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# Measures of antiretroviral adherence for detecting viral non-suppression in people living with HIV

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## ABSTRACT

This is a protocol for a Cochrane Review (Diagnostic test accuracy). The objectives are as follows:

To determine the accuracy of simple measures of adherence, including patient self-report, tablet counts, pharmacy records, electronic monitoring, or composite methods, for detecting non-suppressed viral load in people living with HIV.

## BACKGROUND

### Target condition being diagnosed

Across all fields of medicine, low patient adherence is a barrier to realising the benefits of medication (Nieuwlaat 2014), and is associated with higher mortality (Simpson 2006).

The World Health Organization (WHO) recommends provision of antiretroviral therapy (ART) to all people living with HIV, regardless of CD4 count (WHO 2016). At an individual level, ART reduces the risk of progression to AIDS or death, increases the likelihood of immune recovery, and reduces the risk of sex-

ual transmission to seronegative partners. At a population level, widespread ART may reduce HIV incidence and offers a tool to end the HIV epidemic, as acknowledged within the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90:90:90 target (UNAIDS 2014). This aims that by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained ART, and 90% of all people receiving ART will have viral suppression.

With respect to HIV, for the individual and population level benefits of ART to be realised, patient adherence is essential. Adherence to ART is the primary determinant of viral suppression. In one meta-analysis of observational studies, only 62% of people re-

ceiving ART reported more than 90% adherence (Ortego 2011). Poor adherence increases the risk of transmission, accumulation of resistance mutations, disease progression, and death. Previous systematic reviews indicate a number of possible treatments for poor adherence to ART, indicating the benefit of measuring adherence (Horvath 2012; Kanters 2017; Rueda 2006).

One European Consensus document defines “adherence to medications” as the process by which patients take their medication as prescribed. This term describes multiple behaviours. (Vrijens 2012). There are four measurable subcategories of adherence to medications. These include:

- **initiation:** when a patient takes the first dose of a prescribed medication;
- **implementation:** the extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose;
  - **persistence:** the length of time between initiation and the last dose;
  - **discontinuation:** when a patient stops taking the prescribed medication.

Initiation and discontinuation are discontinuous (stop/start) measures, whereas implementation is a continuous measure. This precludes a single useful quantitative parameter to cover all three. Most research focuses on the implementation phase, that is: the extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen. The implementation component can be expressed via summary statistics which describe the implementation of a dosing regimen over a defined interval of time, for example the proportion of days with the correct number of doses over a given period.

Although the implementation phase of adherence exists within a continuum from 0% to more than 100%, studies typically stratify adherence into dichotomous variables of ‘adherence’ and ‘non-adherence’. There are no specific consensus criteria for identifying these dichotomous categories of ‘adherence’ and ‘non-adherence’. Traditionally, across fields of medicine, trials consider rates of less than 80% to represent non-adherence (Osterberg 2005). With respect to HIV, where non-adherence risks resistance mutations, trials have traditionally considered a threshold of greater than 95% as optimal (Paterson 2000). In practice, the level of adherence required to improve immune function and achieve viral suppression will vary by regimen and by prior history of viral suppression (Haberer 2017). For example, people with a longer-term history of viral suppression may be able to miss more doses without viral rebound (Lima 2010). Indeed, adopting lower adherence thresholds may not effect viral outcomes (Bezabhe 2016).

The definition of viral suppression is standard across guidelines, as an HIV ribonucleic acid (RNA) level below the lower limit of detection of available assays. However, the terminology for describing the absence of viral suppression is heterogeneous across the literature, incorporating concepts such as viral failure, incomplete response, viral rebound, viral blips, and low level viraemia. Table

1 summarises the varying definitions of viral failure used internationally. Of note, the WHO definition incorporates an adherence support intervention before viral failure can be diagnosed.

## Index test(s)

The index test will be measures of adherence that could be utilized in resource-limited settings.

The WHO Guidelines on the use of antiretroviral drugs for treating and preventing HIV identify a need to “determine optimal ways to proactively monitor adherence and identify through simple triage those patients in greatest need of adherence support” (WHO 2016). The guideline document uses terms relating to ‘simple’ on 51 separate instances, but there is no standard definition. However, in context, this relates to a public health approach which is “feasible on a large scale in resource-limited settings”, with decentralization and integration of services, including task shifting. With respect to ‘task shifting’, WHO recommends that trained and supervised community health workers can dispense ART between regular clinical visits (WHO 2016), and suggests that these workers adopt responsibility for monitoring patient adherence (WHO 2017).

In relation to these considerations, this review will focus on measures of adherence that could be used at the ‘community’ or ‘health centre’ level as defined by a previous Cochrane review (Kredo 2014), in a nomenclature reproduced in Table 2. As such, the measure:

- could be administered by trained volunteers, health assistants, nurse aides, and community health workers with a maximum of few months of training;
- would not require infrastructure such as laboratories which are more commonly found at enhanced health centres or hospitals.

This would not preclude use of the measure at higher levels of care. The following measures of adherence behaviour could meet these criteria:

- self-report;
- tablet counts;
- pharmacy records or secondary database analysis, or both;
- electronic monitoring;
- composite measures of the above.

We describe these further below.

### Self-report

The term self-report involves a question, or set of questions, to which a patient responds. The mode of administration may be self-completion, or interviewer administered. The medium may be paper or electronic. There is no consensus taxonomy for self-report within the literature, but in broad terms, self-report questions may include:

- **behavioural questions:** questions asking patients to directly relate their adherence behaviour. In turn, such questions may be:
  - count based: a specific day-by-day enquiry regarding missed doses. For example, *how many doses did you miss yesterday? The day before yesterday? Three days ago?* (Chesney 2000);
  - estimate based: asking people to estimate how they took their treatment over a period of time. This might be based around a visual analogue scale, for example, *mark the point along the line that most closely reflects how much of your HIV medications you have taken in the last month?* (Kabore 2015);
- **attitudinal questions:** these include questions asking patients about knowledge and beliefs, for example:
  - perceived barriers. *Did you ever miss a dose due to forgetfulness?*
  - health beliefs. *Sometimes if you feel worse, do you stop taking your medications?* (Knobel 2002);
  - self-efficacy. *How confident are you that you can take your medicines?* (EACS 2017).

The extent to which attitudinal questions are a valid form of assessment of adherence behaviour is unclear (Stirratt 2015), but inclusion of such questions will not preclude a questionnaire from this review. One previous systematic review covering all fields of medicine identified that the number of questions in self-report adherence measures ranged from one to 30, with a median of eight (Nguyen 2014). It is unlikely that a 30-item questionnaire could be termed 'simple triage', or be used by community health workers. Therefore, this review will exclude self-report containing more than eight questions, or which the review authors deem to be prohibitively complex for use at this level.

### Tablet counts

The provider counts the remaining tablets (or volume of liquid) in previously dispensed bottles and calculates an adherence percentage. This is based on expected versus actual tablets taken over a prescribed dispensing period. Counts may take place in clinic or unannounced (in the form of telephone or home visits).

### Pharmacy records or secondary database analysis, or both

Providers can use dates of prescription refills to calculate adherence measures. These can be broadly considered under three categories (Lam 2015).

- **Medication possession ratio (MPR):** this measures the time for which a person possesses a supply of each medication class available, as a proportion of the time of eligibility for that medication. These measures are most commonly calculated over a three- to 12-month period but may be shorter or longer. We consider that the variability in methods used to calculate MPR

will create challenges to meta-analysis. We will pool MPR data and use subgroup analyses to investigate heterogeneity introduced by different methods.

- **Tablet pickup:** whether a person picks up all or a majority of their prescribed ARVs, categorizing people into either adherent or non-adherent based on a specified criteria.
- **Continuous measures:** the time between prescription refills from the perspective of time gaps (periods of non-adherence) or consumption (medication availability, the days of supply/days between refills).

### Electronic monitoring

Electronic monitoring devices use an embedded microprocessor to record the time and date a person opens a medication box. Health workers may access data from these devices by a cabled or cellular connection. Such devices use box opening as a proxy for medication ingestion, and as such may misclassify dose-taking behaviour. Expert opinion suggests that devices are currently unlikely to be affordable to be used at scale in resource-limited settings, they are likely to become much cheaper in the future (Haberer 2017).

### Composite measures of the above

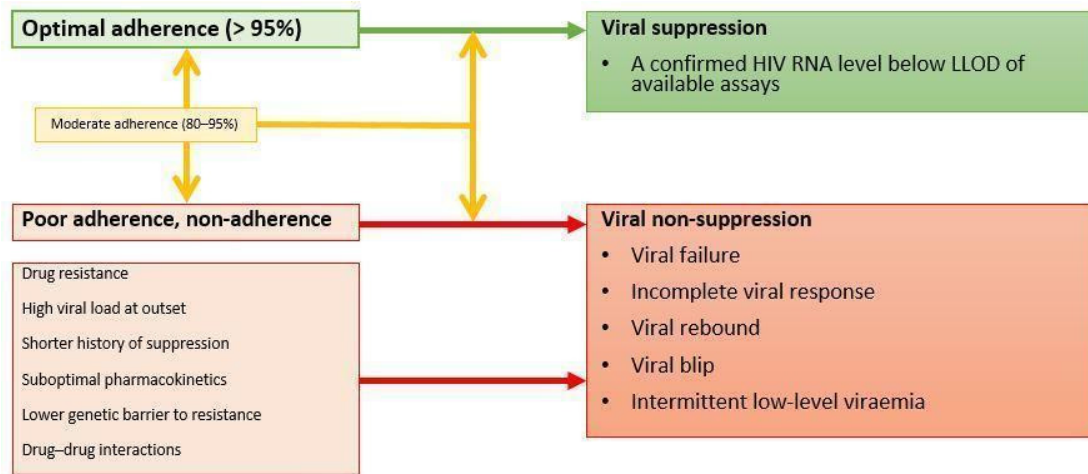
This describes the combination of two or more measures of adherence to give a more accurate impression than a single component can give in isolation.

### Clinical pathway

Under current national and international guidelines, when a person is diagnosed with HIV and linked to care, they are offered ART. After initiation of ART, people attend for clinical review. Clinicians may offer people more frequent clinical reviews in the months following initiation or during intercurrent illness, and less frequent clinical reviews once a person is established on and responding to therapy. Local guidelines and resources may also influence the frequency with which clinicians offer reviews. When people present for these reviews clinicians may apply the index test (measures of adherence).

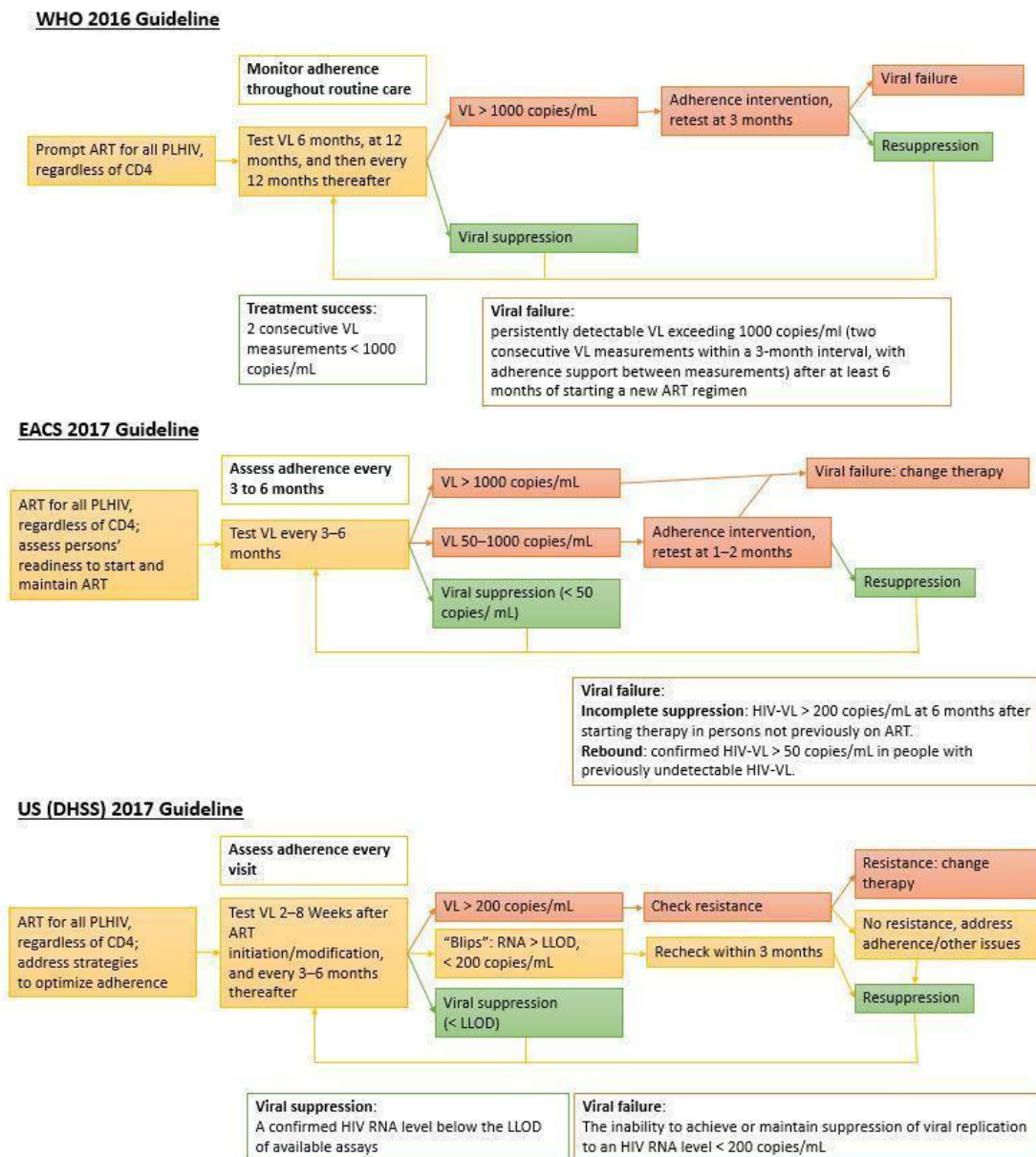
At these reviews, people may also receive viral load monitoring. This is the WHO 'gold standard' for confirmation of treatment response. However, the WHO also advises that viral load monitoring is the 'gold standard' for monitoring adherence (WHO 2016). Indeed, most elevated viral loads are the result of poor adherence (Bonner 2013). However, the relationship between adherence and viral load is not linear. Other patient and drug-related factors will influence viral suppression including drug resistance, viral load at outset of therapy, history of suppression, pharmacokinetics such as absorption, the genetic barrier to resistance offered by the regimen, and drug-drug interactions, as illustrated in Figure 1.

**Figure 1. Patient and drug-related factors that influence viral suppression. LLOD: lower limit of detection; RNA: ribonucleic acid.**



The frequency with which providers offer viral load monitoring, and how the results are acted upon, will vary depending on resource availability. In resource-limited settings, viral load measurement is recommended initially at six months and then routinely 12 monthly thereafter if suppressed (WHO 2016). In more resource-rich settings, viral load monitoring is more frequent, several early viral load measurements may be conducted during the first few months of ART, and routine monitoring is recommended every three to six months. Figure 2 demonstrates simplified clinical pathways as described across current guidelines.

**Figure 2. Simplified clinical pathways described in current guidelines. ART: antiretroviral therapy; LLOD: lower limit of detection; PLHIV: people living with HIV; VL: viral load; WHO: World Health Organization.**



### Prior test(s)

There are no prior tests that occur before the index test. However, elevated viral load measurements at previous visits and clinical findings may influence the decision to use measures of adherence. People may receive the index test (measures of adherence) more frequently when they have evidence of complications from HIV. There are no differences according to age or gender.

### Role of index test(s)

The index tests are already in current clinical use, and used variably across the clinical pathways. If we could better understand which of the available index tests are effective in detection of viral non-suppression, this test could replace the other tests within a given strategy. Another potential role may be as a triage test, to enable more targeted viral load testing.

### Alternative test(s)

Other purported measures of adherence that feature within the literature include:

- **directly observed therapy (DOTs):** DOTs often categorized as a 'direct' measure of adherence. A systematic review of DOTs showed no benefit to viral suppression of directly observed versus self-administered antiretroviral drugs (Ford 2009). We will exclude this because it does not represent 'simple triage', and there is overlap with adherence intervention;
- **therapeutic drug monitoring (TDM):** the absence of a drug with a long half-life gives objective evidence of recent non-adherence. We will exclude this as it is resource intensive, and generally does not give information about longer-term adherence. Other potential caveats include that serum drug levels may not reflect intracellular concentrations, therapeutic thresholds are unclear, and there is great inter- and inpatient variability (DHHS 2017);
- **pharmacological measures to quantify cumulative drug exposure:** in response to the short-term nature of the information given by TDM, new measures are being evaluated to reflect drug intake and metabolism over a period of weeks to months. These include dried blood spot testing and hair testing (Castillo-Mancilla 2018). Dried blood spot testing has not yet been evaluated in relation to clinical outcomes in HIV treatment and requires deep freeze within the laboratory, which is unlikely to be viable in resource-limited settings. Hair sampling requires a person to have and be willing to part with hair, requires specialised laboratory services for processing, and is thus not likely to constitute 'simple triage'. Both these tests have future potential;
- **provider clinical judgement:** a small number of studies have investigated provider's subjective opinions on the likely

adherence behaviour of their patient (Bangsberg 2001; Gross 2002). These represent complex qualitative assessments and are poorly amenable to meta-analysis. Therefore, we will exclude them from this review.

- **tablet identification tests:** the provider asks the patient to identify the tablets they have been prescribed from a selection of images of tablets (Parietti 2001). We will exclude these from this review because these test a patient's knowledge rather than implementation behaviour.

Adherence research has classified measures of adherence as objective and subjective, and direct and indirect. Although such terms appear in the literature, there is no formal taxonomy, and different authors may use the same term to describe different measures. Furthermore, the validity of applying these terms to HIV adherence research is questionable (Williams 2013). Therefore, we will avoid such terminology in this report.

### Downstream impact of index test

The possible downstream consequences according to the four test accuracy categories, are as follows:

- **true positive:** the clinician can perform additional tests (a viral load test, an increased frequency of viral load testing in future), or refer for an effective intervention (adherence support), or both;
- **true negative:** the clinician can continue the normal viral load testing schedule according to local practice;
- **false positive:** the clinician may unnecessarily perform an additional test (viral load) or refer for an intervention (adherence support), or both. The blood test may cause the patient distress. The intervention may inconvenience the patient. Both test and intervention incur costs for the provider;
- **false negative:** the patient will continue to receive the normal viral load testing schedule according to local practice. The patient has viral non-suppression which has not been detected at that clinical review. This may lead to the consequences of transmission of HIV to other people, progression of HIV and the resultant morbidity and mortality, or development of drug resistance.

### Rationale

Although viral load testing is the reference standard measurement of treatment response, it is not universally available. In resource-limited settings, viral load testing may either not be available or not feasible at a high frequency. In this context, WHO has identified a need to identify through simple triage those patients in greatest need of adherence support. This review will seek to recommend



measures of antiretroviral adherence which could be used in resource-limited settings, and determine gaps in the current body of knowledge to inform future research.

## OBJECTIVES

To determine the accuracy of simple measures of adherence, including patient self-report, tablet counts, pharmacy records, electronic monitoring, or composite methods, for detecting non-suppressed viral load in people living with HIV.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

#### Inclusion criteria

- The study assesses index test(s) of interest (measures of adherence), at the time of a viral load measurement. We anticipate that most included studies will be conducted at a single time point. If studies are conducted at multiple time points, we will include them if we are able to extract data from one or more specific time points, rather than aggregate or longitudinal scoring.
- The study reports data comparing the index test(s) of interest to viral load non-suppression, from which we could extract true positive, true negative, false positive, and false negative values.
- The study measures viral load using laboratory-based testing platforms.

We will also include studies which make within-study comparisons of the index test(s) of interest, but will not restrict inclusion only to such studies as we anticipate few such studies exist.

#### Exclusion criteria

- The study does not report the lower limit of detection of the viral load assay used.
- The study uses a viral load assay with a lower limit of detection greater than 400 copies per millilitre.
  - This is because most current laboratory assays have a lower limit of detection of less than 400 copies per millilitre, and there is greater clarity across literature that viral loads of less than 400 copies per millilitre reflect suppression.

- Studies using non-nucleic acid testing approaches.
  - An example of a non-nucleic acid approach is measurement of HIV reverse transcriptase activity, this is a surrogate for HIV viral load measurement, but is not the reference standard.
- Studies using point-of-care tests.

We will exclude retrospective studies or case-control study designs. These are more likely to be subject to bias, in particular in relation to flow and timing: we anticipate that we will not be able to confirm that the timing of the adherence measure and the viral load are simultaneous, or that all patients receiving a given adherence measure will also receive a viral load.

There will be no restrictions on minimal quality standard, minimal sample sizes, or number of cases with viral non-suppression.

#### Participants

We will include studies that recruit HIV-positive adults, adolescents, and children who have been established on ART for longer than six months at the time of assessment.

#### Index tests

The index test will be measures of adherence that could be utilised in resource-limited settings, and will include:

- self-report;
- tablet counts;
- pharmacy records /or secondary database analysis, or both;
- electronic monitoring;
- composite measures of the above.

We will categorize and analyse studies according to the above headings.

There are no specific consensus criteria for identifying adherence versus non-adherence. Studies may report different dichotomized thresholds between 'non-adherent' and 'adherent' in relation to measures of adherence that report implementation of a dosing regimen over a defined interval of time. For example:

- self-report: count- or estimate-based measures of percentage adherence over a given period;
- tablet counts: adherence percentage based on expected versus actual tablets taken over dispensing period;
  - pharmacy records or secondary database analysis, or both: MPR;
  - electronic monitoring: percent of doses received as measured;
  - composite measures of the above given a pooled percentage estimate.

All these measures estimate a percentage of time during which a patient takes the medication as prescribed. Typically, these studies will then dichotomize 'adherence' and 'non-adherence', based on a percentage threshold.

Our definitions for the four test accuracy categories are as follows:

- true positive: the index test correctly identifies non-adherence to ART, and as such, detects a non-suppressed viral load;
- true negative: the index test correctly identifies adherence to ART, and as such, detects a suppressed viral load;
- false positive: the index test misclassifies a person as non-adherent to ART, and fails to detect a suppressed viral load;
- false negative: the index test misclassifies a person as adherent to ART, and fails to detect a non-suppressed viral load.

### Target conditions

The target condition is viral non-suppression. We will define this as an HIV RNA level above the lower limit of detection of the assay used within the study in question.

### Reference standards

We will use a reference standard of non-suppressed viral load, as detected using nucleic acid testing technologies. This will be any viral load which is above the lower limit of detection of the available assay. This varies between assays, ranging from 10 copies per millilitre to 400 copies per millilitre in those which are currently available.

### Search methods for identification of studies

The Cochrane Infectious Diseases Group Information specialists will perform a comprehensive search to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and ongoing).

### Electronic searches

We will search the following databases from 2003 onwards, as these reflect more current ART regimens and viral load thresholds (WHO 2003).

- Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library);
- MEDLINE (PubMed);
- Embase (Ovid);
- Latin American and Caribbean Health Sciences Literature (LILACS);
- CINAHL (EBSCOhost);
- Africa-Wide Information (EBSCOhost); and
- Web of Science (Core Collection (Clarivate Analytics)).

The preliminary search strategy for MEDLINE (PubMed) is presented in [Appendix 1](#). We will adapt it for the other electronic databases, and report all search strategies in full in the final version of the review.

### Searching other resources

To identify additional published, unpublished, and ongoing studies, we will perform the following tasks:

- screen reference lists of included studies and relevant review;
- screen the following conferences from 2016 onwards: International AIDS Society (IAS) conferences: International AIDS Conference, Conference on HIV Science ([www.iasociety.org/Conferences](http://www.iasociety.org/Conferences)), European AIDS Conference ([www.eacsociety.org](http://www.eacsociety.org)), International Conference on HIV Treatment and Prevention Adherence ([www.iedea.org](http://www.iedea.org));
- search the WHO portal for any registered trials;
- contact authors who have published more than once as first or senior author on included studies; and
- handsearch WHO reports on adherence measures.

### Data collection and analysis

#### Selection of studies

Two review authors (PH and RH) will independently scrutinise titles and abstracts identified from our electronic search to identify those which may be eligible. We will retrieve the full-text article of any citation either review author (PH or RH) identifies as potentially eligible. Each review author will independently assess each full-text article for inclusion. We will settle any discrepancies via discussion between review authors, and if further uncertainty remains, consultation with a third review author (IEW). We will name studies according to the surname of the first author and year of publication.

#### Data extraction and management

Two review authors (PH and RH) will independently extract data using a predefined data extraction tool. We will pilot the form on two studies from each adherence measure subtype, and finalise the form thereafter. We will extract data on the following characteristics.

- Author, publication year, study design (as defined by review author).
- Country of study and country income status (low-income, lower middle-income, upper middle-income, high-income), as defined by The World Bank atlas method at the time of data extraction ([World Bank 2018](#)).
- Age and gender of included participants.
- HIV viral load assay used.
- Type of adherence assessment used, alone or as a composite measure, including:
  - for self-report: number of questions, modality (self-completion, interviewer administered), question content (behavioural or attitudinal);
  - for pharmacy data: MPR or tablet pick up.

- Threshold used within the study for definition of dichotomization of optimal and suboptimal adherence.
- QUADAS-2 items (as detailed in [Appendix 2](#))

Two review authors (PH and RH) will then extract results and cross-tabulate data in two-by-two tables, using the following definitions.

- **Disease positive:** people with a viral load above the lower limit of detection used in the study assay.
- **Disease negative:** people with an undetectable viral load using the study assay.
- **Test positive:** people defined as non-adherent within the study, based on dichotomised percentage adherence, using a threshold defined by the study authors.
- **Test positive:** people defined as adherent within the study, based on dichotomised percentage adherence, using a threshold defined by the study authors.

### Assessment of methodological quality

We will use the QUADAS-2 tool to appraise risk of bias and applicability ([Whiting 2011](#)). This includes four domains: patient selection, index test, reference standard, and flow and timing. To tailor the tool for our review, we will add or omit signalling questions for each of the four domains. We have proposed an initial schema for operating the QUADAS-2 tool in [Appendix 2](#). Two review authors (PH and RH) will independently pilot the form with two studies from each adherence measure subtype, and finalise the form thereafter.

### Statistical analysis and data synthesis

For all included studies, we will use the data in the two-by-two tables (the binary test results cross-tabulated with the binary reference standard) to calculate sensitivities and specificities, along with their 95% confidence intervals.

We will present individual study results graphically by plotting estimates of sensitivities and specificities in a forest plot and in receiver operating characteristic (ROC) space. This will facilitate visual assessment of variation in test accuracy. We will use Review Manager 5 for these descriptive analyses and to produce summary ROC curves ([Review Manager 2014](#)).

We will perform meta-analysis for each index test. We anticipate that there is likely to be variation in thresholds between included studies, and this may be explicit or implicit ([Leeftang 2008](#)). Explicit variation may occur when different studies use different percentage adherence thresholds within the same test to define non-adherence. There may also be implicit variation, when the test result depends on an element of interpretative judgement, especially in the case of self-report. Given the anticipated explicit and implicit variation, we will use the hierarchical summary ROC model (HSROC) to pool data (sensitivities and specificities) and to plot a summary ROC (SROC) curve for each index test. The HSROC

model estimates the underlying ROC curve, and thus describes how sensitivity and specificity of the included studies trade off with each other as thresholds vary.

If we encounter a sufficient number of studies that report a common threshold for adherence and non-adherence, we will use the bivariate model, and give the estimate of the summary operating point.

If a study reports more than one threshold, we will use the threshold from the study that is most commonly reported across studies in the meta-analysis.

We will perform meta-analysis using the NLMIXED procedure within the MetaDAS macro for SAS ([Takwoingi 2010](#)).

### Comparing index tests

In the first instance, we will make simple separate comparisons of summary estimates from alternative index tests.

If we encounter a sufficient number of studies that make within-study paired comparisons of the index tests of interest, we will present linked ROC plots, in which the two estimates are joined by a line. This will facilitate visual assessment of change in accuracy within study between the tests. We will perform HSROC analysis restricted to such studies, and compare index tests using type of index test as a covariate within the HSROC model. This will allow us to explore heterogeneity in test positivity (threshold), position of the curve (accuracy), and shape of the curve. This would be the preferred method of analysis, but we anticipate that we may not find such studies.

In the absence of a sufficient number of studies making within-study comparisons, we will make comparisons across index tests, again using type of index test as a covariate within the HSROC model.

### Investigations of heterogeneity

For each index test, we will formally investigate potential sources of heterogeneity, by incorporating covariates to a hierarchical model in our meta-analysis.

- Setting, including income status:
  - this will include World Bank income categories: low-income, lower- to middle-income, upper- to middle-income, and high-income economies.
- Target population in study, as represented by child, adolescent, or adult.
- Lower limit of detection of viral load threshold used within the study.
- Subtype of adherence measure (e.g. by number and content of questions within self-report adherence measures).

Where we use the HSROC model due to variation in thresholds, we will assess the effect of covariates on the accuracy, threshold, and shape parameters. Where we use the bivariate model, we will

assess interaction of covariates with sensitivity or specificity, or both.

These potential sources of heterogeneity are speculative. We propose setting and target population as potential sources given that there are considerable differences in adherence rate between countries, and ages globally. As, to our knowledge, this is the first systematic review in this area, the relevance of these factors is yet to be ascertained.

### Sensitivity analyses

For each index test, we will conduct sensitivity analyses in which we exclude studies for which the QUADAS-2 tool indicates areas of methodological concern. We will exclude studies in which more than four of our six QUADAS-2 domains are high risk. We also plan to assess the impact of risk of bias in relation to conduct and patient flow, and the impact of applicability in terms of whether the measure is likely to be applicable to a resource-limited setting.

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### Assessment of reporting bias

We will not carry out formal assessment of publication bias because there is a lack of sensitive and appropriate statistical methods relevant to this review methodology.

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\* *Indicates the major publication for the study*

**ADDITIONAL TABLES****Table 1. Guidelines for determining viral failure**

Guideline	Threshold
DHHS 2017	Persistent (> 1 reading of > 200 copies/mL) denotes viral failure after 24 weeks on an ARV regimen in a person who has not yet had documented virological suppression on this regimen
EACS 2017	Confirmed (< 1 month) HIV-VL > 50 copies/mL 6 months after starting therapy (initiation or modification) in people on ART. Depending on the HIV-VL assay, this limit could be higher or lower
WHO 2016	Persistently detectable viral load exceeding 1000 copies/mL (i.e. 2 consecutive viral load measurements within a 3-month interval with adherence support between measurements) after ≥ 6 months of starting a new ART regimen

ARV: antiretroviral therapy; HIV-VL: HIV viral load.

**Table 2. Health service nomenclature**

Tier	Highest cadre	Terms often used	Facility and staff	Equipment facilities
Community	Individual with maximum of few months training, paid or unpaid	Family-led care	Family member	HIV tests, counselling, replenish drugs
		Community volunteer	Trained volunteer; health assistants	
		Primary care clinic	Nurse aide or community health workers	
Health centre	Clinical officer or nurse (≥ 2 years' training)	Health centres; district hospitals	Purpose built with ≥ 1 paramedic or nurse with some health assistants	HIV tests; antiretroviral drugs; opportunistic infections medicines; point-of-care laboratories

**Table 2. Health service nomenclature** (Continued)

<b>Health (enhanced) centre</b>	Clinical officer or nurse ( $\geq 2$ years' training)	Health centres, primary health care clinics, district hospitals	Purpose built with $\geq 1$ paramedic or nurse with some health assistants, with input from a doctor (may be via mobile support service)	HIV tests; antiretroviral drugs; opportunistic infections medicines; point-of-care laboratories
<b>Hospital</b>	Doctor	Health centres; district hospitals	Purpose built with $\geq 1$ medical doctor with nurses/paramedics and assistants	CD4 count; medicines; not viral load
<b>Hospital (advanced)</b>	Specialist doctor	District hospital; referral hospital	Purpose built with $\geq 2$ specialist doctors with nurses/paramedics and assistants	Viral load; full investigations

## APPENDICES

### Appendix I. MEDLINE (PubMed) search strategy

#1 Search All Fields (HIV OR hiv-1 OR hiv-2\* OR hiv1 OR hiv2 OR hiv infect\* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun\*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immunodeficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun\*) AND (deficiency syndrome)) OR HIV/AIDS)

#2 Search (HIV infections [MeSH] OR HIV [MeSH])

#3 (#1 OR #2)

#4 Search All Fields (Antiretroviral\* OR ((anti) AND (retroviral\*)) OR ARV\* OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral\*) AND (therap\*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR ((anti) AND (acquired immune-deficiency)) OR ((anti) AND (acquired immun\*) AND (deficienc\*)))

#5 Search (antiretroviral agents [Mesh] OR antiretroviral therapy, highly active [Mesh])

#6 (#4 OR #5)

#7 (#3 AND #6)

#8 Search All Fields (adhere OR adherence OR adhered OR adheres OR nonadherence OR non-adherence OR complies OR complying OR comply OR compliance OR concordance OR patient dropouts OR treatment dropouts OR treatment refusal OR "pill counts" OR "pill counting" OR "pill count" OR "pharmacy records" OR "pharmacy recording" OR "drug counting" OR "drug counts" OR "drug count" OR dispensed OR dispensary OR "pharmacy recorded" OR "pharmacy-recorded")

#9 Search (("Patient Dropouts"[Mesh]) OR ("Patient Compliance"[Mesh]) OR ("Treatment Adherence and Compliance"[Mesh]) OR ("Medication Adherence"[Mesh]))

#10 (#8 OR #9)

#11 Search All Fields (viral non-suppression OR viral suppression OR viral load OR virologic outcome\* OR low level viraemia OR low level viremia OR viral blips OR viral failure OR viral rebound OR incomplete viral response)

#12 Search (“Viral Load”[Mesh]) OR (“Sustained Virologic Response”[Mesh])

#13 (#11 OR #12)

#14 Search (animals [Mesh] NOT humans [Mesh])

#15 (#7 AND #10 AND #13)

#16 (#15 NOT #14)

#17 Sort by: Best Match Filters: Publication date from 1996/01/01

## Appendix 2. QUADAS-2: list of signalling questions, risk of bias, and applicability

Domain	Patient selection	Index test	Reference standard	Flow and timing
<b>Description</b>	We will describe methods of patient selection, and the intended use of the adherence measure in this setting	We will describe the measure of adherence, and how the researchers interpreted it	We will describe the method used to measure viral load and the lower limit of detection of the assay	We will describe any interval between the adherence measure and the viral load measurement
<b>Signalling questions (yes, no, unclear)</b>	<p><b>Consecutive or random sample of patients?</b>  <b>Yes:</b> if authors stated they used random patient sampling or consecutive enrolment  <b>No:</b> when patients were selected, for example, based on previously identified concerns regarding adherence  <b>Unclear:</b> if authors provided insufficient information.</p>	<p><b>Index test results interpreted without knowledge of the results of reference standard?</b>  <b>Yes:</b> if authors clearly reported that the measures of adherence were applied and interpreted before the viral load result was available  <b>No:</b> if authors reported that the measures were applied or interpreted after the viral load was available  <b>Unclear:</b> if authors provided insufficient information.</p>	<p><b>Reference standard likely to correctly classify the target condition?</b>  <b>Yes:</b> if authors clearly reported that a laboratory reference test was used at a manufacturer recommended threshold of lower limit of detection, and this was &lt; 400 copies/mL  <b>No:</b> if authors reported application of a post-hoc threshold.  <b>Unclear:</b> if authors provided insufficient information.</p>	<p><b>Appropriate interval between measure of adherence and viral load measurement?</b>  <b>Yes:</b> if the measure of adherence and the measure of viral load were made on the same day  <b>No:</b> if time period between measure of adherence and viral load was not made on the same day  <b>Unclear:</b> if authors provided insufficient information.</p>
	<p><b>Did the study avoid inappropriate exclusions?</b>  <b>Yes:</b> if there were no inappropriate exclusions.  <b>No:</b> if there was evidence that authors inappropriately excluded certain patients, e.g. those deemed to have limited ability to use electronic monitoring devices, or excluded those with literacy concerns if self-re-</p>	<p><b>Prespecified threshold used?</b>  <b>Yes:</b> if authors reported an a priori threshold value (or values) for adherence  <b>No:</b> if authors determined threshold values post hoc.  <b>Unclear:</b> if authors provided insufficient information.</p>	<p><b>Reference standard results interpreted without knowledge of the index test?</b>  <b>Yes:</b> if authors reported that viral loads were measured and recorded without a priori knowledge of the measure of adherence result  <b>No:</b> if authors reported that viral load was mea-</p>	<p><b>Did all patients receive a viral load, using the same assay, and were all included in the analysis?</b>  <b>Yes:</b> if authors reported that all patients received a viral load using the same assay and all were included in the analysis  <b>No:</b> if only a selection of those with adherence</p>



(Continued)

	port measures were to be self-administered <b>Unclear:</b> if authors provided insufficient information.		sured or recorded with knowledge of the measure of adherence result <b>Unclear:</b> if authors provided insufficient information.	measures have viral load measures, or different assays were used <b>Unclear:</b> if authors provided insufficient information.
<b>Risk of bias (high, low, unclear)</b>	<ul style="list-style-type: none"> <li>• If we answer both signalling questions for a domain 'yes', then we will judge risk of bias as low.</li> <li>• If we answer both signalling questions for a domain 'no', then we will judge risk of bias as high.</li> <li>• If we answer both signalling questions for a domain 'unclear', then we will judge the risk of bias as unclear.</li> <li>• If we answer both signalling questions for a domain differently, the authors will discuss this further to reach a final judgement, and explain the rationale for this judgement within the 'Risk of bias' table.</li> </ul>			
<b>Applicability concerns (high, low, unclear)</b>	<p><i>Are there concerns that the included patients do not match the review question?</i></p> <p><b>High:</b> if some but not all included patients were concurrently receiving interventions to improve their adherence, rather than the same standard of care, and these groups cannot be separated</p> <p><b>Low:</b> if all patients were receiving the same standard of care.</p> <p><b>Unclear:</b> if there was insufficient information to make a judgement.</p>	<p><i>Are there concerns that the index test, its conduct, or interpretation differs from the review question?</i></p> <p><b>High:</b> if the measure of adherence was not truly applicable in a resource-limited setting, e.g. requiring additional remote information infrastructure or analysis</p> <p><b>Low:</b> if the measure of adherence could feasibly be applied in a resource-limited setting</p> <p><b>Unclear:</b> if there was insufficient information to make a judgement.</p>	-	-

## CONTRIBUTIONS OF AUTHORS

PH wrote the contents of this protocol.

RS commented on the draft.

IEW commented on the draft.

CO commented on the draft.

KC commented on the draft.

MMGL commented on the draft.

NF commented on the draft.

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We have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, or expert testimony).

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