**Appendix A.** Description of some of the more complex criteria for evaluating medication adherence interventions

*Method of Assignment*

Selection bias is the extent to which there may be apparent or unapparent systematic differences between study arms at baseline. Selection bias can lead to extreme overestimation or underestimation of the intervention effect. The PRS efficacy criteria require that participants be assigned or allocated to study arms (i.e., an intervention group or a comparison group) randomly or with non-random methods that reduce selection bias. The impact of the selection bias on the intervention effect estimate depends on how the selection mechanism, or factors underlying the selection process, relates to the outcome. Convenience and self–selection are considered as biased allocation methods as they cannot guarantee minimal selection bias.

*Retention Rate*

The retention rate criterion is important because it provides a focus on a factor that is tangible and objective: level of attrition. Participants who come back to complete a study may be more or less likely to respond positively to the intervention than those who are lost to follow-up. This could lead to attrition bias, which could be very large if the reason for attrition between the intervention and comparison arm differs and this reason is associated with the outcome. As the level of attrition is reduced, so is the chance that attrition bias will affect the findings. A systematic review and meta-analysis (Simoni et al, 2006)\* of HIV medication adherence interventions showed the median retention rate for the first post-intervention assessment time point to be 70%. Therefore, the PRS good-evidence criterion requires that, at a minimum, at least 60% of the participants in each group be retained at followed-up. For a study to be considered best-evidence, at least 70% of the participants in each group must be retained or followed-up.

\* Simoni, J. M., Pearson, C. R., Pantalone, D. W., Marks, G., & Crepaz, N. (2006). 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.Syndr., 43(Suppl 1), S23-S35.

*Differential Retention*

It is important to consider both differences in retention levels and mechanisms for attrition (or reason for dropping out of the study). The mechanism for attrition is rarely random and, thus, is always a concern. Even if retention levels are similar between study arms, the reason for attrition could differ by study arms and this reason could be associated with the outcome, resulting in attrition bias. This attrition bias could be very large and, thus, lead to either overestimating or underestimating the intervention effect. Because it is extremely difficult to identify the attrition mechanism and assess the extent to which this mechanism differs by intervention group, we examine the information reported regarding the characteristics associated with differential retention (or attrition) between study arms. Since not all studies have differential retention readily available, its effect on the intervention effect estimate is difficult to quantify, this element is assessed under the limitation section.

Unit of Assignment vs. Unit of Analysis

Assignment of participants or units to study arms may occur at the level of individual, group, community, clinic or other clusters. In some studies, small groups or clusters of persons rather than individual persons are recruited and allocated to study arms. This assignment practice may be used because of feasibility, cost, or the intervention design. For example, persons within the same organizational cluster (e.g., clinic) may be assigned to the same study arm. In this situation, members within a cluster may be more similar than members of different clusters with respect to behaviors or potential response to the intervention. If this relative difference is substantial, findings based on individual–level analyses will be biased and could lead to false positive findings. For studies where group–level or cluster–level assignments are used, hierarchical models or post hoc analytical adjustment methods must be performed to account for potential within cluster correlations.

*Intent-to-Treat Approach and Imputed Data*

An intent-to-treat (ITT) analytic approach holds the original allocation as paramount in importance because deviations from the original allocated study arms may contaminate the treatment comparison and introduce bias. An ITT analysis includes all participants in the study arms to which they were originally allocated, regardless of the treatment, or amount of treatment, they actually received, and regardless of subsequent withdrawal from the intervention, attrition, or deviation from the protocol. Analyses that are limited to those participants who complete the intervention or are retained for follow-up analyses may bias results if partial exposure or drop out is in any way related to the intervention or outcomes. Therefore, the PRS good-evidence criteria requires that, at a minimum, participants must be analyzed in study arms as originally allocated and regardless of actual intervention exposure. For a study to be considered best-evidence, the analysis must also use appropriate methods to impute missing data due to attrition or other reasons.

*Analytic Sample Size*

 Sample size is a critical element to assure an adequate power to detect statistical significance. Including a sufficiently large number of participants in a study is ideal for assuring adequate power, but expensive. On the other hand, if a study is underpowered, it will be statistically inconclusive. To attain sufficient power to detect statistical significance, it typically requires 64-393 per am for median effect sizes and 26-63 per arm for large effect sizes (<http://www.crimesolutions.gov/>). Our analytic sample size requirement of at least 40 participants per arm for good-evidence and 50 participants per arm for best-evidence is within the sample size range for detecting median to large effect sizes. If trying to detect a smaller effect size, a study would need a sample size greater than our minimal requirement.

*Relevant Outcomes*

Relevant outcomes for the PRS efficacy review include biologic viral load, assessed through lab tests or recovered from medical charts, and adherence behaviors, assessed through electronic device monitoring (EDM) or medical event monitoring system (MEMS) caps, pill count, pharmacy refill, or self-reported doses taken or missed. A vast majority of published literature places the most confidence in studies that assess adherence using multiple methods; however, since there is still no “gold standard” for accurate measurement of adherence, and since a vast majority of published literature places the most confidence in studies that assess adherence using multiple methods, no one method of data collection is recommended over another in this review. Behavioral adherence is an important variable to assess because it is considered a pathway that might explain improved biologic outcomes (viral suppression), which is the ultimate goal of antiretroviral treatment. Thus, we require a significant intervention effect on either adherence behavior or viral load to meet the PRS good-evidence criteria, and evidence on both adherence behavior and viral load, to meet best-evidence.

*Length of Follow-Up*

Length of follow-up has been considered by PRS as the time since completion of the intervention. A review of the literature made apparent two distinct types of adherence interventions – “discrete” and “repetitive dosing”. Typically, in a “discrete” intervention (e.g. 5 one-hour education and skills building sessions), all sessions are needed for the individual to receive all components of the intervention and receiving the entire intervention is thought to be important for the desired behavior change. In a “repetitive dosing” intervention, all, or most, components are implemented repeatedly with the intent that continual or repeated exposure may be necessary to achieve the desired behavior change, and that as exposure increases, so does the desired behavior change. These interventions tend not to have an explicit end point, outside the confines of the study period. Assessment time points typically occur at multiple time points that are after the completion of a discrete intervention (PC; post-completion) or after the start of a repetitive dosing intervention (PI; post-initiation) for evaluating intervention effects.

**Appendix B.** Medication Adherence Search for MEDLINE on the OVID Platform

$ = truncation

ab = abstract

ti = title

**HIV/AIDS MeSH and Keywords**

1. HIV Infections/
2. AIDS/
3. HIV Seropositivity/
4. (living adj4 (hiv or aids)).ti,ab
5. HIV positiv$.ti,ab
6. HIV infected.ti,ab
7. or/1-6

**Intervention MeSH and Keywords**

1. Intervention Studies/
2. Case management/
3. Directly Observed Therapy/
4. intervention$.ti,ab
5. (therapy or therapies).ti,ab
6. (treatment or treatments).ti,ab
7. medication event monitor$.ti,ab
8. mems.ti,ab
9. modified directly observed.ti,ab
10. mdot.ti,ab
11. directly administered.ti,ab
12. daart.ti,ab
13. directly observed therapy.ti,ab
14. dot.ti,ab
15. or/8-21

**HAART MeSH and Keywords**

1. Anti-HIV agents/
2. Anti-Retroviral Agents/
3. Antiviral Agents/
4. Antiretroviral Therapy, Highly Active/
5. haart.ti,ab
6. arv.ti,ab
7. art.ti,ab
8. antiretroviral$.ti,ab
9. anti retroviral$.ti,ab
10. antiviral$.ti,ab
11. anti viral$.ti,ab
12. (medication or medications).ti,ab
13. or/23-34

**Adherence MeSH and Keywords**

1. Patient Compliance/
2. Medication Adherence/
3. adher$.ti,ab
4. nonadher$.ti,ab
5. non adher$.ti,ab
6. complian$.ti,ab
7. non complian$.ti,ab
8. noncomplian$.ti,ab
9. viral load.ti,ab
10. (cd4 adj2 (count or counts)).ti,ab
11. or/36-45
12. 7 and 22 and 35 and 46
13. Limit – 1996 -2009, publication types limit to:

Clinical Trial

Controlled Clinical Trial

Corrected and Republished Article

Evaluation Studies

Journal Article

Meta-Analysis

Multicenter Study

Published Erratum

Randomized Controlled Trial

Retraction of Publication

Review

Review Literature

Technical Report

Validation Studies

**Appendix C.** HIV Medication Adherence Manual Search Journal List (n=20)

AIDS
AIDS and Behavior
AIDS Care
AIDS Patient Care and STDs
American Journal of Drug and Alcohol Abuse

Annals of Behavioral Medicine

Annals of Pharmacotherapy

Antiviral Therapy
Clinical Infectious Diseases
Cognitive and Behavioral Practice
Drug and Alcohol Dependence
Health Psychology
HIV Medicine
International Journal of STD & AIDS
JAIDS Journal of Acquired Immune Deficiency Syndromes
Journal of General Internal Medicine

Journal of HIV/AIDS and Social Services

Journal of the Association of Nurses in AIDS Care
Journal of the International Association of Physicians in AIDS Care

Patient Education and Counseling