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Asking about adherence – from flipping the coin to strong evidence

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Summary

In the era of antiretroviral therapy (ART) as prevention for transmission of HIV as well as treatment for HIV-positive individuals irrespective of CD4 cell counts, the importance of adherence has grown. Although adherence is not the only determinant of treatment success, it is one of the only modifiable risk factors. Treatment failure reduces future treatment options and therefore long-term clinical success as well as increases the possibility of developing drug resistant mutations. Drug-resistant strains of HIV can then be transmitted to uninfected or drug-naïve individuals limiting their future treatment options, making adherence an important public-health topic, especially in resource-limited settings.

Adherence should be monitored as a part of routine clinical care; however, no gold standard for assessment of adherence exists. For use in daily clinical practice, self-report is the most likely candidate for widespread use due to its many advantages over other measurement methods, such as low cost and ease of administration. Asking individuals about their adherence behaviour has been shown to yield valid and predictive data – well beyond the mere flip of a coin.

However, there is still work to be done. This article reviews the literature and evidence on self-reported adherence, identifies gaps in adherence research, and makes recommendations for clinicians on how to best utilise self-reported adherence data to support patients in daily clinical practice.

Key words: *antiretroviral therapy; adherence; self-report; surveillance; prevention*

Adherence – definitions and terminology

The World Health Organization (WHO) defines adherence as "the extent to which a person's behaviour – taking medications, following diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider". It is estimated that adherence to long-term therapy for chronic illness in developed countries averages 50% and is even lower in developing countries [1]. Poor adherence leads to poor patient outcomes, increased health care costs, decreases patient safety, and diminishes the effectiveness of improvements in and access to medications.

In the context of HIV, adherence to antiretroviral therapy (ART) can be defined as the "ability of the person living with HIV/AIDS to be involved in choosing, starting, managing, and maintaining a given therapeutic medication regimen to control HIV replication and to improve immune function" [2]. This definition of adherence – with an emphasis on the patient's role in choosing both when to start ART and which ART to take – highlights the movement toward a 'new' paradigm of provider-patient interaction for HIV care as suggested by Noring and colleagues [3]. A key element of the recommendations from this working group was the idea that the term 'adherence' should be replaced with 'treatment maintenance' as it better reflects the collaborative relationship between a patient as proactive participant and a provider as professional guide. In support of this are the European AIDS Clinical Society (EACS) guidelines which emphasise patient readiness to start ART as a key to adherence and successful treatment [4].

Why measure adherence?

Regardless of how one defines and names this concept, the importance of adherence to ART has increased as HIV has become a chronic illness and treatment of HIV requires life-long therapy once initiated. Although adherence is not the only determinant of treatment success, non-adherence is the most critical and one of the only modifiable risk factors leading to a chain of negative clinical outcomes, resulting in both personal and public-health implications.

Treatment failure

The initial goal of ART is to not only attain but maintain an undetectable viral load. Early reports in individuals on non-boosted protease inhibitors (PIs) estimated that they must take 95% of their medication to remain virally suppressed [12]. Several studies were done to explore whether the 95% rule applied to other drug classes and found non-nucleoside reverse transcriptase inhibitors (NNRTI) and boos-

ted PI regimens to be more 'forgiving' – able to achieve and maintain viral suppression despite imperfect medication adherence [13–16]. Recent evidence looking at an integrase inhibitor (raltegravir) found that the risk of virologic failure was 50% after treatment interruptions of 7 days compared to a 15–day interruption on an NNRTI [17]. The majority of patients on potent regimens are able to maintain viral suppression at adherence rates lower than 95% [18–21].

Resistance

Virologic failure not only reduces future treatment options and therefore long-term clinical success but also increases the possibility of developing drug resistant mutations [6, 7, 23]. Studies of the relationship between adherence and resistance in HIV indicate that the relationship is more complicated than originally thought, with each drug class having a unique adherence-resistance relationship [26–29]. Boosted PI regimens – PIs taken with ritonavir (or cobicistat) – allow for more potent viral suppression than unboosted PI regimens [30] and have a longer half-life so PI concentrations remain at subinhibitory concentrations for only a brief time during periods of non-adherence [31]. In addition, this allows for a once daily formulation which for some patients may have a positive impact on adherence [32]. Resistance to PIs usually requires multiple mutations; therefore high level resistance requires both ongoing viral replication and sufficient drug exposure to create a selective advantage for drug-resistant virus [31].

For NNRTI regimens, resistance is associated with interruptions in therapy [33] and develops at a lower level of adherence than PI resistance [34]. Unlike most PI drugs, resistance to the NNRTIs nevirapine and efavirenz requires only a single mutation [35]. However, most NNRTIs have longer half-lives requiring more than one missed dose for the virus to replicate at subinhibitory plasma drug concentrations [36]. The clinical implications of NNRTI resistance are considerable since NNRTI resistance almost universally confers to cross-resistance to first generation NNRTIs [37]. In case of virological failure, the accumulation of NRTI mutation is higher for patients failing a NNRTI regimen compared to patients failing a boosted PI regimen [38]. The mechanism behind the protective effect of PIs on NRTIs remains unclear but has been confirmed in clinical trials and cohorts.

AIDS-defining illness and mortality

Several studies have shown non-adherence to be associated with mortality [39–42] and progression to AIDS [43]. A meta-analysis of the association between adherence and mortality found a pooled odds ratio of death in the subset of HIV studies of 0.53 (95% CI: 0.41 –0.69) in adherent patients compared to non-adherent patients [44].

Public health implications of non-adherence to antiretroviral drugs

The importance of adherence in the life of an HIV-infected person on ART is undisputed. However, the adherence patterns of individuals can also have public health implications. In those already infected with HIV, it is now known that ART reduces the viral load and therefore infectiousness, limiting the risk of onward transmission [45–48]. The test and treat policy – universal HIV testing to enhance the identification of all HIV-positive individuals followed by immediate treatment irrespective of their CD4 cell counts – has been postulated as a potential tool capable of reducing HIV incidence at a population level [49, 50].

Pre-exposure prophylaxis (PrEP), the use of antiretroviral agents by HIV-uninfected persons before potential sexual exposure to HIV-infected partners, is a new approach to HIV prevention and has been approved by the FDA in 2013 [51]. Several double-blind randomised clinical trials have studied the efficacy and tolerance of PrEP to prevent HIV acquisition in high risk groups with varying results with regards to efficacy [52–55]. This large range of efficacy (0–75%) has been mostly linked to adherence to PrEP. Not surprisingly the adherence (and efficacy) was highest in the study that randomised individuals who had sex with an HIV infected stable partner compared to studies where individuals had sexual partners of unknown HIV status. The potential to develop resistance from PrEP can jeopardise the therapeutic use of these drugs in the subsequent treatment of the individual and for the community at large if resistance to the agents spreads more broadly [56, 57]. The low adherence levels reported in some of these studies [54] lend credence to these concerns especially in settings where adherence, viral load, and resistance are not being monitored.

How should adherence be measured?

The importance of adherence as a predictor or determinant of the success of treatment has been clearly documented above, and as such, it would seem clear that the adherence of a patient should be closely monitored. In addition, adherence is a dynamic process and has been shown to vary over time [58–63] and therefore should be measured regularly as part of routine clinical care. However, there is no gold standard for the assessment of adherence nor is there a single optimal tool that enhances adherence to HIV treatment regimens [64].

There are five main methods for adherence measurement: self-report, medication event monitoring system (MEMS), pill count, pharmacy refill, and therapeutic drug monitoring (TDM). Each method has its own strengths and weaknesses and therefore the choice of measurement method often depends on the purpose and intended use of the measurement. Using a combination of methods to measure adherence is likely to provide the most accurate results. Several articles have provided a good overview of measurement methods [65, 66].

Asking about adherence

For the purpose of this article, we will focus on self-reported adherence. Self-report is by far the simplest and most convenient method of measuring adherence. The main advantages are its low cost, low staff and respondent burden, and extreme flexibility [65]. Self-report can measure all four dimensions of adherence behaviour – taking adherence (the extent to which a patient is taking the prescribed medication), timing adherence (the extent to which a patient is adhering to the prescribed schedule for drug intake),

drug holidays (missing several doses of medication in a row), and food restrictions (the extent a patient is adhering to drug intake in relation to food restrictions) [1]. For use in daily clinical practice and management of a patient, self-report comes out as the most likely candidate for widespread use due to its many advantages over other measurement methods especially when considering resource-limited settings.

However, self-report is subject to overreporting [67]. While patients' reporting of non-adherence has been found to be credible [68, 69], their estimate of adherence is often inaccurate [70, 71] overestimating adherence by 10–20% compared to MEMS [72, 73] and 5–10% compared to TDM [69]. A recent study in PrEP in high-risk African women found self-reported adherence to be unreliable with 95% of women reporting taking the drugs on a regular basis whereas only 22% showed evidence of taking the drug on study visits according to TDM [54].

Belli and colleagues suggested the cognitive processes responsible for this overreporting are intentional deception and misremembering [74]. Intentional deception happens as a result of social-desirability bias; the tendency of patient's to answer questions in a manner that will be viewed favourably by others. Respondents may alter their responses if they believe answers will trigger either pleasant or unpleasant reactions. Most of the overreporting of adherence, however, is thought to be due to misremembering [75] which presents a tougher challenge to overcome. When asking about mundane behaviour carried out on a routine basis, it is believed that patients are unable to separate action from intention. So when they report having taken their medication, they may be misremembering their intention to take the medication as the actual act of taking the medication.

There exist many different validated self-report instruments for measuring adherence complicating the comparability and interpretability of study findings. Adherence questions range from global estimates of how much medication was taken using estimation recall to specific inquiries into the exact number of missed doses utilising count-based recall. The methods for administering questionnaires also differ, such as structured interviews and paper or computer self-assessments. Nevertheless, two systematic reviews including a large number of observational studies (mostly count-based) found a robust association between self-reported adherence and viral load over varying measures and recall periods [76] and indicated that self-reported adherence measures can distinguish between clinically meaningful patterns of medication-taking behaviour [77]. Simoni and colleagues found that self-reported adherence was significantly correlated with viral load in 84% of comparisons [76]. Nieuwkerk and Oort compiled 65 studies of self-reported adherence to estimate a pooled odds ratio of having a detectable viral load of 2.31 (95% confidence interval (CI): 1.99–2.68) in non-adherent patients compared to adherent patients [77]. In addition, they found that studies using a threshold for non-adherence below 95% had stronger association with treatment failure suggesting a lower threshold to be more appropriate. Predictive validity for estimation recall has also been established for virologic and immunologic outcomes [78–80].

Strategies to improve accuracy of self-report

Regardless of the evidence of the validity of self-report, it is clear there should be a focus on improving the accuracy of self-report. Review of the literature has identified several issues that need to be considered in the quest for the best self-report tool: what questions should be asked, what recall period should be used, and how the questionnaire should be administered.

Which instrument should be used?

Examples of instruments using estimation recall include the Swiss HIV Cohort Study (SHCS) adherence questionnaire [81, 82], visual analogue scales [83, 84], and the Case Index Questionnaire [80]. A common used example of an instrument with count-based recall is the AIDS Clinical Trial Group (ATCG) questionnaire [85]. Lu and colleagues found that estimation of one's ability to adhere, outperformed count-based measures of adherence in relation to MEMS data [86]. Similarly, Schneider and colleagues found that patient's found it easier to answer questions using Likert scales (in which respondents specify their level of agreement or disagreement on a symmetric agree-disagree scale for a series of statements), which use estimation recall, rather than asking for the specific number of missed doses or percentage adherence [87]. A typical example of a 5–point Likert scale are: strongly disagree, disagree, neither agree nor disagree, agree, strongly agree. Recent guidelines from the EACS recommend using the SHCS adherence questionnaire for routine clinical assessment [4].

What is the optimal recall period?

Several studies suggest ways to minimise misremembering by keeping the recall period relatively short. The optimal recall period for count-based measures is over the last three days [86]. Estimation recall measures have the added benefit of allowing assessment over longer time frames [78] and recent evidence suggests that a recall period of 30 days may be optimal with less overreporting than 3–7 day recall [75, 76, 79, 86].

How should adherence information be collected?

The way in which adherence information is collected – interview with clinician, nurse or pharmacist, paper or computer – will also likely have an effect on the accuracy of the data. Intentional deception can occur both in interviews or with self-administered questionnaires if the respondent thinksthe answers will be provided to their clinician. One option is to use a self-administered questionnaire that patients know will not be shared with their clinician. However, interviews have the advantage that they allow for the discussion of the reason for non-adherence and potential solutions [65]. If proper training is provided, interviews can not only yield accurate adherence data, but contribute to a positive health-care provider-patient relationship, which in turn can have a positive effect on adherence [87]. Williams and colleagues provide several strategies to minimise social desirability bias during interviews such as attempting to normalise non-adherence and avoiding responses to reports implying judgment (positive or negative) [66]. Other strategies include encouraging patients to take longer to respond or using cues to jog patients' memory

[75], such as asking about their regular strategies for taking medication and recent events that might have interrupted their normal routine.

Using adherence in clinical-decision making

As much as adherence research has enlightened the medical community as to the importance of adherence as a *predictor* of clinical outcomes, it still needs to go that one step further and provide clinicians with a clear strategy for using adherence information in routine clinical care as a method of *preventing* negative clinical outcomes. Knowing who is at risk for non-adherence and therefore a good candidate for adherence support or interventions would be extremely valuable information for clinicians. Critical information is missing to allow clinicians to practice evidence-based medicine – defined as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

There are clinics with success stories – Krummenacher and colleagues reported high retention and persistence rates with their interdisciplinary adherence programme that supports patients at risk for non-adherence with MEMS and motivational interviewing [88, 89]. Although this programme as a whole is not transportable to all settings, especially those with limited resources, it still offers an important example of fostering a collaborative relationship between patient and clinician and interdisciplinary teamwork for improved patient care.

So what gaps do researchers need to fill in order for adherence to go from being a predictive concept to a preventative tool?

Improve current measurement tools

Take some of the most promising self-report instruments in use and make changes that may improve accuracy. For example, the SHCS adherence questionnaire consists of 2–items using estimation recall to ask about timing adherence and drug holidays in the last 30 days [82]. This validated instrument [78, 82] could be expanded to cover the timing and food restriction dimensions of adherence, as well as including a visual analogue scale. These modifications could be done working with psychologists in the field of memory and recall to develop a better understanding of how respondents interpret adherence questions and what strategies they use to recall their behaviour and formulate responses. Experts in cognitive interviewing can advise on how best to administer the questionnaire to reduce intentional deception.

Fill the evidence gap

Using selected measurement tools, researchers need to provide ART class or even regimen-based cut-offs for when non-adherence leads to negative clinical outcomes. It has been shown that the majority of patients on potent regimens are able to maintain viral suppression at adherence rates lower than 95% [18–21], however, specific levels according to class or regimen remain unknown. In addition, the simplest regimen is not always the best one for the patient [90]. Understanding specific forgiveness levels of various ART regimens can help patients and clinicians decide which regimen provides the best fit. Moreover, adherence rates initially required to reach undetectable viral loads, may not have the same adherence rate to maintain an undetectable viral load over the long run [22]. Prospective studies for specific regimens are lacking.

Develop surveillance strategies for adherence

There are many unanswered questions as how best to monitor HIV patients and specifically the potential role of adherence. In settings with only limited or no viral load testing, adherence could be used as a proxy for viral load or as an indicator of when viral load testing is warranted. There is some evidence that this strategy could work as well as if not better than CD4 monitoring [91]. There are known risk factors for poor adherence including younger age, side effects, low self-efficacy, lack of social support, and acceptability of the regimen by the patient [58, 81, 92]. Monitoring strategies could be tailored to different risk groups and populations (HIV-negative on PrEP versus HIV-positive on ART) as the challenges in taking daily medication in a healthy person can differ from that of a chronically ill patient.

Develop adherence interventions and support programmes

Once it is known what level of non-adherence should serve as a warning for future treatment failure, clinicians need to know what to do with these at-risk patients. Amico and colleagues did a review of ART adherence interventions and found the effect to be small and varied [93]. Intervention effects tended to be higher in studies which provided didactic information on ART and included interactive discussion of cognitions, motivations, and expectations regarding adherence. Development and testing of adherence interventions makes the most sense when it is clear how best to measure adherence. Once measurement methods are standardised, promising interventions that target those with different levels of non-adherence to provide individual-based support can be tested and adopted into clinical practice.

Conclusions

So, yes, asking about adherence, regardless of how one asks, is better than flipping a coin and can even provide strong evidence. However, it is clear that promising self-assessment tools can be improved upon and then adopted into routine clinical care. Then there is an urgent need to fill the gaps in adherence research. In the era of ART as prevention for acquiring HIV, the consequences of non-adherence have taken on broader public health implications. Clinicians need adherence measures that can be easily implemented in clinical care with clear guidelines as to how to interpret adherence responses so that evidence-based decisions can be made.

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