB and ART drugs concurrently), complexity of regimen, pill fatigue and pill burden may also contribute to poor adherence. [42] Other factors including co-morbidities, WHO stage and CD4 count at ART initiation, lack of transport (money), forgetfulness, inability to get time off work and poor patient-provider relationship have also been cited as contributing to poor adherence [43]. While the literature on strategies to address these factors is too vast to be covered in detail here, ultimately how we intervene should be tailored to the underlying reasons for the lack of adherence.

In addition to patient participation in the process, clinicians treating patients must be active participants in striving for good adherence. The scaling up of ART treatment in sub-Saharan Africa has occurred without a proportionate increase in the number of medical personnel, thereby exacerbating already low provider-patient ratios. [1] As programs expand to include nurses and community health workers in the management of ART, it will be important to monitor the effectiveness of different provider-patient relationships on adherence. Furthermore, as programs explore the impact of test-and-treat strategies (where patients are routinely tested and all found positive start ART immediately) or where guidelines shift to earlier initiation of patients on ART at a CD4 count <500 cells/mm^3, efforts will need to be focused on ensuring that adherence is not compromised. [44]

Adherence continues to be a concern as the scale up of ART continues. At a programmatic level, adherence levels vary greatly across different social and cultural settings and from program to program with non-adherence rates ranging from 50-80%. [11], [45], [46], [47], [48] Non-adherence has the potential to undermine the dramatic improvements in survival seen in resource-limited settings as ART becomes more widely available. [49] Understanding biomedical, social and cultural determinants of adherence in high-risk populations is urgently needed. [20] While of equal importance, a simple, valid and reliable method(s) for detecting the prevalence of and reason for non-adherence is essential to monitor adherence and delay the development of drug resistant viral strains in low-, middle- and high-income countries.

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