Adherence to Biomedical HIV Prevention Methods: Considerations Drawn From HIV Treatment Adherence Research

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Biomedical approaches to HIV prevention (eg, microbicides, antiretroviral preexposure prophylaxis) are undergoing clinical trials to test their efficacy. One key consideration emerging from completed trials is the critical role of adherence to the investigational product. Suboptimal product adherence may compromise clinical trial results and ultimately undermine the effectiveness of biomedical prevention methods in any future real-world use. Efforts to strengthen biomedical HIV prevention product adherence can benefit from existing research methodologies, findings, and interventions developed for adherence to HIV treatment. Research on treatment adherence is most relevant to medication-based biomedical prevention strategies, such as antiretroviral preexposure prophylaxis and acyclovir for herpes simplex virus-2. Three areas where HIV treatment adherence literature can inform research on such biomedical prevention strategies are 1) specialized methods for assessing medication adherence, 2) research findings emphasizing social context as an adherence determinant, and 3) promising behavioral interventions to improve adherence.

Introduction

Twenty-five years into the global HIV/AIDS epidemic, the cornerstone of HIV prevention remains behavioral change. Behavioral interventions have played a critical role in slowing HIV transmission in the United States [1] and internationally [2], but behavior change alone has not been able to halt new transmissions. As a result, there is an urgent need for new and effective HIV prevention strategies that can strengthen and complement behavioral interventions.

To meet the complexities of the HIV pandemic, a variety of biomedical innovations have recently been tested. Biomedical HIV prevention strategies include circumcision, vaccines, microbicides, preexposure prophylaxis (PrEP, in which an HIV-negative individual takes an antiretroviral [ARV] medication daily as chemoprophylaxis), and suppressive therapy for herpes simplex virus-2 (HSV-2) to reduce risks of HIV transmission. With the exception of male circumcision [3], these methods have not demonstrated efficacy in clinical trials to date [4–6]. This reinforces the idea that behavioral intervention will remain an important part of the prevention armamentarium, particularly because the most optimistic prediction is that biomedical interventions will have partial, not complete, efficacy.

Fundamentally, the efficacy of biomedical HIV prevention strategies cannot be determined without documented adherence to the investigational product. Recent studies, however, suggest that product adherence represents an "Achilles heel" for these prevention trials. In a trial testing the microbicide Carraguard (Population Council, New York, NY), participants self-reported product use before 44.1% of sex acts, and only 10% of participants indicated that they always used it before sex [6]. In a phase 2 trial of PrEP among female sex workers in West Africa, participants showed 69% adherence to a daily tenofovir regimen based on a pill count measure [7]. Results from completed trials of acyclovir suppressive therapy against genital herpes as a method for HIV prevention also suggest shortfalls in product adherence. Among high-risk women in Tanzania, adherence above 90% was evident during only approximately 50% of person-years, as assessed by clinic-based pill counts [5]. Overall, the acyclovir and placebo groups showed no significant difference in genital ulcer disease, a marker of genital herpes reactivation, which should be substantially suppressed by acyclovir. This poor response suggests that adherence may have been even lower than recorded by pill count. Among those reporting at least 90% adherence to treatment during the preceding 3-

month period, HSV DNA (as detected by periodic genital sampling) was less common in the acyclovir than the placebo group (5.0% for placebo vs 1.7% for acyclovir), suggesting that adherence was an important determinant of treatment effectiveness.

Recommendations from a recent Institute of Medicine (IOM) report underscore these concerns [8••]. The IOM panel identified product adherence as critical to understanding both the biologic efficacy and the population effectiveness of biomedical HIV prevention strategies:

> For a new biological HIV prevention product to be effective, users must adhere to the prescribed regimen. During a clinical trial, imperfect adherence reduces the product's effectiveness, and also makes it difficult for investigators to assess efficacy. If a trial shows that a product provides an overall benefit, relating the level of protection to the level of adherence is valuable for interpreting the results. Understanding who was protected during the trial and under what circumstances also has important implications for predicting how effective the product will be in real-world settings. (p. 119)

The purpose of this article is to illustrate how scientific advances in HIV treatment adherence can inform efforts to improve the design, execution, monitoring, and interpretation of late-stage biomedical HIV prevention trials and enhance any subsequent public health implementation. Although a comprehensive view of adherence in prevention trials could arguably include a larger set of interrelated concerns (eg, adherence to protocol visits, adherence to risk reduction counseling messages), this article focuses on "adherence to product" because of its fundamental importance to these trials, and due to the suboptimal product adherence observed in trials to date. We first assert the broad relevance of HIV treatment adherence research to biomedical prevention research, and then outline three specific areas where prevention adherence may benefit from advances in treatment adherence, namely adherence assessment, attention to social context as a determinant of adherence, and promising interventions to increase adherence.

Relevance of Treatment Adherence to Prevention Adherence

Research on HIV treatment adherence holds relevance to research addressing biomedical HIV prevention product adherence. We acknowledge that different sets of intrapersonal and interpersonal dynamics may be brought to bear on medical regimens designed for prevention rather than treatment. However, beyond the differences between biomedical treatment and biomedical prevention, there are important commonalities between biomedical methods of HIV prevention and treatment strategies for HIV/AIDS. Three key points of convergence include grounding in a common medical context, congruent behavioral requirements for daily medication regimens, and the health condition of persons undergoing HIV prevention or treatment interventions.

First, by their nature, biomedical HIV prevention methods represent a medicalization of HIV prevention strategies and therefore share a medical context with HIV/AIDS treatment. Many biomedical prevention strategies will require individuals to interact with medical providers to undergo medical procedures (eg, circumcision), receive prescription medications (eg, PrEP and acyclovir for HSV-2), or engage in routine HIV testing to monitor for infection (ie, because continuing PrEP regimens during HIV infection could compromise ARV treatment strategies). The medical context in which many biomedical HIV prevention strategies will be initiated and maintained corresponds closely with medical contexts in which patients initiate and maintain treatment for HIV/AIDS. As a result of this common medical frame, both biomedical HIV prevention and treatment can invoke questions about patient access to medical care, interactions with health care providers, understanding of medical directives, and adherence to prescribed regimens—questions that have been addressed in HIV treatment adherence research.

Second, research on adherence to ARV medications may hold particular relevance for medication-based biomedical prevention strategies. The primary focus of treatment adherence research to date has been adherence to daily ARV regimens, and daily medication regimens are also the basis for biomedical HIV prevention methods such as acyclovir to suppress HSV-2 and PrEP (although episodic regimens may ultimately be tested). In either treatment or prevention, individuals may need to follow these daily medication regimens over an indefinite period of time. Assessing adherence to daily medications for either purpose may necessitate specialized forms of assessment (eg, electronic monitoring, pill counts) and raise common analytic questions (eg, specifying patterns of medication adherence, judging when medication "discontinuation" has occurred). Additionally, it should be noted that treatment adherence research encompasses domains broader than solely ARV medication adherence, including linkage to and retention in medical care [9,10]. Advances in these areas [11] could also inform efforts to advance access to and uptake of biomedical HIV prevention methods.

Third, many patients with HIV must proceed with medical treatment while feeling healthy and asymptomatic, which parallels the conditions under which many HIV-uninfected individuals would experience biomedical HIV prevention. Although HIV treatment initiation in the United States and developing nations still sometimes occurs late in the course of disease progression [12], many HIV-seropositive patients initiate and maintain adherence to ARV medications in the absence of symptoms, and this proportion should increase with ongoing efforts

to expand routine HIV testing [13]. Asymptomatic status may present challenges for adherence; disease severity has been associated with greater ARV adherence, and patients who feel well may skip doses to avoid the comparatively unpleasant experience of medication side effects [14]. It is anticipated that similar concerns among uninfected individuals will challenge adherence to biomedical HIV prevention products.

Adherence Assessment

The results from biomedical HIV prevention trials demonstrate the need for accurate and objective adherence measurement for valid interpretation. Many prevention clinical trials to date have measured adherence through self-reports of adherence behavior and/or counts of pills/products returned to the study site, but these measures may overestimate adherence. The ARV adherence literature indicates that self-reports predictably overestimate adherence by as much as 20% [15] because of factors such as imprecision in memory and social desirability bias (which may be particularly pronounced in highly structured clinical trial settings). Counts of pills returned to clinic or study settings also have been notoriously inaccurate [16,17], because study participants may choose to "dump" unused pills/products before the study appointment as the result of social desirability concerns.

Treatment adherence research can assist prevention trials with assessment methodologies for medication adherence that can improve the validity of self-reports and other forms of indirect, objective assessment. Although there is no "gold standard" adherence measure [18], recent reviews and empiric research offer directions for improving the validity of patient self-reports of medication adherence. To reduce social desirability bias in self-reports, researchers have used introductory language that acknowledges the difficulties of adherence and normalizes reports of nonadherence [19•], as well as self-administered measures such as computer-assisted self-interviews, which have demonstrated advantages in eliciting reports of sensitive behaviors [20]. Clear specification of an assessment time interval is also essential. The commonly used AIDS Clinical Trials Group (ACTG) Adherence Questionnaire [16,21] asks about missed doses over the past 4 days. With the development of simplified regimens, incorporating longer assessment intervals of 7 days [19•] or even 30 days [22] may better capture potentially infrequent instances of nonadherence. Beyond the number of missed doses, self-report assessments using a continuous visual analogue scale as a response format have shown good validity and utility when used in populations with low literacy or numeracy [23,24] and may offer psychometric advantages over other response formats [19•]. These self-report methods can be integrated in prevention trials in which objective measurement of adherence is not feasible because of some logistical barrier.

Whenever possible, however, the incorporation of objective measures of adherence into prevention research trials should be encouraged. Despite advances in optimizing the validity of self-reported adherence data, the persistent concern remains that self-reports overestimate adherence, even when they are conducted with care. Some objective methods may be specific to biomedical prevention methods, such as an innovative approach to assess microbicide use through an examination of applicator staining [25]. However, a variety of objective medication adherence measures have been used with success in the ARV adherence research, and could be employed in biomedical prevention trials. These objective methods include unannounced pill counts, electronic drug monitoring (eg, Medication Event Monitoring System [MEMS] caps), and therapeutic drug monitoring.

Methods of conducting unannounced pill counts merit further consideration. Office-based pill counts may provide an objective measure of adherence, but concerns remain about "pill dumping" before study appointments [16,17]. To avoid this problem, Bangsberg et al. [26] developed a method for conducting unannounced pill counts in the homes of research participants. These unannounced home-based pill counts have shown strong validity but may be costly and labor intensive. More recently, Kalichman et al. [27••] developed an innovative, reliable, and low-cost approach to conducting telephone-based unannounced pill counts. Study participants initially receive training in how to conduct a pill count and are informed that they may be contacted at undisclosed intervals to assess the number of pills that remain untaken. Medication adherence is then assessed over the telephone with research participants at unannounced intervals. For participants who do not have regular telephone access, the researchers have provided cellphones programmed for one-way communication with the research team.

Researchers may wish to incorporate multiple forms of adherence assessment (eg, self-report, objective measures) within any given study [8••,28]. This approach builds on the strengths of different assessment methodologies and can help "triangulate" on actual adherence behavior. Different methods also permit the collection of different types of adherence data. For example, pill counts can provide an estimate of medication adherence over a particular interval, but use of daily self-report assessments or electronic drug monitoring can permit more fine-grained analysis of time-sensitive adherence patterns, which may be particularly important in certain instances, such as clinical trials in which investigators are interested in pill taking that is proximal to sexual behavior.

Social Context as a Determinant of Adherence

To the extent that biomedical prevention studies are biologically effective, better understanding of the behavioral and social determinants of adherence will enhance adherence

and maximize effectiveness during deployment in public health settings. Another lesson from treatment adherence research is that social context is an important determinant of adherence behavior. Researchers of biomedical HIV prevention methods may therefore benefit from examining social factors when seeking to understand adherence in the context of their work. Attention to, assessment of, and accounting for these variables in analyses could help explain variance in adherence to product and resultant clinical outcomes.

It has been contended that differences in ARV adherence rates between African and Western settings may be the result of social contextual factors surrounding HIV treatment. In a meta-analysis of 59 HIV adherence studies conducted in North America and Africa, Mills et al. [29] found that high ARV adherence was achieved by 77% of African patients compared with 55% of North American patients. The African adherence studies in this meta-analysis centered on patients who were among the first to access lifesaving ARV medications in their treatment settings, and these select patients likely had greater medical need, motivation, and resources to access and adhere to medication regimens [30]. Such high rates of adherence could decline over time as African patients initiating therapy encounter the challenges of maintaining long-term adherence, and as treatment availability in these nations becomes more normative and expands beyond those with early access to ARV therapy [30]. Whether high levels of ARV treatment adherence seen in resource-limited settings will be replicated in the context of prevention is unclear. However, we note that following successful clinical trials of circumcision as an HIV prevention method, there has been significant demand for circumcision services from men in many African nations [31]. Much like the introduction of ARV regimens for HIV treatment in resource-poor settings, the provision of biomedical HIV prevention strategies with proven efficacy to at-risk populations in high-prevalence settings could result in high interest, uptake, and adherence.

Emerging findings from HIV treatment adherence studies are bringing greater attention to other social and structural influences on adherence behavior. Structural factors related to the availability of and ease of access to medications, including pharmacy stock-outs and costs associated with transportation to clinics, are important determinants of ARV treatment adherence in resource-limited settings [32]. In the context of clinical trials in which supplies are assured and patients receive assistance with transportation, these may not be major determinants of biomedical HIV prevention adherence, but they could affect the wider-scale public implementation of such strategies. Adherence to ARV treatment has also been demonstrated to be influenced by societal HIV/AIDS stigma [33], which can inhibit adherence in public settings. Uninfected individuals who take PrEP may experience similar concerns when taking ARV medication doses within interpersonal contexts. Interpersonal relationships may also influence ARV adherence, as social support and serostatus disclosure by HIV patients have been found to relate to ARV adherence and treatment outcomes [34,35]. Those who receive PrEP are likely to be in high-risk situations and relationships—perhaps with serodiscordant partners. There are concerns that, in the context of limited HIV treatment, individuals may share medicines with HIV-infected relationship partners, compromising their own adherence to the prevention regimen.

On a more proximate level, we recognize that adherence to an experimental agent in a double-blind placebo-controlled trial may be different from adherence to an oral drug with proven efficacy deployed in a community setting. PrEP adherence is likely to be influenced by beliefs in PrEP efficacy, as had been observed with ARV adherence [21], and adherence in clinical trials may be compromised because participants do not know whether the experimental agent will be efficacious or whether they are receiving placebo or active drug. Although adherence behavior in a randomized controlled trial (RCT) may be different from adherence to a proven agent deployed as a community-based intervention, comprehensive characterization of adherence behavior in the experimental setting—including attitudes, beliefs, perceived stigma, social support, and other contextual factors—may be critical to fully determine whether incomplete protection is the result of lack of biologic efficacy or lack of adherence.

Adherence Intervention

Intervention research targeting patient adherence to ARV medications can inform efforts to enhance adherence to biomedical HIV prevention methods. Research to date has produced a small but growing set of interventions with demonstrated efficacy in improving ARV adherence. For example, a meta-analysis of 19 RCTs of ARV adherence interventions found that intervention participants were 1.5 times as likely to report 95% adherence and 1.25 times as likely to achieve an undetectable viral load compared with participants in comparison conditions [36••]. That said, medication adherence remains a highly challenging phenomenon to address, even in the context of administering an essential, lifesaving treatment such as ARV medications. Therefore, HIV prevention investigators seeking to adapt and apply successful treatment adherence interventions must be mindful of the strengths and limitations of each approach in order to select the intervention most suitable for their settings. Some of the ARV adherence interventions in the meta-analysis by Simoni et al. [36••] did not demonstrate efficacy for improving adherence, and the increases in adherence post intervention tend to be short term. To maximize adherence to biomedical HIV prevention strategies within the context of clinical trials, robust adherence initiatives and a combination of multimodal approaches will most likely

be necessary. In the following paragraphs, we identify a set of promising interventions and strategies drawn from the ARV adherence research domain.

Cognitive-behavioral approaches

Most of the interventions that have demonstrated efficacy in improving ARV adherence have employed cognitive-behavioral approaches and other strategies in combination [36••]. An example of a basic and brief approach consisted of three 45- to 60-minute sessions delivered by a nurse; the program used education, motivational interviewing, and client-centered therapeutic techniques to address cognitive, emotional, social, and behavioral determinants of ARV adherence [37]. Comparatively brief adherence interventions such as this one could be conducted in the context of existing study visits in clinical trial protocols. Alternatively, cognitive-behavioral adherence counseling has also shown effectiveness when delivered by telephone. Participants in an ACTG protocol who received weekly telephone counseling from a nurse over 12 weeks showed greater ARV adherence than those who received a standard baseline counseling package, and this effect persisted through a 64-week follow-up [38]. Finally, other behavioral techniques involve the use of support technologies and devices. The use of medication pillboxes, for example, has been associated with greater ARV adherence [39]; this simple and low-cost strategy could potentially enhance medication adherence in prevention trials.

Based on the available evidence, we would consider the deployment of basic cognitive-behavioral approaches (eg, the routine provision of pillboxes, cognitive-behavioral counseling) to be an important first step toward maximizing adherence in the context of prevention trials. In the multicenter HIV Prevention Trials Network (HPTN) 039 trial to test acyclovir for HIV prevention among African women and men who have sex with men in the Americas [40], participants received monthly adherence counseling, including clinic-based pill counts and weekly reminder pillboxes, which may have aided adherence. Adherence in this trial was better (90% or higher at 73% of quarterly visits) than in other recent prevention trials.

Social support for adherence

Another promising strategy to improve adherence is social support, which can heighten motivation and offer practical assistance for a treatment regimen. For example, a four-session intervention designed to foster practical support for adherence from a relationship partner and delivered to HIV-serodiscordant couples by a nurse practitioner produced short-term gains in ARV adherence among the HIV-seropositive partners in these relationships [41]. Partner support could also be marshaled in the context of biomedical HIV prevention trials that target individuals in HIV-serodiscordant relationships. The involvement of a relationship partner in an adherence intervention may be particularly relevant for biomedical prevention approaches such as microbicides, whose adoption and use could have implications for sexual practices and satisfaction within relationship dyads.

Contingency management

Because clinical trials are focused on determining product efficacy under tightly controlled conditions rather than effectiveness in real-world use, prevention interventionists may also want to consider additional innovative, unconventional steps to enhance adherence among trial participants. One potential approach is contingency management, which offers research participants small financial incentives and rewards—often through prize drawings—in exchange for objectively demonstrated treatment adherence (eg, electronic monitoring of medication adherence through MEMS). This method has been shown to improve both adherence to ARV and viral load in HIV-seropositive drug users [42]. Although the application of contingency management to widespread public health implementation remains to be determined because of political or resource constraints, its cost-effectiveness could be well justified in the context of clinical trials in which there is a premium on maximizing adherence among trial participants.

Home visits and modified directly observed therapy

Although potentially resource intensive, adherence may also be enhanced through outreach methods that provide adherence support and counseling through in-home visits from research or clinical personnel, rather than requiring participants to travel to study sites. For example, ARV adherence among HIV-seropositive patients was improved through brief home visits and counseling by a nurse or community worker with tapered frequency over 1 year [43]. Investigators have also adapted directly observed therapy (DOT), drawn from tuberculosis treatment protocols, for application to long-term HIV/AIDS treatment. Modified DOT (mDOT) approaches typically employ a research assistant, community-based outreach worker, or friend/family member who observes/administers one medication dose per day, and who may be trained to provide additional counseling and support for treatment adherence. Pearson et al. [44] describe one efficacious mDOT approach conducted in a resource-limited setting in Mozambique. In addition, Goggin et al. [45] provide guidance on the conduct of these programs.

Conclusions

The IOM and other leaders in the field of HIV prevention have concluded that increased attention to product adherence is essential for the successful conduct and interpretation of clinical trials for biomedical HIV prevention strategies [8••,46]. We share these concerns, and assert that the success of ongoing and future biomedical HIV prevention trials will require enhanced efforts to under-

stand, monitor, and improve adherence. Accurate and valid measurement of product use is essential to assess adherence, to identify poorly adherent individuals who may need additional adherence support, and to accurately determine the relationship between product adherence and study outcomes. There is a significant risk that promising intervention strategies could be sidelined or discarded if trials show inconclusive efficacy due to adherence problems. Biomedical HIV prevention may benefit from scientific advances in assessment and intervention for ARV medication adherence. Investigators are also encouraged to incorporate measures of potential social contextual determinants of product adherence, including HIV stigma, disclosure, product sharing, and structural factors. Regardless of whether a novel intervention is efficacious, understanding when and why participants did not adhere to the product regimen can provide insights to inform the design and delivery of subsequent trials. Every possible effort should be made to strengthen adherence in these critically needed, complex, and expensive trials, and to ensure that these efforts are guided by the best available evidence.

Note

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Disclosures

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Holtgrave D: **Evidence-based efforts to prevent HIV infection: an overview of current status and future challenges.** *Clin Infect Dis* 2007, **45(Suppl 4):**S293–S299.
2. Green EC, Halperin DT, Natulya V, Hogle JA: **Uganda's HIV prevention success: the role of sexual behavior change and the national response.** *AIDS Behav* 2006, **10:**335–346.
3. Gray RH, Kigozi G, Serwadda D, et al.: **Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial.** *Lancet* 2007, **369:**657–666.
4. Padian NS, van der Straten A, Ramjee G, et al.: **Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial.** *Lancet* 2007, **370:**251–261.
5. Watson-Jones D, Weiss HA, Rusizoka M, et al.: **Effect of herpes simplex suppression on incidence of HIV among women in Tanzania.** *N Engl J Med* 2008, **358:**1560–1571.
6. Cohen J: **Microbicide fails to protect against HIV.** *Science* 2008, **319:**1026–1027.
7. Peterson L, Taylor D, Roddy R, et al.: **Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial.** *PLoS Clin Trials* 2007, **2:**e27.
8. •• Lagakos SW, Gable AR, eds: *Methodological Challenges in Biomedical HIV Prevention Trials*. Washington DC: National Academies Press; 2008.

This IOM committee report summarizes the methodologic challenges in late-stage nonvaccine biomedical HIV prevention trials, with a special focus on microbicide and PrEP trials, along with recommendations for pretrial research and planning.

9. Giordano TP, Gifford AL, White AC, et al.: **Retention in care: a challenge to survival with HIV infection.** *Clin Infect Dis* 2007, **44:**1493–1499.
10. Stirratt MJ, Gordon CM: **HIV treatment adherence research and intervention: current advances and future challenges.** *J HIV/AIDS Soc Serv* 2007, **6:**9–22.
11. Bradford JB: **The promise of outreach for engaging and retaining out-of-care persons in HIV medical care.** *AIDS Patient Care STDS* 2007, **21(Suppl 1):**S85–S91.
12. Fisher M: **Late diagnosis of HIV infection: major consequences and missed opportunities.** *Curr Opin Infect Dis* 2008, **21:**1–3.
13. Branson BJ: **Current HIV epidemiology and revised recommendations for HIV testing in health-care settings.** *Med Virol* 2007, **79(Suppl 1):**S6–S10.
14. Gao X, Nau DP, Rosenbluth SA, et al.: **The relationship of disease severity, health beliefs and medication adherence among HIV patients.** *AIDS Care* 2000, **12:**387–398.
15. Arnsten JH, Demas PA, Farzadegan H, et al.: **Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring.** *Clin Infect Dis* 2001, **33:**1417–1423.
16. Miller LG, Hays RD: **Measuring adherence to antiretroviral medications in clinical trials.** *HIV Clin Trials* 2000, **1:**36–46.
17. Bell DJ, Kapitao Y, Sikwese R, et al.: **Adherence to antiretroviral therapy in patients receiving free treatment from a government hospital in Blantyre, Malawi.** *J Acquir Immune Defic Syndr* 2007, **45:**560–563.
18. Chesney MA: **The elusive gold standard. Future perspectives for HIV adherence assessment and intervention.** *J Acquir Immune Defic Syndr* 2006, **43(Suppl 1):**S149–S155.
19. • Simoni JM, Kurth AE, Pearson, CR, et al.: **Self-report measures of antiretroviral therapy adherence: a review with recommendations for HIV research and clinical management.** *AIDS Behav* 2006, **10:**227–245.

Review of 77 self-report measures of ARV adherence, varying in item content, format, and response items, with recommended items and strategies for HIV research and clinical management.

20. Bangsberg DR, Bronstone A, Chesney MA, Hecht FM: **Computer-assisted self-interviewing (CASI) to improve provider assessment of adherence in routine clinical practice.** *J Acquir Immune Defic Syndr* 2002, **31(Suppl 3):**S107–S111.
21. Chesney MA, Ickovics JR, Chambers DB, et al.: **Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments.** *AIDS Care* 2000, **12:**255–266.
22. Lu M, Safren SA, Skolnik PR, et al.: **Optimal recall period and response task for self-reported HIV medication adherence.** *AIDS Behav* 2008, **12:**86–94.
23. Kalichman SC, Cain D, Fuhrel A, et al.: **Assessing medication adherence self-efficacy among low-literacy patients: development of a pictographic visual analogue scale.** *Health Educ Res* 2004, **20:**24–35.
24. Oyugi JH, Byakika-Tusiime J, Charlebois ED, et al.: **Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting.** *J Acquir Immune Defic Syndr* 2004, **36:**1100–1102.

25. Hogarty K, Kasowitz A, Herold BC, Keller MJ: **Assessment of adherence to product dosing in a pilot microbicide study.** *Sex Transm Dis* 2007, **34:**1000–1003.
26. Bangsberg DR, Hecht FM, Charlebois ED, et al.: **Comparing objective measures of adherence to HIV antiretroviral therapy: electronic medication monitors and unannounced pill counts.** *AIDS Behav* 2001, **5:**275–281.
27.•• Kalichman SC, Amarai CM, Stearns H, et al.: **Adherence to antiretroviral therapy assessed by unannounced pill counts conducted by telephone.** *J Gen Int Med* 2007, **22:**1003–1006.
Documents the high reliability of unannounced phone-based pill counts as an economically and logistically feasible objective method for monitoring medication adherence.
28. Liu H, Golin CE, Miller LG, et al.: **A comparison study of multiple measures of adherence to HIV protease inhibitors.** *Ann Intern Med* 2001, **134:**968–977.
29. Mills EJ, Nachega JB, Buchan I, et al.: **Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis.** *JAMA* 2006, **296:**679–690.
30. Bangsberg DR, Ware N, Simoni J: **Adherence without access to antiretroviral therapy in sub-Saharan Africa?** *AIDS* 2006, **20:**140–141.
31. Johnson KE, Quinn TC: **Update on male circumcision: prevention success and challenges ahead.** *Curr Infect Dis Rep* 2008, **10:**243–251.
32. Oyugi JH, Byakika-Tusiime J, Ragland K, et al.: **Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda.** *AIDS* 2007, **21:**965–971.
33. Ware NC, Wyatt MA, Tugenberg T: **Social relationships, stigma and adherence to antiretroviral therapy for HIV/AIDS.** *AIDS Care* 2006, **18:**904–910.
34. Ramadhani HO, Thielman NM, Landman KZ, et al.: **Predictors of incomplete adherence, virologic failure, and antiviral drug resistance among HIV-infected adults receiving antiretroviral therapy in Tanzania.** *Clin Infect Dis* 2007, **45:**1492–1498.
35. Behforouz HL, Farmer PE, Mukherjee JS: **From directly observed therapy to accompagnateurs: enhancing AIDS treatment outcomes in Haiti and in Boston.** *Clin Infect Dis* 2004, **38(Suppl 5):**S429–S436.
36.•• Simoni JM, Pearson CR, Pantalone DW, et al.: **Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load: a meta-analytic review of randomized controlled trials.** *J Acquir Immune Defic Synd* 2006, **43(Suppl 1):**S23–S35.
Evaluates the state of the science for HIV treatment adherence interventions, strengths and limitations of the interventions, and moderators of effect size.
37. Pradier C, Bentz L, Spire B, et al.: **Efficacy of an educational and counseling intervention on adherence to highly active antiretroviral therapy: French prospective controlled study.** *HIV Clin Trials* 2003, **4:**121–131.
38. Reynolds NR, Testa MA, Su M, et al.: **Telephone support to improve antiretroviral medication adherence: a multisite, randomized controlled trial.** *J Acquir Immune Defic Synd* 2008, **47:**62–68.
39. Petersen ML, Wang Y, van der Laan MJ, et al.: **Pillbox organizers are associated with improved adherence to HIV antiretroviral therapy and viral suppression: a marginal structural model analysis.** *Clin Infect Dis* 2007, **45:**908–915.
40. Celum C, Wald A, Hughes J, et al.: **Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial.** *Lancet* 2008, **371:**2109–2119.
41. Remien RH, Stirratt MJ, Dolezal C, et al.: **Couple-focused support to improve HIV medication adherence: a randomized controlled trial.** *AIDS* 2005, **19:**807–814.
42. Rosen MI, Dieckhaus K, McMahon TJ, et al.: **Improved adherence with contingency management.** *AIDS Patient Care STDS* 2007, **21:**30–40.
43. Williams AB, Fennie KP, Bova CA, et al.: **Home visits to improve adherence to highly active antiretroviral therapy: a randomized controlled trial.** *J Acquir Immune Defic Syndr* 2007, **42:**314–321.
44. Pearson CR, Micek MA, Simoni JM, et al.: **Randomized control trial of peer-delivered, modified directly observed therapy for HAART in Mozambique.** *J Acquir Immune Defic Syndr* 2007, **46:**238–244.
45. Goggin K, Liston RJ, Mitty JA: **Modified directly observed therapy for antiretroviral therapy: a primer from the field.** *Public Health Rep* 2007, **122:**472–481.
46. Gray RH, Wawer MJ: **Randomised trials of HIV prevention.** *Lancet* 2007, **370:**200–201.