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Accuracy of measures for antiretroviral adherence in people living with HIV (Review)

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[Diagnostic Test Accuracy Review]

Accuracy of measures for antiretroviral adherence in people living with HIV

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ABSTRACT

Background

Good patient adherence to antiretroviral (ART) medication determines effective HIV viral suppression, and thus reduces the risk of progression and transmission of HIV. With accurate methods to monitor treatment adherence, we could use simple triage to target adherence support interventions that could help in the community or at health centres in resource-limited settings.

Objectives

To determine the accuracy of simple measures of ART 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 and receiving ART treatment.

Search methods

The Cochrane Infectious Diseases Group Information Specialists searched CENTRAL, MEDLINE, Embase, LILACS, CINAHL, African-Wide information, and Web of Science up to 22 April 2021. They also searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov for ongoing studies. No restrictions were placed on the language or date of publication when searching the electronic databases.

Selection criteria

We included studies of all designs that evaluated a simple measure of adherence (index test) such as self-report, tablet counts, pharmacy records or secondary database analysis, or both, electronic monitoring or composite measures of any of those tests, in people living with HIV and receiving ART treatment. We used a viral load assay with a limit of detection ranging from 10 copies/mL to 400 copies/mL as the reference standard. We created 2 × 2 tables to calculate sensitivity and specificity.

Data collection and analysis

We screened studies, extracted data, and assessed risk of bias using QUADAS-2 independently and in duplicate. We assessed the certainty of evidence using the GRADE method. The results of estimated sensitivity and specificity were presented using paired forest plots and tabulated summaries. We encountered a high level of variation among studies which precluded a meaningful meta-analysis or comparison of adherence measures. We explored heterogeneity using pre-defined subgroup analysis.

Main results

We included 51 studies involving children and adults with HIV, mostly living in low- and middle-income settings, conducted between 2003 and 2021. Several studies assessed more than one index test, and the most common measure of adherence to ART was self-report.

- **Self-report questionnaires** (25 studies, 9211 participants; very low-certainty): sensitivity ranged from 10% to 85% and specificity ranged from 10% to 99%.

- **Self-report using a visual analogue scale (VAS)** (11 studies, 4235 participants; very low-certainty): sensitivity ranged from 0% to 58% and specificity ranged from 55% to 100%.

- **Tablet counts** (12 studies, 3466 participants; very low-certainty): sensitivity ranged from 0% to 100% and specificity ranged from 5% to 99%.

- **Electronic monitoring devices** (3 studies, 186 participants; very low-certainty): sensitivity ranged from 60% to 88% and the specificity ranged from 27% to 67%.

- **Pharmacy records or secondary databases** (6 studies, 2254 participants; very low-certainty): sensitivity ranged from 17% to 88% and the specificity ranged from 9% to 95%.

- **Composite measures** (9 studies, 1513 participants; very low-certainty): sensitivity ranged from 10% to 100% and specificity ranged from 49% to 100%.

Across all included studies, the ability of adherence measures to detect viral non-suppression showed a large variation in both sensitivity and specificity that could not be explained by subgroup analysis. We assessed the overall certainty of the evidence as very low due to risk of bias, indirectness, inconsistency, and imprecision.

The risk of bias and the applicability concerns for patient selection, index test, and reference standard domains were generally low or unclear due to unclear reporting. The main methodological issues identified were related to flow and timing due to high numbers of missing data. For all index tests, we assessed the certainty of the evidence as very low due to limitations in the design and conduct of the studies, applicability concerns and inconsistency of results.

Authors' conclusions

We encountered high variability for all index tests, and the overall certainty of evidence in all areas was very low. No measure consistently offered either a sufficiently high sensitivity or specificity to detect viral non-suppression. These concerns limit their value in triaging patients for viral load monitoring or enhanced adherence support interventions.

PLAIN LANGUAGE SUMMARY

Are there good ways to find out if people living with HIV are taking their medicines every day?

The issue

For people with HIV, taking their HIV medicines every day (adherence), is vital to keep HIV under control. The best way to measure peoples' adherence to HIV medicines is with 'viral load testing', which tells us how much virus there is in the blood. Viral load testing is not available everywhere, such as in places where there is lack of funds. If we could measure adherence with a more readily available measure, this might help detect people who need more help with taking their medicines.

Aim of this review

To find out if simple measures of adherence can tell us whether people might not be taking their medication every day and might then have higher (detectable) viral loads. These people might be helped by extra viral load monitoring. This could then prevent them developing complications from HIV or passing HIV to other people.

What we found

We looked at 51 studies involving children and adults with HIV that happened between 2003 and 2021. These studies tested different ways to measure adherence, including surveys or rating scales filled out by patients, counting of patients' pills, pharmacy notes, or gadgets.

All the measures we looked at did not help find patients who might not be taking their medications and who had higher viral loads. Different studies showed very different results. We could not explain these differences by whether the studies included children or adults, whether they were in richer or poorer areas, or what cut off they used to say if the viral load was high. This also meant that we could not combine the studies.

What are the implications of this review?

Based on the results, it is uncertain that simple measures of adherence to ART treatment can help find people living with HIV who may have a higher viral load. Still, there may be other values to trying to measure adherence that this review cannot show.

Reporting how current the evidence is

The evidence is up-to-date to 22 April 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table 1: all index tests

Question: what is the diagnostic accuracy of the different index tests to measure adherence to ART for detecting viral non-suppression?				
Population	HIV-positive children and adults who have been established on ART for longer than six months at the time of assessment			
Index tests	• self-report; • tablet counts; • pharmacy records or secondary database analysis, or both; • electronic monitoring; • composite measures of the above.			
Target condition	Viral non-suppression			
Reference standard	Non-suppressed viral load, as detected by nucleic acid testing technologies, ranging from 10 copies to 400 copies/mL			
Action/clinical implications	***Low sensitivity:*** failures to detect non-adherence. Consequences of false negatives: disease progression, resistance, transmission ***Of greater clinical importance***	***Low specificity:*** adherent people incorrectly identified. Consequences of false positives: increased viral load (VL) monitoring, patient inconvenience ***Of lesser clinical importance***		
Findings				
Type of index test	**Studies and participants (viral non-suppression, %)**	**Sensitivity range (95% CI range)**	**Specificity range (95% CI range)**	**Certainty of the evidence (GRADE)**
Index test: self-report All participants ≥ 95% adherence threshold Any viral load threshold	25 studies N = 9211 (1813, 20%)	10% to 85% (0% to 91%)	10% to 99% (7% to 100%)	⊕### **VERY LOW** [a,b,c,d]
Index test: VAS All participants ≥ 95% adherence threshold Any viral load threshold	11 studies N = 4235 (1479, 35%)	0% to 58% (0% to 85%)	55% to 100% (46% to 100%)	⊕### **VERY LOW** [c,d,e,f]
Index test: tablet counts All participants ≥ 95% adherence threshold Any viral load threshold	12 studies N = 3466 (504, 15%)	0% to 100% (0% to 100%)	5% to 99% (2% to 100%)	⊕### [c,d,g,h] **VERY LOW**

Index test: pharmacy records or secondary database All participants ≥95% adherence threshold Any viral load threshold	6 studies N = 2254 (552, 24%)	17% to 88% (11% to 92%)	9% to 95% (5% to 97%)	⊕### **VERY LOW** [c,d,i,j]
Index test: electronic monitoring All participants ≥ 95% adherence threshold Any viral load threshold	3 studies N = 186 (55, 30%)	60% to 88% (36% to 100%)	27% to 67% (11% to 80%)	⊕### **VERY LOW** [k,l,m,n]
Index test: composite measure All participants Different thresholds* Any viral load threshold	9 studies N = 1513 (407, 27%)	10% to 100% (4% to 100%)	49% to 100% (35% to 100%)	⊕### **VERY LOW** [c,d,o,p]

[a]Downgraded one level for limitations in the design and conduct of the studies due to patient selection (5 studies high risk, 7 studies unclear risk); administration and/or interpretation of the adherence measure (index test) (17 studies unclear risk); administration and/or interpretation of the viral load test (reference standard) (6 studies unclear risk); and flow and timing of the study, including missing participant data (12 studies high risk, 2 studies unclear risk)

[b]Downgraded one level for indirectness due to applicability concerns in relation to the population (2 studies high concern, 8 studies unclear concern); the measure of adherence used (index test) (3 studies unclear concern); and the viral load assessment used (reference standard) (6 studies unclear concern)

[c]Downgraded two levels for inconsistency due to the extreme heterogeneity observed between the studies, both for sensitivity and specificity

[d]The evidence was not downgraded further due to imprecision as this was explained by the inconsistency observed between the studies.

[e]Downgraded one level for limitations in the design and conduct of the studies due to patient selection (3 studies high risk, 3 studies unclear risk); administration and/or interpretation of the adherence measure (index test) (8 studies unclear risk); administration and/or interpretation of the viral load test (reference standard) (4 studies unclear risk); and flow and timing of the study, including missing participant data (6 studies high risk, 2 studies unclear risk)

[f]Downgraded one level for indirectness due to applicability concerns in relation to the population (2 studies high concern, 2 studies unclear concern); the measure of adherence used (index test) (4 studies unclear concern); and the viral load assessment used (reference standard) (4 studies unclear concern)

[g]Downgraded one level for limitations in the design and conduct of the studies due to patient selection (3 studies high risk, 4 studies unclear risk); administration and/or interpretation of the adherence measure (index test) (1 study high risk, 9 studies unclear risk); administration and/or interpretation of the viral load test (reference standard) (4 studies unclear risk); and flow and timing of the study, including missing participant data (7 studies high risk, 3 studies unclear risk)

[h]Downgraded one level for indirectness due to applicability concerns in relation to the population (3 studies high concern, 2 studies unclear concern); the measure of adherence used (index test) (3 studies unclear concern); and the viral load assessment used (reference standard) (4 studies unclear concern).

[i]Downgraded two levels for limitations in the design and conduct of the studies due to patient selection (3 studies high risk, 1 study unclear risk); administration and/or interpretation of the adherence measure (index test) (5 studies unclear risk); administration and/or interpretation of the viral load test (reference standard) (2 studies unclear risk); and flow and timing of the study, including missing participant data (5 studies high risk)

[j]Downgraded one level for indirectness due to applicability concerns in relation to the population (3 studies unclear concern); the measure of adherence used (index test) (3 studies unclear concern) and the viral load assessment used (reference standard) (2 studies unclear concern).

[k]Downgraded one level for limitations in the design and conduct of the studies due to patient selection (1 study unclear risk); administration and/or interpretation of the adherence measure (index test) (3 studies unclear risk); and flow and timing of the study, including missing participant data (1 study high risk)

[l]Downgraded one level for indirectness due to applicability concerns in relation to the population (1 study high concern); and the measure of adherence used (index test) (3 studies unclear concern)

[m]Downgraded one level for inconsistency due to the heterogeneity observed between the studies, both for sensitivity and specificity
[n]Downgraded one level for imprecision due to small sample size. The evidence was not downgraded further due to imprecision as this was explained by the inconsistency observed between the studies.
[o]Downgraded one level for limitations in the design and conduct of the studies due to patient selection (1 study high risk, 4 studies unclear risk); administration and/or interpretation of the adherence measure (index test) (7 studies unclear risk); administration and/or interpretation of the viral load test (reference standard) (4 studies unclear risk); and flow and timing of the study, including missing participant data (4 studies high risk, 2 studies unclear risk)
[p]Downgraded one level for indirectness due to applicability concerns in relation to the population (1 study high concern, 3 studies unclear concern); the measure of adherence used (index test) (3 studies unclear concern); and the viral load assessment used (reference standard) (3 studies unclear concern).

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 a 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 sexual 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 realized, 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 receiving 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 have identified treatments for people who achieve poor adherence to ART, thus illustrating the importance of measuring adherence in order to identify people who may benefit from such treatments (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), although more recent studies suggest a lower threshold be applied (Shilpa 2015). 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 affect 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 summarizes 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 is defined as any 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). 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 such as task shifting. With respect to ‘task shifting', the 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's adherence (WHO 2017).

In relation to these considerations, this review focuses 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 a few months of training;
- would not require infrastructure such as laboratories which are more commonly found at referral health centres or hospitals.

This would not preclude the 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 such as:
  - count-based questions: 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 questions: asking people to estimate how they took their treatment over a period of time. This might be based around a visual analogue scale (VAS), for example, *mark the point along the line that most closely reflects how much of your HIV medications you have taken in the lastmonth?* (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 excludes self-report containing more than eight questions, or which the review authors deem to be prohibitively complex for use at community or health centre 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 be 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 pick-up:** whether a person picks up all or most of their prescribed ARTs, categorizing people into either adherent or non-adherent based on 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 although devices are currently unaffordable 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

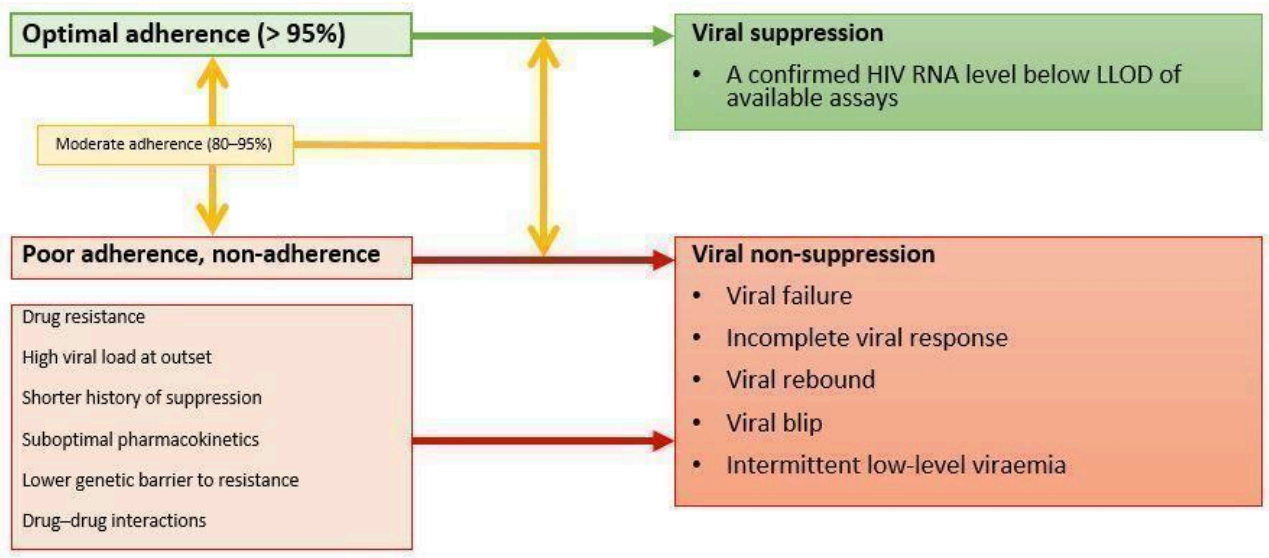
This describes the combination of two or more measures of adherence to give a more accurate impression than a single measure in isolation.

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).

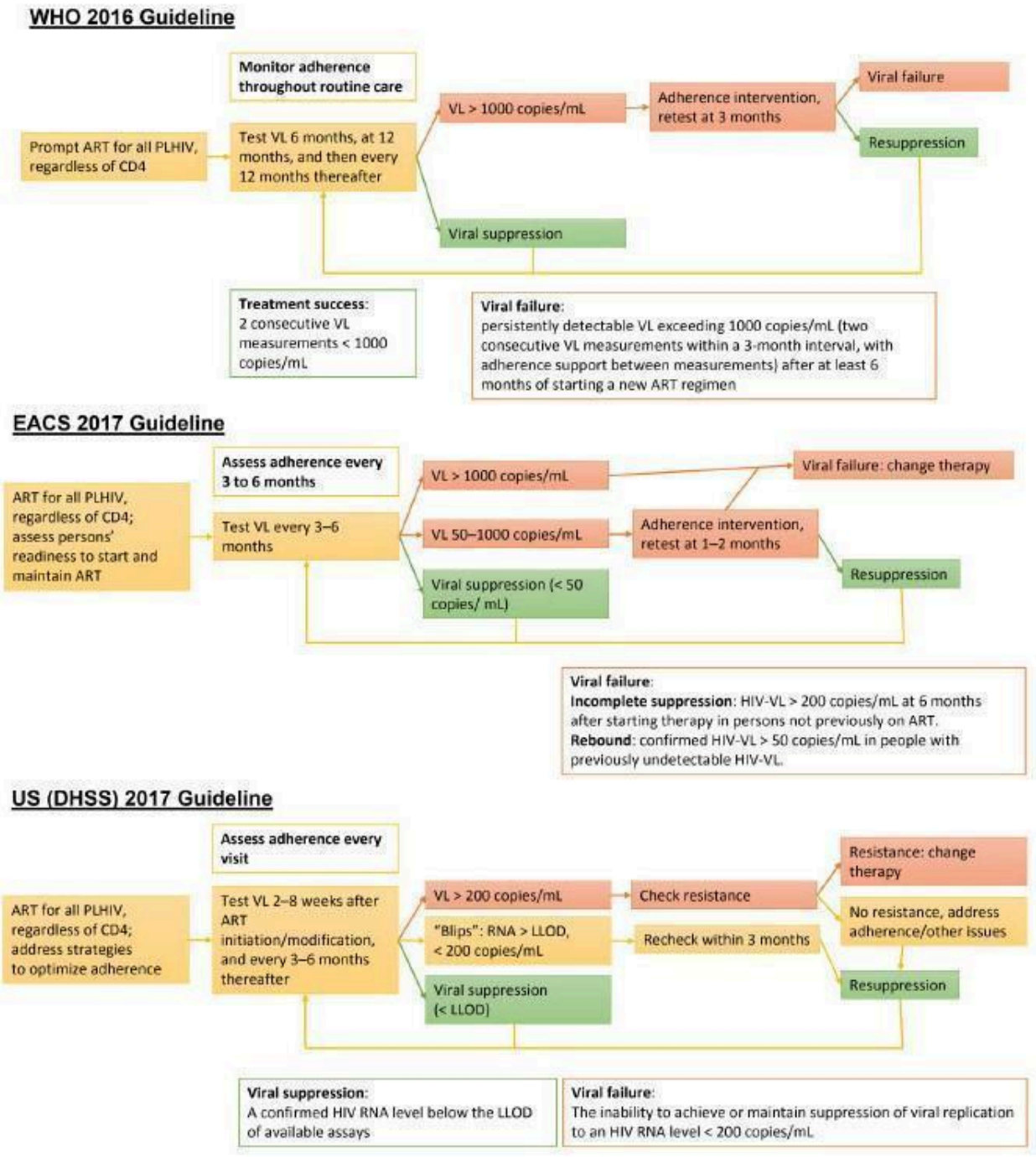
At these clinical appointments, people may also undergo viral load monitoring. This is the WHO ‘gold standard' for confirmation of treatment response. The WHO also advises that viral load monitoring is the ‘gold standard' for monitoring adherence (WHO 2016). Indeed, most elevated viral loads are the 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. Abbreviations: 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, a 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. Abbreviations: 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 due to HIV. There are no differences according to age or gender.

Role of index test(s)

The index tests already in current clinical practice are used variably across the clinical pathways. If we could better understand which among all available index tests is more effective to determine viral non-suppression, this test could replace other tests within a given strategy. Additionally, an index test can be used as a triage test to enable more targeted viral load testing.

Alternative test(s)

Other measures of adherence include:

- **directly observed therapy** (DOTs): DOTs are 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 have excluded 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 have excluded this as it is resource intensive, and generally does not give information about longer-term adherence. Other potential caveats include the following issues: serum drug levels may not reflect intracellular concentrations, therapeutic thresholds are unclear, and there is great inter- and intrapatient 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 specialized 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 have excluded 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 (Parienti 2001). We have excluded 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 have avoided 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 (TP)** *(the index test correctly identifies non-adherence to ART, and as such, detects a non-suppressed viral load):* 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 (TN)***(the index test correctly identifies adherence to ART, and as such, detects a suppressed viral load):* the clinician can continue the normal viral load testing schedule according to local practice;
- **false positive (FP)** *(the index test misclassifies a person as non-adherent to ART, and fails to detect a suppressed viral load):* 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 (FN)** *(the index test misclassifies a person as adherent to ART, and fails to detect a non-suppressed viral load):* 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.

Systematic review evidence demonstrates that a number of interventions may ameliorate non-adherence, and either improve reported adherence (for example, text-messaging), or viral suppression (for example counselling or supporter interventions). The effects of interventions may be modest and wane over time (Kanters 2017).

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, the WHO has identified a demand to select through a simple triage those patients in greatest need of adherence support. This review seeks to recommend measures of antiretroviral adherence which could be used in resource-limited settings and to determine gaps in the current body of knowledge to inform future research.

OBJECTIVES

To determine the accuracy of simple measures of ART 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 and receiving ART treatment.

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 anticipated that most included studies would be conducted at a single time point. If studies were conducted at multiple time points, we included them if we were able to extract data from one or more specific time points, rather than aggregate or longitudinal scoring.
- The study reported 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 measured viral load using laboratory-based testing platforms.

We included observational studies (cross-sectional and prospective cohort studies) and randomized studies that provided sufficient data to create the 2 x 2 table to calculate sensitivity and specificity.

We also included studies which made within-study comparisons of the index test(s) of interest, but did not restrict inclusion only to such studies as we had anticipated few such studies existed.

Exclusion criteria

- The study did not report the lower limit of detection of the viral load assay used.
- The study used a viral load assay with a lower limit of detection greater than 400 copies/mL.
  - This is because most current laboratory assays have a lower limit of detection of less than 400 copies/mL, and there is greater clarity across literature that viral loads of less than 400 copies/mL 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.
- Studies using point-of-care tests.

We excluded 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 anticipated that we would not be able to confirm that the timing of the adherence measure and the viral load was simultaneous, or that all patients receiving a given adherence measure would also receive a viral load.

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

Participants

We included studies that recruited HIV-positive adults, adolescents, and children who had been established on ART for longer than six months at the time of assessment.

Index tests

The index tests included measures of adherence that could be utilized in resource-limited settings:

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

We categorized and analysed 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;
- electronic monitoring: per cent 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 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 defined this as an HIV RNA level above the lower limit of detection of the assay used within the study in question.

Reference standards

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

Search methods for identification of studies

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

Electronic searches

We searched 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)).

We completed a preliminary search in July 2018, and adapted the search for other electronic databases. We updated the search in January 2020, and April 2021 (Appendix 1).

Searching other resources

We searched the WHO International Clinical Trials Registry Platform (ICTRP) and the ClinicalTrials.gov Clinical Study Register (www.clinicaltrials.gov).

We also screened reference lists of included studies and relevant reviews.

Data collection and analysis

Selection of studies

We merged studies identified by the keyword searches of different databases and removed duplicate reports. Review authors and collaborators from Cochrane Crowd independently scrutinized titles and abstracts from the electronic search to identify those which were potentially eligible (see summary of the protocol Appendix 2). Each study was screened by two independent authors or collaborators before inclusion or exclusion. Where there was disagreement, the first authors (PH/RS) adjudicated. We retrieved the full-text article for citations which the initial title and abstract screening identified as potentially eligible. Review authors (RS, KP and GV) independently assessed each full-text article for inclusion. We settled any discrepancies via discussion between review authors, and consultation with a third review author (PH) if further uncertainty remained. We identified studies according to the surname of the first author and year of publication.

Data extraction and management

We screened studies and extracted data independently, in duplicate. We also assessed the risk of bias and applicability concerns independently, in duplicate. We piloted the form on two studies from each adherence measure subtype, and finalized the form thereafter. We extracted 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 3).

Review authors (GV, KP, RS, YS) then extracted results and cross-tabulated data in 2 x 2 tables.

Assessment of methodological quality

We used 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 changed signalling questions for each of the four domains. We have proposed an initial schema for operating the QUADAS-2 tool in Appendix 3. Review authors (KP,GV, YS and RS) independently piloted the form with two studies from each adherence measure subtype, and finalized the form thereafter. The final form for assessment of methodological quality is presented in Appendix 4 (changes to the previous form were highlighted). Risk of bias and applicability were completed for each of the included studies independently and in duplicate (GV, KP, YS). Disagreements and discrepancies were resolved by consultation between review authors, with the addition of a third author if agreement could not be reached.

We assessed the certainty of the evidence using the GRADE approach.

Statistical analysis and data synthesis

For all included studies, we used the data in the 2 x 2 tables (the binary test results cross-tabulated with the binary reference standard) to calculate sensitivity and specificity along with their 95% confidence intervals.

We have presented individual study results graphically by plotting estimates of sensitivities and specificities in a forest plot in order to facilitate visual assessment of variation in test accuracy. We used Review Manager 5 for these descriptive analyses (Review Manager 2014). For the main analysis, we used a 95% threshold or a binary (yes/ no) threshold. We chose this for the main analysis as it was commonly used and made clinical sense to the authors. However, we also conducted additional analysis using other thresholds (e.g. 80% adherence). We had planned to perform meta-analysis for each index test, but we were not able to pool the data due to the high heterogeneity among studies (see Investigations of heterogeneity). Since no pooling was not done due to heterogeneity, for the CI rangewe reported the lowest and the highest end of the confidence intervals across the studies that evaluated the same adherence test.

Comparing index tests

We made simple separate comparisons of summary estimates from alternative index tests. We did not encounter sufficient numbers of studies that made within-study paired comparisons of the same index tests to perform more detailed comparative analyses.

Investigations of heterogeneity

For each index test, we had planned to investigate heterogeneity by incorporating covariates to a hierarchical model in our meta-analysis. However, given that we were not able to perform meaningful meta-analysis, we instead investigated heterogeneity by subgrouping studies according to predefined categories.

These categories included:

- Setting, including income status:
  - this included the following 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 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).

These potential sources of heterogeneity were speculative. In addition, where stated within the results, we assessed those studies which had yielded tests with high sensitivity and specificity to assess whether there were shared characteristics.

Sensitivity analyses

We planned to conduct sensitivity analyses for each index test in which we would have excluded studies for which QUADAS-2 indicates areas of methodological concern. We also planned excluding studies in which more than four of the six QUADAS-2 domains were high risk. We also planned 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 was likely to be applicable to a resource-limited setting. However, due to the high heterogeneity across/among studies, we decided against conducting sensitivity analyses as it was unlikely to influence any conclusions.

Assessment of reporting bias

We did not carry out formal assessment of publication bias because of the lack of sensitive and appropriate statistical methods for this review methodology.

Assessment of overall certainty of the evidence

We prepared a summary of findings table to present the main results and key information regarding the certainty of evidence assessed using the GRADE approach (Schünemann 2008; Schünemann 2020a; Schünemann 2020b). As recommended, we rated the certainty of evidence as high (not downgraded), moderate (downgraded by one level), low (downgraded by two levels), or very low (downgraded by more than two levels) based on four domains: risk of bias, indirectness, inconsistency, imprecision (but not publication bias). For each outcome, the certainty of evidence starts as high when there are high-quality observational studies (cross-sectional or cohort studies) that enrolled participants with diagnostic uncertainty. When we found a reason for downgrading, we used our judgement to classify the reason as either serious (downgraded by one level) or very serious (downgraded by two levels) and recorded them in the footnotes. We applied the GRADE judgements for the GRADE domains as follows:

- Risk of bias: we used QUADAS-2 to assess the risk of bias.
- Indirectness: we used QUADAS-2 for concerns of applicability.
- Inconsistency: we carried out prespecified analyses to investigate potential sources of heterogeneity and downgraded when we could not explain the inconsistency in the accuracy estimates.
- Imprecision: we looked at the CIs of sensitivity and specificity estimates and at the unexplained heterogeneity of the results.
- Publication bias: we did not evaluate publication bias due to the lack of validated methods for diagnostic test accuracy reviews.

Equity

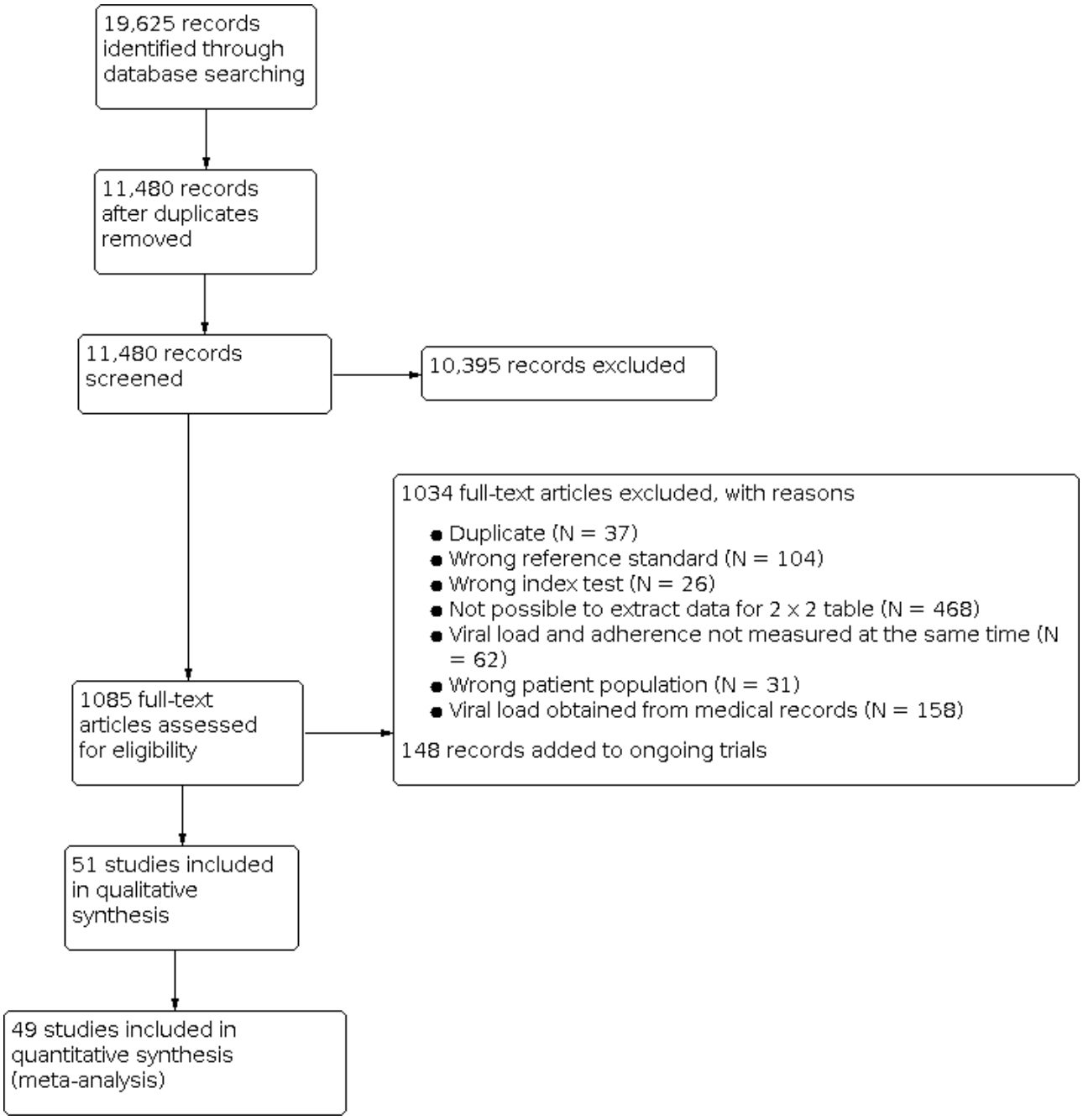
We did not plan our review with direct consideration of equity a priori. However, we recognize that there is a hypothetical potential for differences in adherence measure test accuracy between advantaged and disadvantaged populations. We considered the PROGRESS-Plus framework, which incorporates "Place of residence, Race/ethnicity/culture/language, Occupation, Gender or sex, Religion, Education, Socioeconomic status, Social capital and other characteristics ('Plus') such as sexual orientation, age and disability)" (Oxman 2009; Welch 2022). Our pre-planned subgroup analyses incorporated age and gender, and also income setting (which may relate to place of residence, and socioeconomic status).

RESULTS

Results of the search

Figure 3 (Moher 2009) shows the flow of studies in the review. We identified 19,625 references from three searches: an initial search in July 2018, a repeat search in January 2020 and a last search in April 2021. From these, after removing duplicates, we identified 11,480 unique references. We considered 10,395 irrelevant to our review on initial screening. We screened 1085 references for inclusion, of which we excluded 1034 with reasons.

Figure 3. Study flow diagram



Fifty-one unique studies met our inclusion criteria and are included in the review.

Exclusions were mainly due to studies reporting duplicate data from another study (n = 37), wrong reference standard (n = 104), wrong index test (n = 26), insufficient data for the 2 x 2 table (n = 468), viral load and adherence not measured at the same time (n = 62), wrong patient population (n = 31), and viral load obtained from medical records (n = 158). We recorded the excluded studies and the reasons for their exclusion in Additional tables 3 to 9 (Table 3; Table 4; Table 5; Table 6; Table 7; Table 8; Table 9).

We also identified 148 ongoing trials (see Table 10).

Description of included studies

See Characteristics of included studies.

1. Self-report

1.1 Questionnaires

We identified 26 studies including 11,607 participants that used self-report questionnaires to estimate viral non-suppression (Avong 2015; Bajunirwe 2009; Coker 2015; Duarte 2015; Ekstrand 2010; El-Khatib 2010; Fokam 2017; Haberer 2011; Landes 2021; Mbengue 2019; McMahon 2013; Meya 2009; Mogosetsi 2018; Navarro 2014; Oette 2006; Orrell 2017; Paolillo 2017; Parker 2017; Pasquau 2018; Phillips 2019; Pulido 2009; Sangeda 2014; Segeral

2010; Segeral 2018; Tabb 2018; Zoufaly 2013). Three were RCTs (Coker 2015; Parker 2017; Pasquau 2018), nine cross-sectional (Avong 2015; El-Khatib 2010; Fokam 2017; Meya 2009; Phillips 2019; Segeral 2010; Segeral 2018; Tabb 2018; Zoufaly 2013), and the remaining 14 studies used a cohort design. A total of 9703 participants were included in the analysis, of whom 5640 had viral non-suppression. Four studies were conducted in children (Duarte 2015; Fokam 2017; Haberer 2011; Zoufaly 2013), two in mixed populations (Orrell 2017; Tabb 2018), and all others included only adults. Studies were conducted in different settings: 11 in low-income (Avong 2015; Bajunirwe 2009; Coker 2015; Haberer 2011; Landes 2021; McMahon 2013; Meya 2009; Sangeda 2014; Segeral 2010; Segeral 2018; Tabb 2018), three in lower-middle-income (Ekstrand 2010; Fokam 2017; Zoufaly 2013), five in upper-middle-income (El-Khatib 2010; Mbengue 2019; Mogosetsi 2018; Orrell 2017; Phillips 2019), and six in high-income settings (Navarro 2014; Oette 2006; Paolillo 2017; Parker 2017; Pasquau 2018; Pulido 2009). One was conducted in a mixed setting (Duarte 2015).

Regarding the threshold for adherence, 20 studies used 100% or a binary threshold (adherent/non-adherent) (Bajunirwe 2009; Coker 2015; Duarte 2015; Fokam 2017; Landes 2021; Mbengue 2019; McMahon 2013; Meya 2009; Mogosetsi 2018; Oette 2006; Orrell 2017; Pasquau 2018; Paolillo 2017; Parker 2017; Phillips 2019; Pulido 2009; Sangeda 2014; Segeral 2010; Segeral 2018; Tabb 2018), four used 95% (Avong 2015; Haberer 2011; Ekstrand 2010; Zoufaly 2013), one used 90% (Navarro 2014), three used 80% (Haberer 2011; Phillips 2019; Segeral 2018), one used 75% (Zoufaly 2013), and one used 60% (Navarro 2014).

For the viral load, two studies used 40 copies/mL (Landes 2021; Orrell 2017), 10 used 50 copies/mL (Bajunirwe 2009; Fokam 2017; Haberer 2011; Mogosetsi 2018; Navarro 2014; Oette 2006; Paolillo 2017; Pasquau 2018; Phillips 2019; Pulido 2009), four used 200 copies/mL (McMahon 2013; Parker 2017; Pasquau 2018; Zoufaly 2013), one used 250 copies/mL (Segeral 2018), and 12 used 400 copies/mL (Avong 2015; Bajunirwe 2009; Coker 2015; Duarte 2015; Ekstrand 2010; El-Khatib 2010; Mbengue 2019; Meya 2009; Phillips 2019; Sangeda 2014; Segeral 2010; Tabb 2018).

Please note that some of the studies used more than one threshold.

1.2 Visual analogue scale

We identified 14 studies including 5852 participants that used VAS to estimate viral non-suppression (Cerutti 2016; Cohen 2012; Dziva 2017; Ekstrand 2010; Gill 2010; Haberer 2011; Jiamsakul 2014; Labhardt 2012; McMahon 2013; Mbengue 2019; Meya 2009; Nelson 2010; Sangeda 2014; Segeral 2018). Seven were cohort studies, four were cross-sectional, two were RCTs and one was a prospective clinical trial. A total of 5151 participants were included in the analyses, of whom 2499 had viral non-suppression. Two studies were conducted in children (Dziva 2017; Haberer 2011), one in a mixed population (Labhardt 2012) and the remaining eleven studies in adults. Studies were conducted in different settings: seven in low-income (Dziva 2017; Haberer 2011; Labhardt 2012; McMahon 2013; Meya 2009; Sangeda 2014; Segeral 2010), three in lower-middle income (Cerutti 2016; Ekstrand 2010; Gill 2010), one in upper-middle income (Mbengue 2019), and three in mixed settings (Cohen 2012; Jiamsakul 2014; Nelson 2010).

Regarding the threshold for adherence, two studies used 100% (Sangeda 2014; Segeral 2010), 11 used 95% (Cerutti 2016; Cohen 2012; Dziva 2017; Ekstrand 2010; Gill 2010; Haberer 2011; Jiamsakul 2014; Labhardt 2012; McMahon 2013; Nelson 2010; Sangeda 2014), three used 90% (Mbengue 2019; Sangeda 2014; Segeral 2010), one used 80% (Haberer 2011), and one used a binary threshold (adherent/non-adherent) (Meya 2009).

For the viral load threshold one study used 40 copies/mL (Labhardt 2012), three used 50 copies/mL (Cohen 2012; Haberer 2011; Nelson 2010), one used 80 copies/mL (Cerutti 2016), one used 200 copies/mL (McMahon 2013), and seven used 400 copies/mL (Dziva 2017; Gill 2010; Jiamsakul 2014; Mbengue 2019; Meya 2009; Sangeda 2014; Segeral 2010).

To note that some of the studies used more than one threshold.

2. Tablet counts

We identified 13 studies including 4899 participants that used tablet counts to estimate viral non-suppression (Apisarnthanarak 2010; Bonjoch 2006; Cerutti 2016; Coker 2015; Davies 2008; Gill 2010; Haberer 2011; Kitkungvan 2008; Mariana 2018; Moosa 2019; Okonji 2012; Orrell 2017; Sangeda 2014). Seven were cohort studies, three used a cross-sectional design, one was an RCT, and two were subanalyses of published RCTs. A total of 3808 participants were included in the analyses, of whom 2335 had viral non-suppression. Nine studies included adults (Apisarnthanarak 2010; Bonjoch 2006; Cerutti 2016; Coker 2015; Gill 2010; Mariana 2018; Moosa 2019; Okonji 2012; Sangeda 2014), two included children (Davies 2008; Haberer 2011), and the other two were conducted in mixed populations (Kitkungvan 2008; Orrell 2017). Studies were conducted in different settings: four in low-income (Coker 2015; Haberer 2011; Okonji 2012; Sangeda 2014), four in lower-middle-income (Cerutti 2016; Gill 2010; Kitkungvan 2008; Mariana 2018), four in upper-middle-income (Apisarnthanarak 2010; Davies 2008; Moosa 2019; Orrell 2017), and one in high-income (Bonjoch 2006).

Regarding the threshold for adherence, one used 100% (Sangeda 2014), 12 used 95% (Apisarnthanarak 2010; Bonjoch 2006; Cerutti 2016; Coker 2015; Gill 2010; Haberer 2011; Kitkungvan 2008; Mariana 2018; Moosa 2019; Okonji 2012; Orrell 2017; Sangeda 2014), three used 90% (Bonjoch 2006; Davies 2008; Sangeda 2014), one used 85% (Sangeda 2014), two used 80% (Haberer 2011; Sangeda 2014), three used 75% (Apisarnthanarak 2010; Kitkungvan 2008; Sangeda 2014), one used 70% (Sangeda 2014), one used 65% (Sangeda 2014), one used 60% (Sangeda 2014), two used 55% (Kitkungvan 2008; Sangeda 2014), and one used 50% (Sangeda 2014).

For the viral load threshold, two used 40 copies/mL (Mariana 2018; Orrell 2017), four used 50 copies/mL (Apisarnthanarak 2010; Bonjoch 2006; Haberer 2011; Kitkungvan 2008), one used 80 copies/mL (Cerutti 2016), and the remaining six studies used 400 copies/mL.

To note that some of the studies used more than one threshold. We excluded Davies 2008 from the quantitative analysis because the adherence threshold was not relevant for the analysis of this review.

3. Pharmacy records or secondary databases

We identified seven studies including 2882 participants that used pharmacy records or other secondary databases to estimate viral non-suppression (Anude 2013; Hassan 2014; McMahon 2013; Messou 2011; Navarro 2014; Orrell 2017; Sangeda 2014). Six were

cohort studies and one was a cross-sectional study. A total of 2449 were included in the analyses, of whom 1298 had viral non-suppression. Five studies included adults (Anude 2013; McMahon 2013; Messou 2011; Navarro 2014; Sangeda 2014), and the other two studies included a mixed population. Studies were conducted in different settings: four in low-income (Hassan 2014; McMahon 2013; Messou 2011; Sangeda 2014), one in lower-middle-income (Anude 2013), one in upper-middle-income (Orrell 2017), and one in high-income (Navarro 2014).

Regarding the thresholds used to determine adherence, two studies used 100% (McMahon 2013; Sangeda 2014), six used 95% (Anude 2013; Hassan 2014; McMahon 2013; Messou 2011; Orrell 2017; Sangeda 2014), two used 90% (Navarro 2014; Sangeda 2014), one used 85% (Sangeda 2014), two used 80% (Messou 2011; Sangeda 2014), one used 75% (Sangeda 2014), one used 70% Sangeda 2014), two used 65% (Messou 2011; Sangeda 2014), two used 60% (Navarro 2014,Sangeda 2014), one used 55% (Sangeda 2014), and two used 50% (Messou 2011; Sangeda 2014).

To note that some of the studies used more than one threshold.

For the viral load threshold, one used 40 copies/mL (Orrell 2017), one used 50 copies/mL (Navarro 2014), one used 200 copies/mL (McMahon 2013), one used 300 copies/mL (Messou 2011), and three used 400 copies/mL (Anude 2013; Hassan 2014; Sangeda 2014).

4. Electronic monitoring devices

We identified five studies including 475 participants that used electronic monitoring devices to estimate viral non-suppression (Evans 2016; Farley 2003; Gill 2010; Haberer 2011; Orrell 2017). All were cohort studies. A total of 392 participants were included in the analysis, of whom 92 had viral non-suppression. Two studies included children (Farley 2003; Haberer 2011), two studies included adults (Evans 2016; Gill 2010), and one study included both children and adults (Orrell 2017). Studies were conducted in different settings; one in low-income (Haberer 2011), one in lower-middle-income (Gill 2010), two in upper-middle-income (Evans 2016; Orrell 2017), and one in high-income (Farley 2003).

Regarding the thresholds for adherence, three studies used 95% (Evans 2016; Gill 2010; Haberer 2011), and four studies used 80% (Evans 2016; Farley 2003; Haberer 2011; Orrell 2017). To note that some of the studies used more than one threshold.

For the viral load threshold, one study used 40 copies/mL (Orrell 2017), one study used 50 copies/mL (Haberer 2011), and three studies used 400 copies/mL (Evans 2016; Farley 2003; Gill 2010).

5. Composite measure of adherence

We identified nine studies including 1901 participants that used composite measures of adherence to estimate viral non-suppression (Jayaweera 2003; Mbengue 2019; McMahon 2013; Mutwa 2014; Orrell 2003; Ortega 2004; Parienti 2010; Segeral 2010; Spire 2008). Three studies were cross-sectional and six studies used a cohort design. A total of 1513 participants were included in the analysis, of whom 858 had viral non-suppression. Only one study included children (Mutwa 2014), and one study did not report on participants age (Jayaweera 2003). All the other studies included adults. Studies were conducted in different settings; four in low-income (McMahon 2013; Mutwa 2014; Segeral 2010; Spire 2008), two in upper-middle-income (Mbengue 2019; Orrell 2003), and three in high-income (Jayaweera 2003; Ortega 2004; Parienti 2010).

Regarding the thresholds for adherence, one study used 100% (Segeral 2010), three studies used 95% (Mutwa 2014; Orrell 2003; Parienti 2010), one used 90% (Ortega 2004), one used 80% (Parienti 2010), one used 70% (Parienti 2010), and four used a binary threshold (adherent/ non-adherent of high/low) without providing exact details on percentage (Jayaweera 2003; Mbengue 2019; McMahon 2013; Spire 2008).

For the viral load threshold, two studies used 40 copies/mL (Mutwa 2014; Spire 2008), one study used 50 copies/mL (Parienti 2010), one study used 200 copies/mL (McMahon 2013), and six studies used 400 copies/mL (Jayaweera 2003; Mbengue 2019; Orrell 2003; Ortega 2004; Parienti 2010; Segeral 2010).

To note that some of the studies used more than one threshold

Methodological quality of included studies

We evaluated these studies for risk of bias in the following QUADAS-2 domains (Whiting 2011): participant selection, index test, reference standard, and participant flow. Figure 4 and Figure 5 provide a summary of the overall methodological quality for included studies.

Figure 4. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies

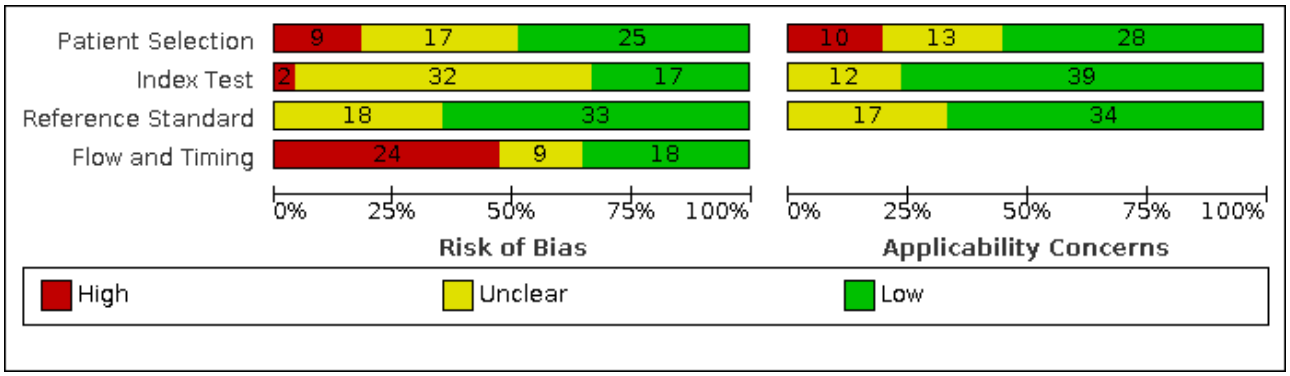
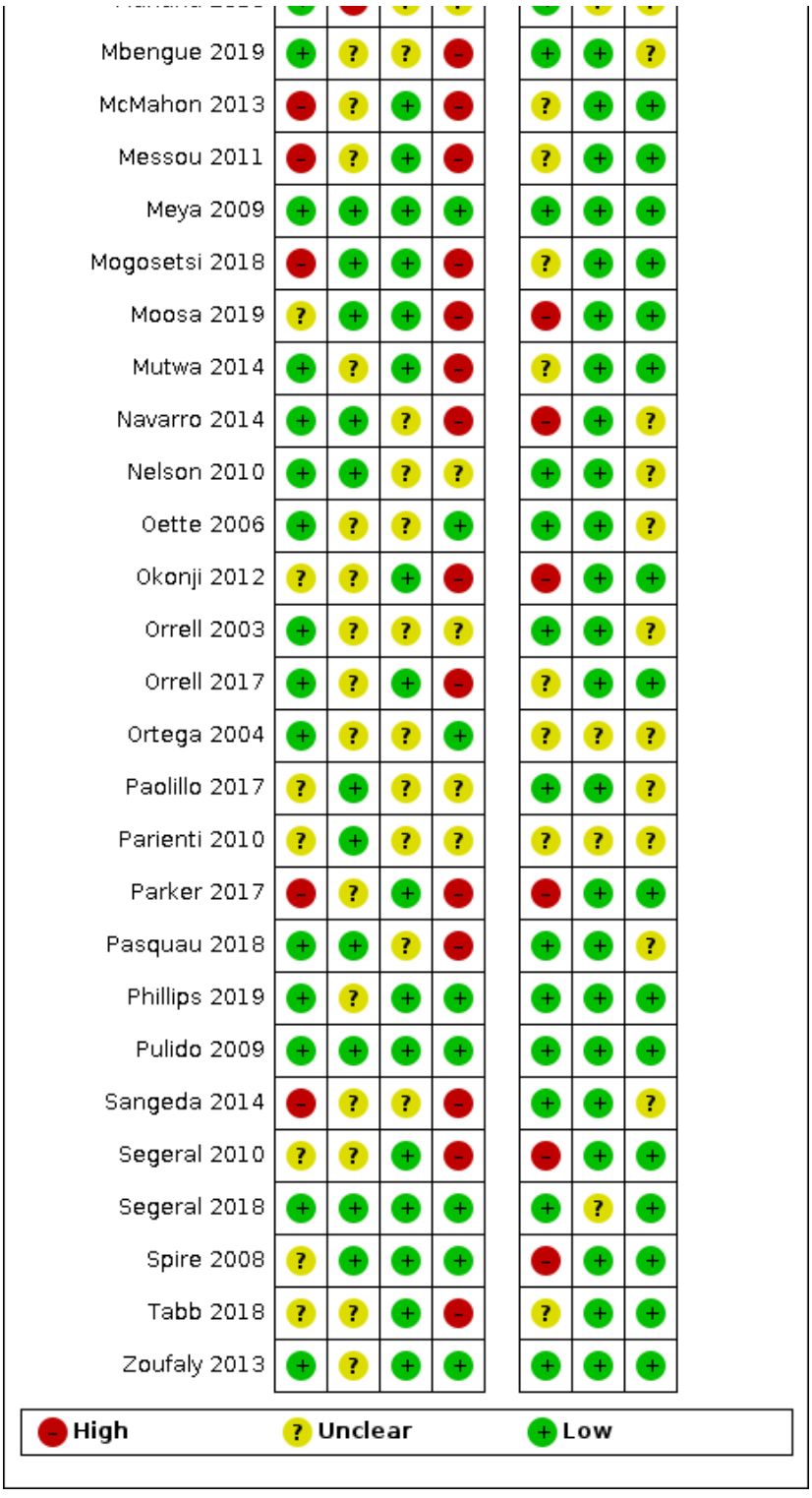


Figure 5. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

Figure 5. (Continued)



Patient selection (QUADAS-2, domain 1)

In the patient selection domain, we considered nine studies at high risk of bias due to strict inclusion criteria with a risk for inappropriate exclusions. Seventeen studies were rated as unclear risk as it was unclear if a consecutive or random sample of patients was enrolled or they had few details on patient selection criteria, or both. The remaining studies (n = 25) were considered as low risk.

Regarding applicability, 10 studies were rated at high concern and thirteen studies were considered at unclear concern due to patient sampling (e.g. studies only included people with a history of low adherence or viral non-suppression, people receiving support to increase adherence). The remaining studies (n = 28) were rated as low concern.

Index test (QUADAS-2, domain 2)

In the index test domain, we judged two studies at high risk of bias; in one study adherence was dichotomized as ≥ 90% or < 90% as this threshold explained the largest amount of variability in the outcome (Davies 2008), and in another study there was no information on how the index test was conducted (Mariana 2018). Most studies (n = 32) were rated as unclear because there was no information on whether the index tests were interpreted without knowledge of the results of the reference standard, or if prespecified thresholds were used. The remaining studies were rated as low risk as they used a validated scale to measure adherence.

Regarding applicability, 12 studies were rated as unclear concern due to their potential complexity (e.g. long questionnaires, composite measure requiring calculations, costs of electronic monitoring devices). The remaining 39 studies were judged as low concern.

Reference standard (QUADAS-2, domain 3)

In the reference standard domain, we rated 18 studies at unclear risk of bias as there was no information to assess whether the reference standard results were interpreted without knowledge of the results of the index test or the test used to determine viral load was not described. The remaining studies (n = 33) were rated as low risk.

Regarding applicability, 17 studies were judged as unclear as there were no details on the assay used to determine viral load. The remaining studies (n = 34) were rated as low concern.

Flow and timing (QUADAS-2, domain 4)

In the flow and timing domain, we judged 24 studies to be at high risk of bias. The main reason was the high number of missing participants for the analysis (higher than 20%). Nine studies were considered at unclear concern as the interval between the adherence measure and the viral load measurement was not clear, or there was no information on the type of assay used.

Findings

The main findings are presented in Summary of findings 1. Across all included studies, the ability of measures of adherence to detect viral non-suppression showed a large variation in both sensitivity and specificity that could not be explained by subgroup analysis.

1. Self-report

1.1 Questionnaires

Studies using self-report questionnaires for the detection of viral non-suppression showed a large variation in both sensitivity and specificity that we could not explain by subgroup analyses or narrative review. See 'Summary of findings' table 2 in Appendix 5.

For the main analysis (Figure 6; Figure 7), we selected studies using a 100% adherence threshold (or binary yes/no) and studies using a 95% adherence threshold (25 studies with 9211 participants, of whom 1813 had viral non-suppression). The variation in point estimates for sensitivity ranged from 5% to 91% and for specificity ranged from 10% to 100%. The certainty of the evidence was assessed as very low due to risk of bias, indirectness, and inconsistency. Due to the high heterogeneity, we did not pool these studies.

Figure 6. Self-report questionnaires, various thresholds* [main analysis] *cut-off used was either ≥ 95% or 100%

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Avong 2015	84	185	15	218	0.85 [0.76, 0.91]	0.54 [0.49, 0.59]
McMahon 2013	25	105	9	31	0.74 [0.56, 0.87]	0.23 [0.16, 0.31]
Phillips 2019	34	26	15	62	0.69 [0.55, 0.82]	0.70 [0.60, 0.80]
Fokam 2017	28	64	14	38	0.67 [0.50, 0.80]	0.37 [0.28, 0.47]
Haberer 2011	13	29	7	24	0.65 [0.41, 0.85]	0.45 [0.32, 0.60]
Parker 2017	106	458	68	1017	0.61 [0.53, 0.68]	0.69 [0.67, 0.71]
Pulido 2009	9	27	6	79	0.60 [0.32, 0.84]	0.75 [0.65, 0.82]
Coker 2015	45	2	44	224	0.51 [0.40, 0.61]	0.99 [0.97, 1.00]
Pasquau 2018	6	51	7	125	0.46 [0.19, 0.75]	0.71 [0.64, 0.78]
Bajunirwe 2009	10	16	18	131	0.36 [0.19, 0.56]	0.89 [0.83, 0.94]
Tabb 2018	31	41	60	95	0.34 [0.24, 0.45]	0.70 [0.61, 0.77]
Mbengue 2019	13	24	36	90	0.27 [0.15, 0.41]	0.79 [0.70, 0.86]
Zoufaly 2013	27	23	94	86	0.22 [0.15, 0.31]	0.79 [0.70, 0.86]
Oette 2006	13	11	48	136	0.21 [0.12, 0.34]	0.93 [0.87, 0.96]
Segeral 2018	28	192	107	990	0.21 [0.14, 0.29]	0.84 [0.82, 0.86]
Meya 2009	10	52	39	395	0.20 [0.10, 0.34]	0.88 [0.85, 0.91]
Paolillo 2017	46	33	192	264	0.19 [0.15, 0.25]	0.89 [0.85, 0.92]
Landes 2021	16	321	67	37	0.19 [0.11, 0.29]	0.10 [0.07, 0.14]
Ekstrand 2010	10	11	45	136	0.18 [0.09, 0.31]	0.93 [0.87, 0.96]
Orrell 2017	1	143	5	20	0.17 [0.00, 0.64]	0.12 [0.08, 0.18]
Duarte 2015	19	10	104	224	0.15 [0.10, 0.23]	0.96 [0.92, 0.98]
Segeral 2010	11	23	63	160	0.15 [0.08, 0.25]	0.87 [0.82, 0.92]
Sangeda 2014	7	14	48	93	0.13 [0.05, 0.24]	0.87 [0.79, 0.93]
Mogosetsi 2018	1	12	7	78	0.13 [0.00, 0.53]	0.87 [0.78, 0.93]
El-Khatib 2010	10	32	92	740	0.10 [0.05, 0.17]	0.96 [0.94, 0.97]

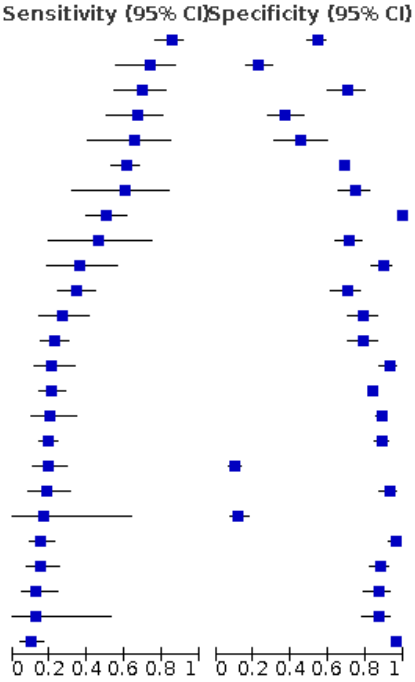
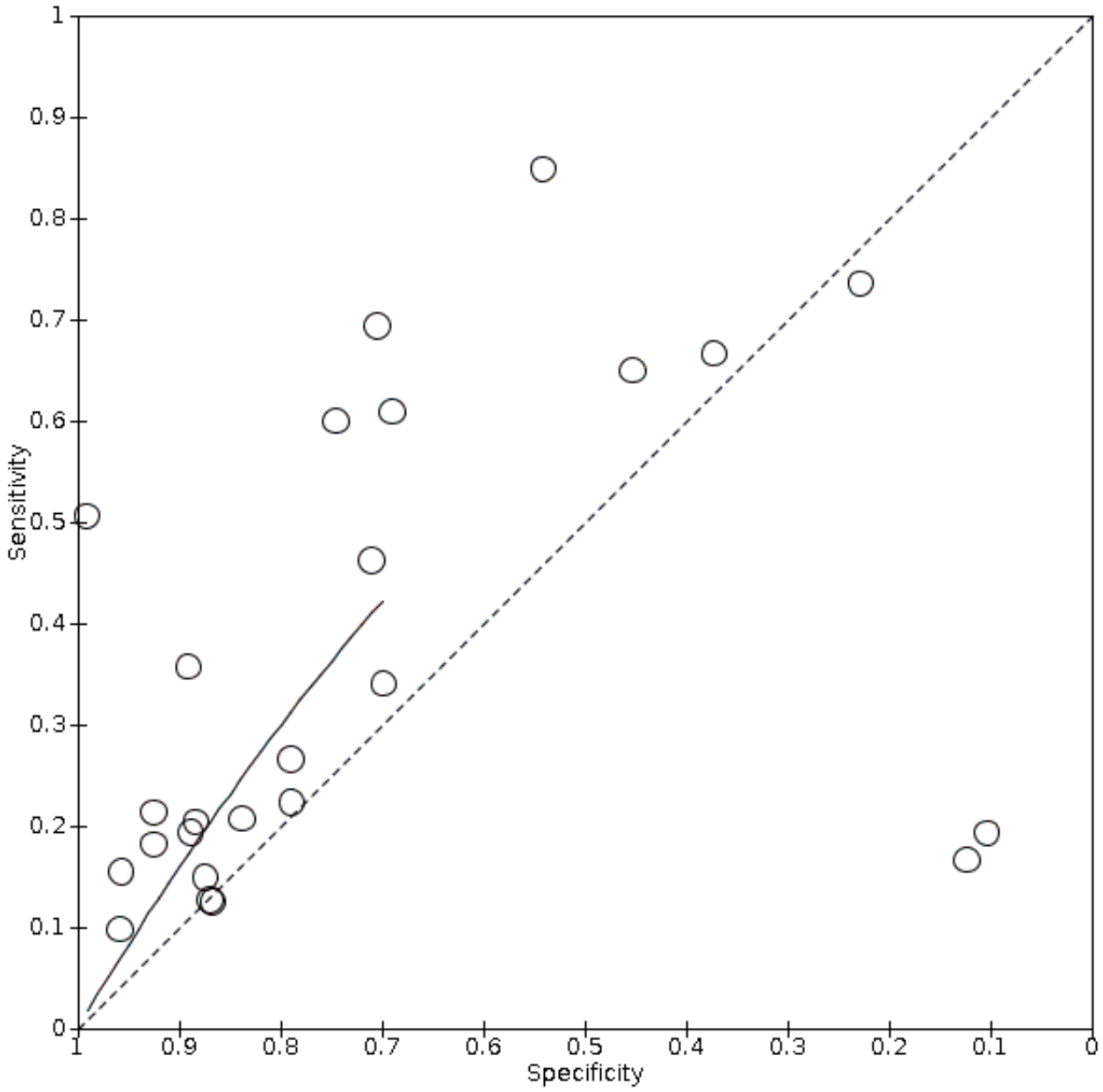


Figure 7. Summary ROC Plot of 1 [Main analysis] Self-report, various thresholds*. *cut-off used was either ≥ 95% or 100%



We explored heterogeneity by looking at adherence threshold, type of questionnaire, population, viral load threshold used, and setting. None of these prespecified subgroups could explain the heterogeneity observed.

- **Adherence threshold** (Appendix 6) **-100% cut-off** (21 studies, N = 8204): sensitivity ranged from 18% to 85% and specificity ranged from 10% to 99%; **95% cut-off** (4 studies, N = 1007): sensitivity ranged from 18% to 85% and specificity ranged from 45% to 93%.
- **Type of questionnaire** (Appendix 6) - **1 item only** (12 studies, N = 4997): sensitivity ranged from 10% to 74% and specificity ranged from 10% to 96%; **2 to 4 items** (8 studies, N = 1922): sensitivity ranged from 13% to 69% and specificity ranged from 70% to 99%; **5 or more items** (5 studies, N = 2292): sensitivity ranged from 21% to 85% and specificity ranged from 54% to 84%.
- **Population** (Appendix 6) - children (4 studies, N = 804): sensitivity ranged from 15% to 67% and specificity ranged from 37% to 96%; adults (19 studies, N = 8011): sensitivity ranged from 10% to 85% and specificity ranged from 10% to 99%.
- **Viral load threshold** (Appendix 6) - **40 to 50 copies/mL** (11 studies, N = 2290): sensitivity ranged from 14% to 69% and specificity ranged from 10% to 93%; **200 to 400 copies/mL** (13 studies, N = 6664): sensitivity ranged from 10% to 85% and specificity ranged from 23% to 99%.

- **Setting** (Appendix 6) - **low-income** (11 studies, N = 4135): sensitivity ranged from 13% to 85% and specificity ranged from 10% to 99%; **lower-middle-income** (3 studies, N = 576): sensitivity ranged from 18% to 67% and specificity ranged from 37% to 93%; **upper-middle-income** (5 studies, N = 1141): sensitivity ranged from 10% to 69% and specificity ranged from 12% to 96%; **high-income** (5 studies, N = 2702): sensitivity ranged from 19% to 61% and specificity ranged from 69% to 93%.

In addition to prespecified subgroup analyses, we further explored the highest and lowest performing studies using self-report questionnaires, as this was the largest group of studies. We aimed to identify characteristics in common that we had not previously considered when developing the protocol. We were not able to identify any shared characteristics between those studies having or showing the highest or the lowest sensitivity estimates.

Three studies also looked at the diagnostic accuracy of a 80% adherence threshold (Haberer 2011; Phillips 2019; Segeral 2010; N = 1527; Appendix 6). Sensitivity ranged from 8% to 41% and specificity ranged from 81% to 97%.

One study was excluded from the quantitative analyses as the adherence thresholds used were not relevant for our analyses (60% and 90%) (Navarro 2014).

1.2 Visual analogue scale

Studies using visual analogue scale questionnaires for the detection of viral non-suppression showed a large variation in both sensitivity and specificity that we could not explain by subgroup analyses See 'Summary of findings' table 3 in Appendix 5.

Eleven studies including 4235 participants (of whom 1479 had viral non-suppression) used a 95% adherence threshold (Cerutti 2016; Cohen 2012; Dziva 2017; Ekstrand 2010; Gill 2010; Haberer 2011; Jiamsakul 2014; Labhardt 2012; McMahon 2013; Nelson 2010; Sangeda 2014), and were included in the main analysis (Figure 8; Figure 9). The variation in point estimates for sensitivity ranged from 0% to 58% and for specificity ranged from 55% to 100%. The certainty of the evidence was assessed as very low due to risk of bias, indirectness, and inconsistency. Due to the high heterogeneity, we did not pool these studies.

Figure 8. Self-report using VAS; threshold: ≥ 95% adherence [main analysis]

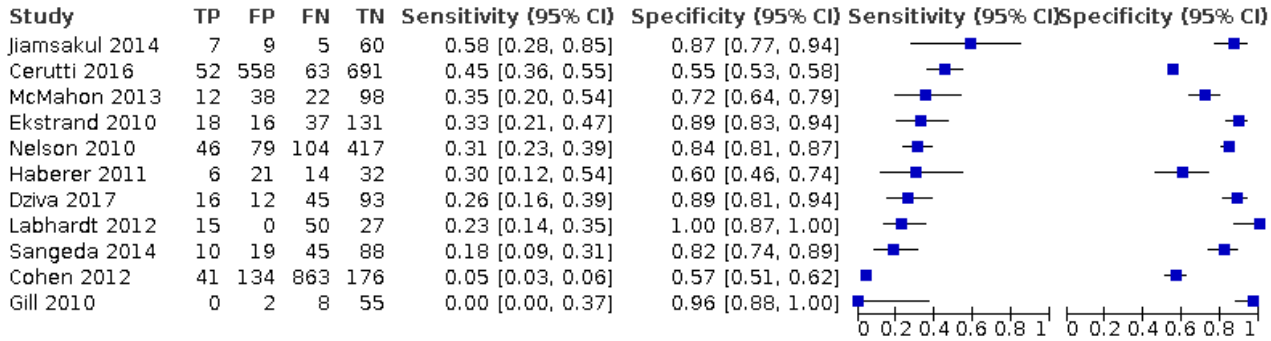
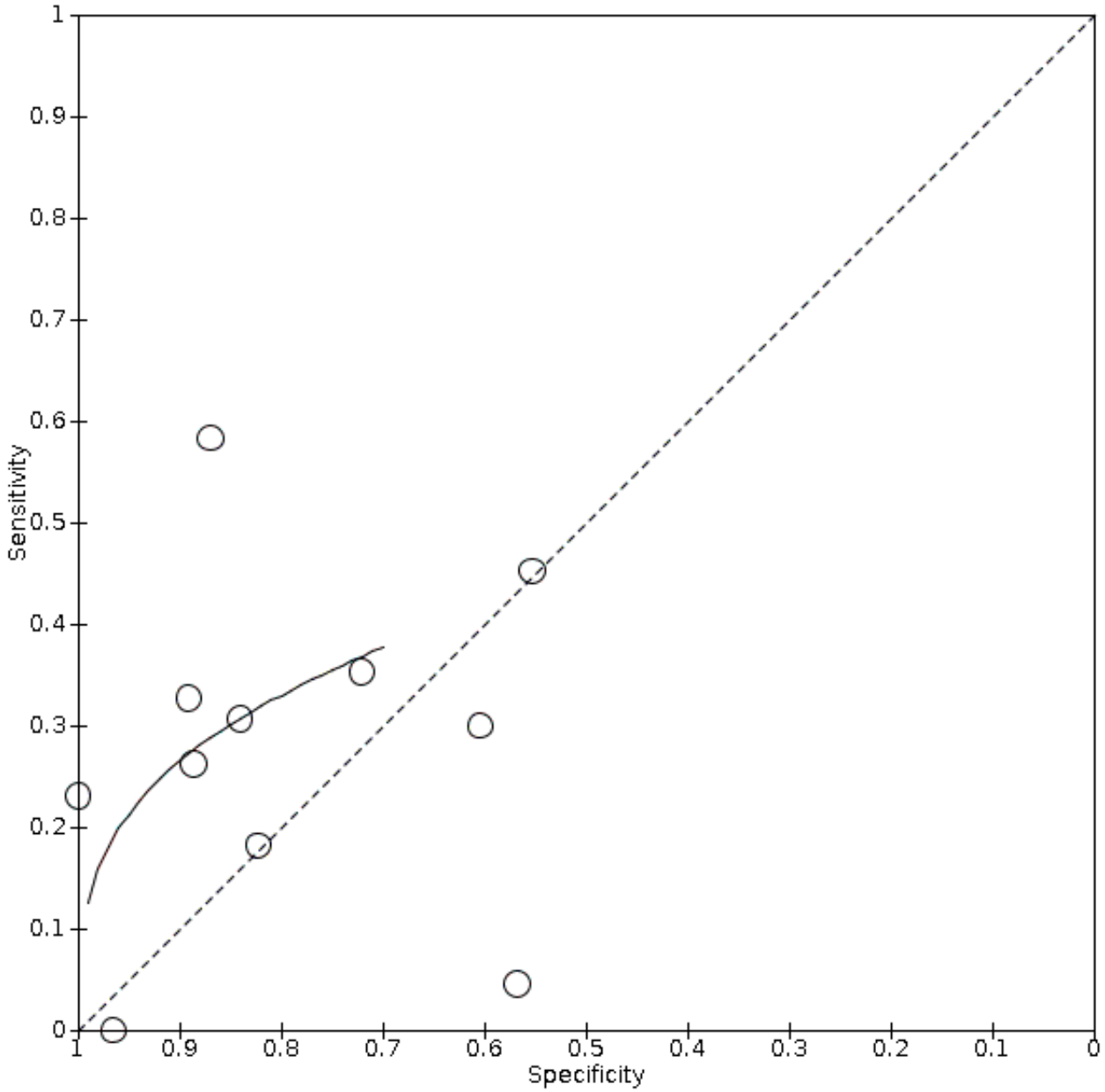


Figure 9. Summary ROC Plot of 16 [Main analysis] Self-report VAS; threshold: ≥ 95% adherence



We explored heterogeneity by looking at population, viral load threshold used, and setting. None of these prespecified subgroups could explain the heterogeneity we observed.

- **Population** (Appendix 7) - **children** (2 studies, N = 239): sensitivity ranged from 26% to 30% and specificity ranged from 60% to 89%; **adults:** sensitivity ranged from 0% to 58% and specificity ranged from 57% to 96%.
- **Viral load threshold** (Appendix 7) - **40 to 100 copies/mL** (6 studies, N = 3591): sensitivity ranged from 5% to 45% and specificity ranged from 55% to 100%; **200 to 400 copies/mL** (5 studies, N = 644): sensitivity ranged from 0% to 58% and specificity ranged from 72% to 96%.
- **Setting** (Appendix 7) - **low-income** (5 studies, N = 663): sensitivity ranged from 18% to 35% and specificity ranged from 60% to 100%; **lower-middle-income** (3 studies, N = 1631): sensitivity ranged from 0% to 45% and specificity ranged from 55% to 96%.

In addition, three studies also looked at the diagnostic accuracy of a 90% adherence threshold (N = 582, Appendix 7). Sensitivity ranged from 3% to 24% and specificity ranged from 88% to 95%. Another study with 73 participants used 80% as an adherence cut-off (Appendix 7). In this study, sensitivity was 20% (ranging from 6% to 44%) and specificity was 81% (ranging from 68% to 91%).

One study was excluded from the quantitative analyses (Meya 2009) as the authors used an unclear definition for treatment adherence.

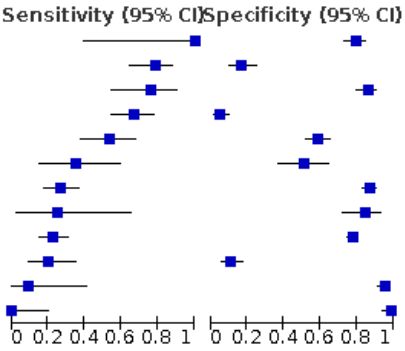
2. Tablet counts

Studies using pharmacy records for the detection of viral non-suppression showed a large variation in both sensitivity and specificity that we could not explain by subgroup analyses (See 'Summary of findings' table 4 in Appendix 5).

Twelve studies including 3466 participants (of whom 504 had viral non-suppression) used a 95% adherence threshold and were included in the main analysis (Figure 10). Again, these studies showed a large variation in both sensitivity and specificity that could not be explained. The variation in point estimates of sensitivity ranged from 0% to 100% and the specificity ranged from 5% to 99%. The certainty of the evidence was assessed as very low due to risk of bias, indirectness, and inconsistency. Due to the high heterogeneity, we did not pool these studies.

Figure 10. Tablet counts; threshold: ≥ 95% adherence [main analysis]

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kitkungvan 2008	4	40	0	155	1.00 [0.40, 1.00]	0.79 [0.73, 0.85]
Sangeda 2014	43	89	12	18	0.78 [0.65, 0.88]	0.17 [0.10, 0.25]
Apisarnthanarak 2010	19	25	6	149	0.76 [0.55, 0.91]	0.86 [0.80, 0.90]
Bonjoch 2006	47	144	23	8	0.67 [0.55, 0.78]	0.05 [0.02, 0.10]
Coker 2015	25	93	22	133	0.53 [0.38, 0.68]	0.59 [0.52, 0.65]
Haberer 2011	7	26	13	27	0.35 [0.15, 0.59]	0.51 [0.37, 0.65]
Okonji 2012	24	44	66	300	0.27 [0.18, 0.37]	0.87 [0.83, 0.91]
Gill 2010	2	9	6	48	0.25 [0.03, 0.65]	0.84 [0.72, 0.93]
Cerutti 2016	26	275	88	941	0.23 [0.15, 0.32]	0.77 [0.75, 0.80]
Orrell 2017	9	119	35	15	0.20 [0.10, 0.35]	0.11 [0.06, 0.18]
Moosa 2019	1	11	10	211	0.09 [0.00, 0.41]	0.95 [0.91, 0.98]
Mariana 2018	0	1	16	81	0.00 [0.00, 0.21]	0.99 [0.93, 1.00]



We explored heterogeneity by looking at population, viral load threshold used, and setting. None of these prespecified subgroups could explain the heterogeneity we observed.

- **Population** (Appendix 8) - **children** (1 study; N = 73): sensitivity was 35% (ranged from 15% to 59%) and specificity was 51% (ranged from 37% to 65%); **adults** (9 studies; N = 3016): sensitivity ranged from 0% to 78% and specificity ranged from 5% to 99%. The two remaining studies were conducted with mixed populations.
- **Viral load threshold** (Appendix 8) - **40 to 80 copies/mL** (7 studies; N = 2299): sensitivity ranged from 0% to 100% and specificity ranged from 11% to 99%; **400 copies/mL** (5 studies; N = 1167): sensitivity ranged from 9% to 78% and specificity ranged from 17% to 95%.
- **Setting** (Appendix 8) - **low-income** (4 studies, N = 942): sensitivity ranged from 27% to 78% and specificity ranged from 17% to 87%; **lower-middle-income** (4 studies: N = 1692): sensitivity ranged from 0% to 100% and specificity ranged from 77% to 99%; **upper-middle-income** (3 studies; N = 610): sensitivity ranged from 9% to 76% and specificity ranged from 11% to 95%; **high-income** (1 study; N = 222): sensitivity was 67% (ranged from 55% to 78%) and specificity was 5% (2% to 10%).

Two studies also looked at the diagnostic accuracy of an 80% adherence threshold (Haberer 2011; Sangeda 2014; N = 235 participants). Sensitivity ranged from 0% to 35% and specificity ranged from 69% to 100%.

We excluded one study from the quantitative analyses as the adherence threshold used was not relevant for our analyses (90%) (Davies 2008).

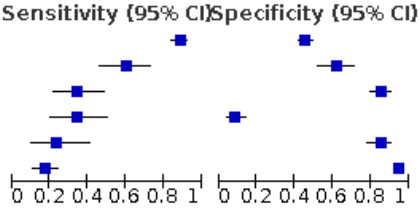
3. Pharmacy records or secondary database analysis

Studies using pharmacy records for the detection of viral non-suppression showed a large variation in both sensitivity and specificity that we could not explain by subgroup analyses (see 'Summary of Findings' table 5 in Appendix 5).

Six studies including 2254 participants (of whom 552 had viral non-suppression) used a 95% adherence threshold (Anude 2013; Hassan 2014; McMahon 2013; Messou 2011; Orrell 2017; Sangeda 2014), and were included in the main analysis (Figure 11). The sensitivity ranged from 17% to 88% and the specificity ranged from 9% to 95%. The certainty of the evidence was assessed as very low due to risk of bias, indirectness, and inconsistency. Due to the high heterogeneity, we did not pool these studies.

Figure 11. Pharmacy records; threshold: 95% adherence [main analysis]

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Messou 2011	205	377	27	316	0.88 [0.84, 0.92]	0.46 [0.42, 0.49]
Sangeda 2014	33	41	22	66	0.60 [0.46, 0.73]	0.62 [0.52, 0.71]
Hassan 2014	18	25	34	147	0.35 [0.22, 0.49]	0.85 [0.79, 0.90]
Orrell 2017	14	125	27	12	0.34 [0.20, 0.51]	0.09 [0.05, 0.15]
McMahon 2013	8	21	26	119	0.24 [0.11, 0.41]	0.85 [0.78, 0.90]
Anude 2013	24	24	114	429	0.17 [0.11, 0.25]	0.95 [0.92, 0.97]



We explored heterogeneity by looking at population, viral load threshold used, and setting. None of these prespecified subgroups could explain the heterogeneity we observed.

- **Population** (Appendix 9) - **adults** (4 studies, N = 1893): sensitivity ranged from 17% to 88% and specificity ranged from 46% to 95%. The two remaining studies were conducted with mixed populations.
- **Viral load threshold** (Appendix 9) - **40 copies/mL** (1 study, N = 178): sensitivity was 34% (ranged from 20% to 51%) and specificity was 9% (5% to 15%); **200 to 400 copies/mL** (5 studies, N = 2076): sensitivity ranged from 17% to 88% and specificity ranged from 46% to 95%.
- **Setting** (Appendix 9) - **low-income** (4 studies; N = 1485): sensitivity ranged from 24% to 88%; specificity ranged from 46% to 85%; **lower-middle-income** (1 study; N = 591): sensitivity was 17% (ranged from 11% to 25%) and specificity was 95% (ranged from 92% to 97%); **upper-middle-income** (1 study; N = 178): sensitivity was 34% (ranged from 20% to 51%) and specificity was 9% (ranged from 5% to 15%).

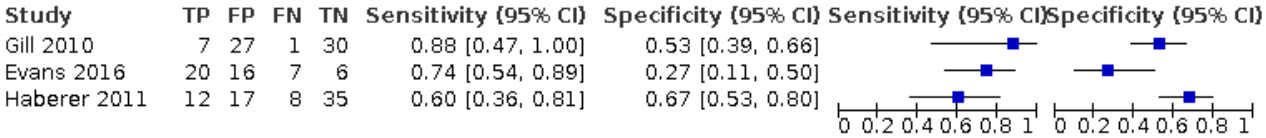
Three studies looked at the diagnostic accuracy of an 80% adherence threshold (Messou 2011; Navarro 2014; Sangeda 2014; N = 1211; Appendix 9). Sensitivity ranged from 25% to 82% and specificity ranged from 73% to 88%.

4. Electronic monitoring devices

Studies using electronic monitoring devices for the detection of viral non-suppression showed a large variation in both sensitivity and specificity that we could not explain by subgroup analyses (see 'Summary of Findings' table 6 in Appendix 5).

Three studies including 186 participants (of whom 55 had viral non-suppression) used a 95% adherence threshold (Evans 2016; Gill 2010; Haberer 2011), and were included in the main analysis (Figure 12). Sensivity ranged from 60% to 88% and specificity ranged from 27% to 67%. The certainty of the evidence was assessed as very low due to risk of bias, indirectness, inconsistency, and imprecision. Due to the high heterogeneity, we did not pool these studies.

Figure 12. Electronic monitoring; threshold: ≥ 95% adherence [main analysis]



We explored heterogeneity by looking at population, viral load threshold used, and setting. None of these prespecified subgroups could explain the heterogeneity we observed.

- **Population** (Appendix 10) - **children** (1 study, N = 72): specificity was 60% (ranged from 36% to 81%) and specificity was 67% (ranged from 53% to 80%); **adults** (2 studies, N = 114): sensitivity ranged from 74% to 88% and specificity ranged from 27% to 53%.
- **Viral load threshold** (Appendix 10) - **50 copies/mL** (1 study, N = 72) specificity was 60% (ranged from 36% to 81%) and specificity was 67% (ranged from 53% to 80%); **400 copies/mL:** (2 studies, N = 114): sensitivity ranged from 74% to 88% and specificity ranged from 27% to 53%.
- **Setting** (Appendix 10) - **low-income** (1 study, N = 72): specificity was 60% (ranged from 36% to 81%) and specificity was 67% (ranged from 53% to 80%); **lower-middle-income** (1 study, N = 65): sensitivity was 88% (ranged from 47% to 100%); **upper-middle-income** (1 study, N = 49): sensitivity was 74% (ranged from 54% to 89%) and specificity was 27% (ranged from 11% to 50%).

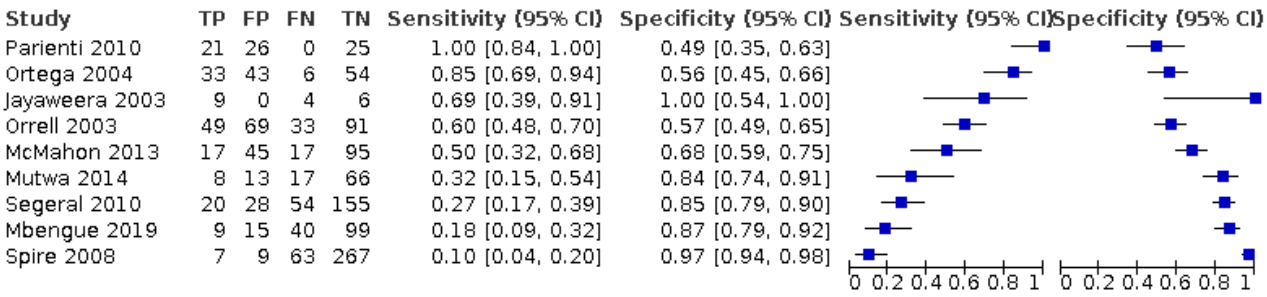
Four studies (Evans 2016; Farley 2003; Haberer 2011; Orrell 2017) looked at the diagnostic accuracy of a 80% adherence threshold (N =327, Appendix 10). Sensitivity ranged from 24% to 89% and specificity ranged from 7% to 96%.

5. Composite measures

Studies using composite measures of adherence for the detection of viral non-suppression showed a large variation in both sensitivity and specificity that we could not explain by subgroup analyses (see 'Summary of Findings' table 7 in Appendix 5).

We identified nine studies including 1513 participants that used a composite adherence measure to estimate viral non-suppression (Jayaweera 2003; Mbengue 2019; McMahon 2013; Mutwa 2014; Orrell 2003; Ortega 2004; Parienti 2010; Segeral 2018; Spire 2008), of whom 407 had viral non-suppression. All studies were included in the main analysis (Figure 13). Sensitivity ranged from 10% to 100% and specificity ranged from 49% to 100%. The certainty of the evidence was assessed as very low due to risk of bias, indirectness, and inconsistency. Due to the high heterogeneity, we did not pool these studies. We explored heterogeneity by looking at adherence threshold, population, viral load threshold, and setting.

Figure 13. Composite measure; different adherence thresholds* [main analysis] *cut-off used was either ≥ 95% or 100%



- **Adherence threshold** (Appendix 11) - **100% adherence** (6 studies, N = 1095): sensitivity ranged from 10% to 85% and specificity ranged from 56% to 100%; **> 95% adherence** (3 studies, N = 418): sensitivity ranged from 32% to 100% and specificity ranged from 49% to 84%.
- **Population** (Appendix 11) - **children** (1 study, N = 104): sensitivity was 32% (ranged from 15% to 54%) and specificity was 84% (ranged from 74% to 91%); **adults** (7 studies, N = 1390): sensitivity ranged from 10% to 100% and specificity ranged from 49% to 97%. One study did not report on the population.
- **Viral load threshold** (Appendix 11) - **40 to 50 copies/mL** (3 studies, N = 522): sensitivity ranged from 10% to 100% and specificity ranged from 49% to 97%; **200 to 400 copies/mL** (7 studies, N = 1063): sensitivity ranged from 18% to 100% and specificity ranged from 57% to 100%.
- **Setting** (Appendix 11) - **low-income** (4 studies, N = 881): sensitivity ranged from 10% to 50% and specificity ranged from 68% to 97%; **upper-middle-income** (2 studies, N = 405): sensitivity ranged from 18% to 60% and specificity ranged from 57% to 87%; **high-income** (2 studies, N = 227): sensitivity ranged from 69% to 100% and specificity ranged from 49% to 100%

DISCUSSION

Summary of main results

The aim of this review was to determine the diagnostic accuracy of different adherence measures to detect non-suppressed viral load in people living with HIV. We identified 51 studies, and the main findings are presented in Summary of findings 1.

- Self-report using questionnaires: sensitivity ranged from 10% to 85% and specificity ranged from 10% to 99% (25 studies, 9211 participants; very low-certainty).
- Self-report using VAS: sensitivity ranged from 0% to 58% and the specificity ranged from 55% to 100% (11 studies, 4235 participants; very low-certainty).
- Tablet counts: sensitivity ranged from 0% to 100% and the specificity ranged from 5% to 99% (12 studies, 3466 participants; very low-certainty).
- Pharmacy records or secondary databases: sensitivity ranged from 17% to 88% and the specificity ranged from 9% to 95% (6 studies, 2254 participants; very low-certainty).
- Electronic monitoring devices: sensitivity ranged from 60% to 88% and the specificity ranged from 27% to 67% (3 studies, 186 participants; very low-certainty).
- Composite measure: sensitivity ranged from 10% to 100% and the specificity ranged from 49% to 100% (9 studies, 1513 participants; very low-certainty).

None of the methods of measure of adherence had a consistent sensitivity to detect viral non-suppression. We did not perform meta-analysis because we encountered significant heterogeneity between the studies that we could not explain by population (children and adults), viral load threshold used (above or below 100 copies/mL) or setting (low-income, lower-middle-income, upper-middle-income, high-income).

Risk of bias is presented in Figure 5 The category in which we most frequently identified high risk of bias was with regards to flow and timing. Within this category, concerns related to uncertainty regarding whether viral load and adherence were measured contemporaneously, and large amounts of missing data.

Strengths and weaknesses of the review

To our knowledge, this review represents the largest systematic collation of data in the field, including detailed assessment of the certainty of evidence provided from the field.

As stated in our protocol and background, 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. A decrease in adherence could precede the viral non-suppression by a number of weeks. Patients who have historically had excellent adherence and viral suppression may experience 'blips' without any of these factors appearing to be at play. Such blips may correct on retesting, and not considered viral non-suppression in clinical practice. Patients may experience low-level viraemia that may be of questionable clinical significance.

Notwithstanding the non-linear relationship, a potential lag between non-adherence and viral load rise, the phenomena of 'blips', and low-level viraemia, we made a pragmatic decision to use a non-suppressed viral load as the target condition. We considered this likely to offer the best objective measure of the success of ART, and it is a clinically relevant measure. Moreover, our objective was in part to understand if there was a role for simple adherence measures in settings where viral loads were less available. We recognize that this encapsulates a broad definition but we feel this was a necessary simplification to allow for the

variation in definitions used for viral failure internationally (Figure 2). In subgroup analysis, we did not detect that changing the viral load threshold used influenced the findings. We do not feel that the target condition we chose, nor the phenomena described above including non-linear relationships, lags, blips, and low-level viraemia, could explain the low overall sensitivities seen across studies, or explain the high variation or heterogeneity seen across studies.

We included studies which had not been conceived as diagnostic test accuracy studies; rather, they were studies of other methodologies that included measures of adherence at the same time as viral load measurement and thus allowed us to extract data for 2 x 2 tables. Examples included studies aiming to describe adherence within a cohort, evaluations of adherence interventions, and randomized controlled trials comparing ART regimens. However, in an exploratory analysis of our data, we did not find that study design or objective could explain the heterogeneity we observed.

Our search identified other studies which stated they had measured adherence and viral load contemporaneously, which were similar to design studies that we included, but did not report all the data required for the 2 x 2 tables (for example, RCTs in which the text mentioned adherence had been measured, but did not report the relevant results). The author team agreed that it was not feasible to contact study authors in these instances. Given the large number of studies included in this review, we do not think that inclusion of such data would substantively influence the conclusions.

We did not perform formal subgroup analysis according to type of ART or specific ART regimens. The use of more or less 'forgiving' regimens may influence the relationship between adherence and viral non-suppression. However, the setting may to some extent reflect ART regimens used, and these did not explain heterogeneity.

In some instances, we compiled different thresholds (for example, for composite measures). This was a pragmatic decision to allow comparison of data from studies. Again, we do not think that this could explain the low sensitivities and specificities encountered, or the high variation in point estimates.

We did not make equity considerations part of the review framework and the outset, but our pre-planned subgroup analyses to some extent addressed equity considerations, including considerations on patient characteristics and income setting. Some measures of adherence might have lower accuracy in different populations due to complex influences. For example, an individual suffering from stigma due to HIV, compounded by intersectional stigma due to other characteristics (for example gender or race), might additionally fear the sense of moral judgement and labelling associated with perceived poor adherence (Eshun-Wilson 2019); this could influence their response to questions. It is beyond the scope of the methodology of this review to address complex concerns such as these in depth, and we do not consider that this would change the conclusions of the review.

Applicability of findings to the review question

The applicability domains of our QUADAS-2 assessment help determine the applicability of our findings to the review question, as described in the Methodological quality of included studies. We had low concern for patient selection applicability in most studies (55%), as these studies took place in unselected populations. We had low concern for index test applicability for most studies (74%), as they were easily implementable in all settings. For only 2% of studies, did we have high applicability concerns, as we felt the tests were too complex to administer or required expensive electronic devices. Finally, we also had low concern for reference standard applicability for most studies (67%), as study authors clearly described the viral load assay used. Overall, we feel that the findings can therefore be considered applicable to the objective of our review, which was to understand whether simple measures of adherence could be used to detect viral non-suppression in diverse settings.

Agreements and disagreements with other studies or reviews

To our knowledge, the current review represents the only systematic review of measures of adherence in HIV to formally assess diagnostic test accuracy. Almeida-Brasil 2019 is a meta-analysis including observational studies that compared adherence measures, and calculated odds ratios for a given test to detect virological failure. This, therefore, allowed for some pairwise comparison of tests without reporting sensitivity and specificity. The authors concluded that low cost measures (such as self-report) appeared equally as effective as higher cost measures such as electronic monitoring. To some extent, our review mirrors this conclusion, in so much as there was insufficient sensitivity to reliably detect viral non-suppression for all tests. Other reviews that included different approaches to measuring adherence in HIV have largely taken a narrative approach, for example, Spinelli 2020. Such reviews are valuable in appraisal of the benefits and disbenefits of using these measures clinically, but do not capture the variation and uncertainty we report.

AUTHORS' CONCLUSIONS

Implications for practice

We encountered a wide variety of adherence measures including numerous self-report measures, tablet counts, pharmacy records, electronic monitoring, and composite measures. Across groupings of similar measures, no one modality consistently offered a sufficiently high sensitivity to detect viral non-suppression. Given the variation and inconsistency between studies of the same type of adherence measure, it is not possible to recommend one type of adherence measure over another. Incorporating individual measures into composite measures do not seem to improve sensitivity above and beyond an individual method.

There is, therefore, no one adherence test that might helpfully offer an alternative to frequent viral load measurement in settings where viral load measurement was less available. This highlights the ongoing importance of viral load measurement, and ensuring access to it at individual and programmatic level. In addition, none of the adherence measures studied consistently offered a high specificity such that it might be used to identify targeted individuals who might benefit most from evidence-based adherence interventions, such as text-messaging, counselling, or supporter interventions.

Guideline and policy should recognize the high uncertainty, and probable overall limited ability of these tests to detect non-suppressed viral loads. Nevertheless, there may be other

qualitative benefits to attempting to measure adherence that are beyond the scope of this review to detect.

Implications for research

Given the low overall sensitivity and specificity of these adherence measures to detect a non-suppressed viral load, and vast variation in point estimates, we do not consider that further adaptation and evaluation of these measures would yield significant improvements in diagnostic test accuracy. Further research might more helpfully look to reducing costs of viral load monitoring, or of reducing costs of alternative measures of objectively quantifying adherence, such as measuring drug modalities with a longer half-life in plasma, dried blood spots, or urine. The benefit of electronic devices when used to identify and act upon missed doses in real-time has yet to be fully determined.

Studies of adherence interventions should consider the uncertainty around the measures used, and may better focus on clinical outcomes including viral load, over self-reported adherence.

When considering equity, the lack of a suitable alternative to viral load assessment may have a further negative effect on people living with HIV in lower-income areas where viral load testing may be less available. Inequities could hypothetically explain some of the vast variation observed, and qualitative methodologies may be best placed to investigate this.

This review did not compare formal measures of adherence to qualitative assessment of a patient's probable adherence by healthcare providers. Future research could ask if the additive value of formal measures of adherence, as represented by the index tests in this review, above and beyond clinical assessment of adherence by healthcare providers, justifies their use in clinical practice. Qualitative research could helpfully ask whether the administration of adherence measures in practice offers clinical benefits or harms beyond predicting viral non-suppression, but this is beyond the scope of this review.

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Editorial and peer-reviewer contributions

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The following people conducted the editorial process for this review update.

CIDG Contact Editor: Dr Lawrence Mbuagbaw; DTA Contact Editor: Ms Marta Roqué

- Sign-off Editor (final editorial decision): Professor Paul Garner
- Managing Editor (collated comments, provided editorial guidance to authors, edited the article): Dr Deirdre Walshe
- Copy Editor (copy editing and production): Anne Lethaby, Cochrane Copy Edit Support
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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anude 2013

Study characteristics	
Patient Sampling	• Target population: adults • Recruitment: a cohort of 2585 initially ART-naïve adults who started HAART between April 2008 and February 2009 were followed up for 12 months in three representative government hospitals in Nigeria: University of Abuja Teaching Hospital, Abuja (UATH), University of Benin Teaching Hospital, Benin (UBTH) and Asokoro District Hospital, Asokoro, Abuja (ADH). Inclusion criteria: ART-naïve adults who started HAART between April 2008 and February 2009 • Exclusion criteria: not reported • Study design: prospective cohort study

Patient characteristics and setting	• Country: Nigeria
	  ◦ World Bank Income classification: low-middle-income
	  ◦ Study setting: hospital-based (three representative government hospitals in Nigeria: University of Abuja Teaching Hospital, Abuja (UATH), University of Benin Teaching Hospital, Benin (UBTH) and Asokoro District Hospital, Asokoro, Abuja (ADH))
	• Study dates: April 2008 to February 2009
	• Age of population (median, IQR): 35 years, 30 to 41
	• Gender (male %): 36.3
	• Participants included/analysed: 628/591

Anude 2013 *(Continued)*

- First or second-line regimen: first-line
  - Type of ART: the choice of HAART combination was both guided by national treatment protocols and the discretion of the attending physician but generally consisted of one of three first line regimens (TDF + 3TC + NVP/EFV; AZT + 3TC + NVP/EFV; stavudine + 3TC + NVP/EFV)
  - Time on ART at enrolment: treatment-naïve
  - Time on ART at measurement of viral load and adherence: 12 months

Index tests	Number of index tests used: 2
	
	Types of index tests: pharmacy records and self-report
	
	• Test 1. Pharmacy records
	  ○ Validated scale: not applicable
	  ○ Tool description: pharmacy refill records (no further details)
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%
	• Test 2. Self-report
	  ○ Validated scale: not reported
	  ○ Tool description: self-report (no further details provided)
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%
	
	The study only reported usable 2 x 2 data for this review for the pharmacy records.

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: viral load testing was done by quantitative PCR for HIV-1 RNA in human plasma using Roche Amplicor version 1.5, Roche Diagnostics, Basal, Switzerland. • Definition of viral non-suppression: HIV viral load level > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no clear information on timing, just that it was measured at 12 months • All patients received same reference standard: yes • Missing data: 2585 initially included in the cohort, 805 (31%) of patients were lost to follow-up at 12 months, 628 out of the 1780 patients alive and active on the programme at 12 months were randomly selected for indepth interviews and laboratory work-up with detailed virologic and immunologic testing. Of those, 591 had data available for inclusion. Missing data > 10%
Comparative	
Notes	Conflicts of interest: none declared Funding source: supported by the US Government Centers for Disease Control and Prevention Cooperative Agreement Number: PS000651. Chuka Anude was funded by the US National Institutes of Health Fogarty AIDS International Training Research Program (AITRP, NIH 2-D43-TW001041-11) Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Anude 2013 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			

Anude 2013 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Apisarnthanarak 2010

Study characteristics	
Patient Sampling	• Target population: patients whose HIV level was suppressed at month 6 to < 50 copies/mL were followed up to ascertain achievement of durable HIV suppression at year 3 • Recruitment: patients who were prescribed a regimen of fixed-dose, twice-daily stavudine, 3TC, and NVP and enrolled in a study at Thammasat hospital • Inclusion criteria: not reported • Exclusion criteria: not reported • Study design: prospective cohort study

Patient characteristics and setting	• Country: Thailand
	  ◦ World Bank Income classification: upper-middle-income
	  ◦ Study setting: hospital- and home-based
	• Study dates: April 2003 to January 2007
	• Age of population (years), median (range): 37 (15 to 61)
	• Gender (male %): 32
	• Participants included/analysed: 199/199
	• First or second-line regimen: first-line
	  ◦ Type of ART: stavudine, 3TC and NPV
	  ◦ Time on ART at enrolment: not reported
	  ◦ Time on ART at measurement of viral load and adherence: 6, 12, 18, 24, 30, 36 months

Index tests	Number of index tests used: 1
	
	Types of index tests: tablet counts
	
	• Test 1. Tablet counts
	  ◦ Validated scale: not applicable
	  ◦ Tool description: at each routine medical encounter, the pharmacist calculated the ratio of pills taken divided by the total number of pills prescribed for the interval period. The unannounced home visits were randomly conducted by trained adherence counselling educators twice monthly and included pill counts... the mean pill count ratios (based on scheduled and unannounced visits) were calculated.
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 95%; 75%

Apisarnthanarak 2010 *(Continued)*

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: no details provided on the assay used • Definition of viral non-suppression: HIV viral load > 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing ("The unannounced home visits were randomly conducted by trained adherence counseling educators twice monthly and included pill counts ... the mean pill count ratios (based on scheduled and unannounced visits were calculated for each 6-month period of observation, and the HIV load was determined every 6 months") • All patients received same reference standard: not reported • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: L.M.M. is a consultant to WW Epidemiology at GlaxoSmithKline, Inc. A.A.: no conflicts Funding source: Thammasat University Infectious Diseases and Infection Control Research Fund Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	

Apisarnthanarak 2010 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	

Avong 2015

Study characteristics	
Patient Sampling	• Target population: adult AIDS patients who had been treated with combination ART for at least 12 months • Recruitment: at the time the study was conducted, about 11,208 AIDS patients were ever enrolled and were on ART according to programme implementation report provided by the Institute of Human Virology, Nigeria – managers of the ART clinic • Inclusion criteria: participants comprised adult AIDS patients who had been treated with combination antiretroviral therapy (cART) for at least 12 months as at May 2010 • Exclusion criteria: patients who were less than 18 years, critically ill or hospitalized and could not be interviewed as well as those who were not currently taking ARV • Study design: cross-sectional

Patient characteristics and setting	• Country: Nigeria
	  ◦ World Bank Income classification: low-middle income
	  ◦ Study setting: hospital-based (tertiary level)
	• Study dates: 2004 to 2010
	• Age of population (years), median (IQR): men: 42 (38 to 44); female: 36 (30 to 40)
	• Gender (male %): 49.4

Avong 2015 *(Continued)*

- Participants included/analysed: 537/502
- First or second-line regimen: HAART mixed regimens
  - Type of ART: first-line: AZT/3TC + NVP or EFV; AZT/3TC/NVP; 3TC/NVP/d4T; TDF/FTC + EFV or NVP and second-line: TDF + 3TC + LPV/r
  - Time on ART at enrolment: 12 months (mean duration of therapy was 43 months with a range of 16 to 70 months)
  - Time on ART at measurement of viral load and adherence: 12 months (mean duration of therapy was 43 months with a range of 16 to 70 months)

Index tests	Number of index tests used: 1
	
	Types of index test: self-report
	
	• Test 1. Self-report
	  ○ Validated scale: not applicable
	  ○ Tool description: self-reported adherence was assessed in five different ways (not missing a dose, correct dose, correct frequency, correct schedule and effective adherence).Threshold categories used as cut-off for optimal adherence: a participant was considered adherent (i.e. OPTIMAL adherence) if reported complying with the correct schedule, dose, frequency at a level of 95–100% and if not missing any dose in the past 3 days.
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Roche Cobas AmpliPrep TaqMan (Cobas Amplicor; Roche Diagnostics, Switzerland) • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this is a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: yes • Missing data: during the data cleaning, it was found that 28 participants had incomplete prescription refill data and one was less than 18 years. Thus, 35 participants were excluded leaving 502 participants whose data was entered into the analysis. Missing data < 10%
Comparative	
Notes	Conflicts of interest: none declared Funding source: this publication was made possible by UMB AITRP Fogarty Grant Number 5-D43 TWO 10441 from the United States' National Institutes of Health's Forgarty International Center awarded to Dr. William Blattner of the Institute of Human Virology, University of Maryland, Baltimore. Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		

Avong 2015 *(Continued)*

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Avong 2015 *(Continued)*

Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Bajunirwe 2009

Study characteristics	
Patient Sampling	• Target population: adults with HIV who received ART for at least 6 months • Recruitment: all patients who received ART since December 2004, the programme's inception, and of patients who initiated ART through December 2006 • Inclusion criteria: adult patients (18 years) who received ART for at least 6 months and attended clinic at least once between April and December 2006 • Exclusion criteria: no exclusions of those who met eligibility criteria • Study design: prospective cohort study

Patient characteristics and setting	• Country: Uganda
	  ◦ World Bank Income classification: low-income
	  ◦ Study setting: hospital-based (Kitagata Hospital, a government-owned district hospital located in the Bushenyi district of rural southwestern Uganda)
	• Study dates: April to December 2006
	• Age of population; not reported
	• Gender (male %): 39.8
	• Participants included/analysed: 175/175
	• First or second-line regimen: first-line
	  ◦ Type of ART: fixed-dose combination of stavudine + 3TC + NVP
	  ◦ Time on ART at enrolment: at least 6 months
	  ◦ Time on ART at measurement of viral load and adherence: at least 6 months

Index tests	Number of index tests used: 2
	
	Types of index tests: self-report and tablet counts
	
	• Test 1. Self-report
	  ◦ Validated scale: not reported
	  ◦ Tool description: three-day recall of adherence; patients were considered nonadherent if they missed at least 1 antiretroviral pill and 100% adherent if they had not
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 100%
	• Test 2. Tablet counts
	  ◦ Validated scale: not applicable
	  ◦ Tool description: pill count data performed routinely by the dispenser who would ask patients to bring with them pill bottles and unused medications; percentage adherence was calculated as the fraction of doses assumed taken among the total number of doses dispensed since the scheduled clinic visit.
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 100%

Bajunirwe 2009 *(Continued)*

	The study only reported usable 2 x 2 data for this review for the self-report measure.
Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: CD4 count and plasma HIV RNA concentration using the Roche Amplicor v1.5 assay • Definition of viral non-suppression: HIV viral load > 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing; however, both measures at baseline • All patients received same reference standard: yes • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: this study was funded, in part, by grants from the Fogarty International Center AIDS International Training and Research Program (TW00011) and the Centers For AIDS Research (AI36219). Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	

Bajunirwe 2009 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Bonjoch 2006

Study characteristics	
Patient Sampling	• Target population: adults with HIV who had been receiving an NVP-containing HAART regimen for at least 2 years • Recruitment: participants were identified by unselected consecutive recruitment from outpatient clinic visits during a total period of 4 months. • Inclusion criteria: adult HIV-1-infected patients were included if they had been receiving an NVP-containing HAART regimen for at least 2 years, regardless of the reason for its initiation (first-line, salvage, or simplification). • Exclusion criteria: patients who discontinued treatment with NVP within the first 2 years due to adverse events

Patient characteristics and setting	• Country: Spain
	  ◦ World Bank Income classification: high-income
	  ◦ Study setting: 12 tertiary care hospitals in Spain
	• Study dates: not reported

Bonjoch 2006 *(Continued)*

- Age of population (years), median (IQR): 41 (37 to 46)
- Gender (male %): 70.8
- Participants included/analysed: 613/222
- First or second-line regimen: first-line, salvage, or simplification
  - Type of ART: regardless of the reason for initiation (first-line, salvage, or simplification)
  - Time on ART at enrolment: at least 2 years
  - Time on ART at measurement of viral load and adherence: not reported, at least 2 years

Index tests	Number of index tests used: 1
	
	Types of index tests: tablet counts
	
	• Test 1. Tablet counts
	  ○ Validated scale: not applicable
	  ○ Tool description: the proportion of compliance was calculated by dividing the number of pills consumed during the last month by the number of pills prescribed in the same period.
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 90%; 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: not reported • Definition of viral non-suppression: HIV viral load > 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this was a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: not reported • Missing data: data on adherence and viral load only available for 222/613. Missing data > 10%
Comparative	
Notes	Conflicts of interest: none declared Funding source: not reported Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		

Bonjoch 2006 *(Continued)*

Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Cerutti 2016

Study characteristics			

Cerutti 2016 *(Continued)*

Patient Sampling	• Target population: patients on ART ≥ 6 months attending routine follow-up visits between May 5, 2014 and June 17, 2014 • Recruitment: consecutive sample enrolled • Inclusion criteria: all patients on ART ≥ 6 months attending routine follow-up visits between May 5, 2014 and June 17, 2014 and willing to participate received viral load measurement and extensive comorbidity screening, including assessment for alcohol use disorder and depressive symptoms. • Exclusion criteria: being on ART < 6 months, history of treatment interruption ≥ 7 days during the last 3 months, receiving second-line ART • Study design: cross-sectional

Patient characteristics and setting	• Country: Lesotho
	  ◦ World Bank Income classification: lower-middle-income
	  ◦ Study setting: two rural districts, Butha-Buthe and Thaba-Tseka in Lesotho
	• Study dates: May to June 2014
	• Age of population (years), median (IQR): 43.6 (34.5 to 53.5)
	• Gender (male %): 31
	• Participants included/analysed: 1389/1330 (tablet count); 1390/1364 (self-report)
	• First or second-line regimen: first-line
	  ◦ Type of ART: not reported
	  ◦ Time on ART at enrolment: at least 6 months
	  ◦ Time on ART at measurement of viral load and adherence: not reported; at least 6 months

Index tests	Number of index tests used: 2
	
	Types of index tests: Self-report and tablet counts
	
	• Test 1. Self-reported (VAS)
	  ◦ Validated scale: yes
	  ◦ Tool description: self-reported adherence using a visual analogue scale (VAS): Adherence reports were obtained from clinical notes
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 95%
	• Test 2. Tablet counts
	  ◦ Validated scale: not applicable
	  ◦ Tool description: the proportion of compliance was calculated by dividing the number of pills consumed during the last month by the number of pills prescribed in the same period.
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: viral RNA was prepared using an automated extractor (NucliSENS easyMAG, Biomerieux, Switzerland) • Definition of viral non-suppression: HIV viral load > 80 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this was a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: yes

Cerutti 2016 *(Continued)*

	• Missing data: self-report data available for 1330/1388 and pill count data available for 1364/1388. Missing data < 10%
Comparative	
Notes	Conflicts of interest: none declared Funding source: the Swiss Foundation for Excellence and Talent in Biomedical Research through a grant to ND Labhardt Trial registry: NCT02126696

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Cerutti 2016 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Cohen 2012

Study characteristics	
Patient Sampling	• Target population: treatment-naïve, HIV-1-infected adults with baseline viral load greater than or equal 5000 copies/mL and confirmed viral sensitivity to the background nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs) • Recruitment: no details reported, participants of two RCTs • Inclusion criteria: treatment-naive, HIV-1-infected adults with baseline viral load greater than or equal 5000 copies per millilitre and confirmed viral sensitivity to the background nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs) (assessed using the vircoTYPE HIV-1 assay) • Exclusion criteria: documented presence of any NTI resistance-associated mutation (RAM) from a list of 39; active clinically significant disease (e.g. pancreatitis, cardiac dysfunction, active and significant psychiatric disorder, adrenal insufficiency, or hepatic impairment), renal impairment, pregnancy or breastfeeding • Study design: pooled analysis of 2 RCTs

Patient characteristics and setting	• Country: each trial was conducted in 21 countries, with some overlap of countries (USA, Canada, Australia, South Africa, several countries in Europe, several in Asia, and several in Latin America). More than half the participants across the trials were from the combined USA, Canada, Europe & Australia regions.
	  ◦ World Bank Income classification: high-income
	  ◦ Study setting: not reported
	• Study dates: not reported
	• Age of population (years): not reported
	• Gender (male %): not reported
	• Participants included/analysed:1368/1214
	• First or second-line regimen: first-line
	  ◦ Type of ART: PI-based second-line regimen. Both groups combined: RPV 25 mg with EFV placebo once daily or EFV 600 mg with RPV placebo once daily, both in addition to (i) a fixed background N[t]RTI regimen of TDF and emtricitabine in the ECHO trial, or (ii) an N[t]RTI regimen based on the investigator's choice of TDF/FTC, zidovudine/lamivudine, or abacavir/3TC in the THRIVE trial.2: RPV

Cohen 2012 *(Continued)*

	25 mg with EFV placebo once daily, in addition to (i) a fixed background N[t]RTI regimen of TDF and emtricitabine in the ECHO trial, or (ii) an N[t]RTI regimen based on the investigator's choice of TDF/FTC, zidovudine/lamivudine (3TC), or abacavir/3TC in the THRIVE trial.3: EFV 600 mg with RPV placebo once daily, both in addition to (i) a fixed background N[t]RTI regimen of TDF and emtricitabine in the ECHO trial, or (ii) an N[t]RTI regimen based on the investigator's choice of TDF/FTC, zidovudine/lamivudine (3TC), or abacavir/3TC in the THRIVE trial ◦ Time on ART at enrolment: treatment-naïve ◦ Time on ART at measurement of viral load and adherence: 6 months
Index tests	Number of index tests used: 1 Types of index tests: self-report • Test 1. Self-report questionnaire ◦ Validated scale: yes (M-MASRI) ◦ Tool description: Modified Medication Adherence Self-Report Inventory (M-MASRI); prescribed ◦ Blinding: no information ◦ Threshold prespecified: yes ◦ Adherence threshold used: 95%
Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Amplicor HIV-1 monitor test version 1.5 (Roche, Basel, Switzerland) • Definition of viral non-suppression: HIV viral load > 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but all data meant to be from week 48 • All patients received same reference standard: yes • Missing data: there were a total of 1368 patients between both trials, but only 1214 were included in the analysis (686/627; and 682/587 for each trial, respectively). Overall missing data < 10%
Comparative	
Notes	Conflicts of interest: C.J.C. has received research funding from Janssen, Gilead Sciences, Bristol-Myers Squibb (BMS), Merck, Tobira and ViiV Healthcare. He is on advisory boards for Gilead Sciences, Janssen, Merck, Tobira and BMS. He has received speaker honoraria from Janssen, Gilead Sciences, BMS and Merck prior to January 2011. J.M.M. has acted as a consultant, participated in advisory boards, has received speaker fees and has been an investigator for clinical trials for Janssen, ViiV Healthcare, Gilead Sciences, BMS, Abbott Laboratories, Boehringer Ingelheim (BI) and Merck, Sharp, and Dohme (MSD) Funding source: C.J.C. has received research funding from Janssen, Gilead Sciences, Bristol-Myers Squibb (BMS), Merck, Tobira and ViiV Healthcare. He is on advisory boards for Gilead Sciences, Janssen, Merck, Tobira and BMS. He has received speaker honoraria from Janssen, Gilead Sciences, BMS and Merck prior to January 2011. J.M.M. has acted as a consultant, participated in advisory boards, has received speaker fees and has been an investigator for clinical trials for Janssen, ViiV Healthcare, Gilead Sciences, BMS, Abbott Laboratories, Boehringer Ingelheim (BI) and Merck, Sharp, and Dohme (MSD) Trial registry: NCT00540449 & NCT00543725
Methodological quality	

Cohen 2012 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Cohen 2012 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	

Coker 2015

Study characteristics	
Patient Sampling	• Target population: HIV-infected individuals initiating care and treatment from August 2006 to January 2008 • Recruitment: no details reported, participants of an RCT • Inclusion criteria: 18 years and older, tested positive for HIV-1 antibodies, treatment-naive and enrolled into the US PEPFAR-funded Institute of Human Virology Nigeria's AIDS Care and Treatment in Nigeria (ACTION) programme • Exclusion criteria: not reported • Study design: RCT

Patient characteristics and setting	• Country: Nigeria
	  ◦ World Bank Income classification: low-middle income
	  ◦ Study setting: hospital-based (Aminu Kano Teaching Hospital, Northern Nigeria)
	• Study dates: August 2006 to January 2008
	• Age of population (years), mean (SD): 33 (8.13)
	• Gender (male %): 43.17
	• Participants included/analysed: 421/276
	• First or second-line regimen: first-line
	  ◦ Type of ART: d4T-based, ZDV-based, TDF-based
	  ◦ Time on ART at enrolment: treatment-naïve
	  ◦ Time on ART at measurement of viral load and adherence: 9 months

Index tests	Number of index tests used: 2

Coker 2015 *(Continued)*

	Types of index tests: self-report and pharmacy records
	• Test 1. Self-report questionnaire
	  ○ Validated scale: yes (Mannheimer 2006).
	  ○ Tool description: self-report adherence measure was derived from an interview-administered Case Adherence Index Questionnaire (Mannheimer 2006). Threshold for self-report described as a score of ≤ 10 or > 10
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used: 100%
	• Test 2. Tablet counts
	  ○ Validated scale: not applicable
	  ○ Tool description: cumulative pharmacy (Rx) refill rates. This was calculated as days of medication dispensed divided by days between visits multiplied by 100. A cut-off of < 95% Rx refill rate was used to define non-adherence
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used: 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Roche Cobas AmpliPrep TaqMan (Copas Amplicor;Roche Diagnostics) • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: not explicit, but likely to be at the same time ("We assessed all variables and risk factors for viral load suppression (< 400 copies/mL) at the end of the study using the Chi-square or Fisher exact test and student t-test") • All patients received same reference standard: yes • Missing data: 70% of original sample attended 9-month follow-up, 276/421 had viable VL sample. Missing data > 10 %
Comparative	
Notes	Conflicts of interest: none declared Funding source: Doris Duke Charitable Foundation under the ORACTA (Grant # 2005051) to Dr. William A. Blattner and Abbott Investigator Initaite Study Agreement to Dr. Nicaise Ndembi Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Coker 2015 *(Continued)*

Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Davies 2008

Study characteristics	
Patient Sampling	• Target population: HIV-infected children commenced on antiretroviral triple therapy • Recruitment: consecutive sample, all children that commenced therapy were eligible and agreed to participate • Inclusion criteria: selection criteria for commencement of ART needed to be met, in addition, the following limited social criteria needed to be met: having an identifiable caregiver to administer medication and attend clinic appointments; resident in Cape Town for at least 3 months; caregiver compliance with last 3 clinic appointments and caregiver willingness to comply with ongoing regular clinic attendance and monitoring. • Exclusion criteria: not reported • Study design: prospective cohort study

Patient characteristics and setting	• Country: South Africa
	  ○ World Bank Income classification: upper-middle-income
	  ○ Study setting: hospital-based (part of the ART program of the Red Cross Children's Hospital, a tertiary care institution in Cape Town, South Africa)
	• Study dates: July 2002 to January 2004
	• Age of population (months), median (IQR): 37 (16 to 61)
	• Gender (male %): 57.57
	• Participants included/analysed: 122/88
	• First or second-line regimen: first-line
	  ○ Type of ART: the majority of children were commenced on stavudine, 3TC and EFV (children > 10 kg or > 3 years) or RTV (children < 10 kg or < 3 years) as no other PI was readily available in suitable formulation and dosage in South Africa at the time
	  ○ Time on ART at enrolment: treatment-naïve
	  ○ Time on ART at measurement of viral load and adherence: 12 months

Index tests	Number of index tests used: 1
	
	Types of index tests: tablet counts
	
	• Test 1. Tablet counts
	  ○ Validated scale: not applicable
	  ○ Tool description: at every monthly visit for one year, caregivers were requested to return all empty medicine containers and unused medication. A dedicated programme pharmacist measured the amount of unused medication volumetrically for syrups/solutions and by pill count for tablets/capsules. The percentage adherence for each antiretroviral medication was calculated by dividing actual use (determined from returned containers and unused medication) by expected use.
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 90%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: no details provided on the assay used ("Viral load determined using standard laboratory methods") • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing; adherence was a composite measure of annual average percentage adherence; viral load taken at 12 months • All patients received same reference standard: not reported

Davies 2008 *(Continued)*

- Missing data: 88/122 children included in the analysis. Missing data > 10%

Comparative	
Notes	Conflicts of interest: none declared Funding source: donations to fund the programme were received from Syfrets Trust Ltd, Merck (Pty) Ltd, Bristol-Myers Squibb Foundation, Durbanville High School, and the University of Cape Town. Mary-Ann Davies and Andrew Boulle receive support from the International Epidemiological Databases to Evaluate AIDS in Southern Africa (IeDEASA) collaboration which is funded by the National Institutes for Health (NIH; U01 AI069924-01). Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	No		
Could the conduct or interpretation of the index test have introduced bias?		High risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			

Davies 2008 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Duarte 2015

Study characteristics	
Patient Sampling	• Target population: Infants (≤ 12 months of age) who were born to women diagnosed with HIV infection either prior to or during pregnancy or within 1 month postpartum and (ii) HIV-infected infants, children and adolescents (≤ 21 years of age) • Recruitment: no details reported • Inclusion criteria: infants (≤ 12 months of age) who were born to women diagnosed with HIV infection either prior to or during pregnancy or within 1 month postpartum and (ii) HIV-infected infants, children and adolescents (≤ 21 years of age) • Exclusion criteria: not reported • Study design: prospective cohort study

Patient characteristics and setting	• Country: Brazil, Mexico and Peru
	  ○ World Bank Income classification: Brazil (low-income and upper-middle-income during that time), Mexico (upper-middle-income), Peru (low-income)
	  ○ Study setting: clinic-based (14 clinical sites, 12 in Brazil, 1 each in Peru and Mexico)
	• Study dates: 2002 to October 2007
	• Age of population (years), mean (range): 5.0 (< 1 to 11)
	• Gender (male %): 50.0

Duarte 2015 *(Continued)*

	• Participants included/analysed: 387/361 (index test 1) 387/367 (index test 2) at 6 months; 387/357 (index test 1) and 387/360 (index test 2) at 12 months.
	• First or second-line regimen: second-line
	  ○ Type of ART: 95% of the children were on combination ART
	  ○ Time on ART at enrolment: not reported
	  ○ Time on ART at measurement of viral load and adherence: 6 and 12 months

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ○ Validated scale: yes
	  ○ Tool description: structured questionnaire developed for use by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) as part of standard practice in PACTG (Pediatric AIDS Clinical Trials Group) studies. The interview was administered in Spanish or Portuguese by a member of the clinical care or research team to the person with primary responsibility for medication administration. The participant/caregiver was asked to identify the ARV medications and number of doses (not number of pills) prescribed each day. ART adherence was derived based on the total number of doses missed during the three-day period prior to a study visit and the total number of expected doses for all of the ARVs included in the participant's treatment regimen at the time of the visit. (1) The measure was expressed in the form of a continuous measure of percent adherence calculated as binary indicator of perfect (100%) adherence. (2) Participants/caregivers were also asked to recall when they/the child last missed a dose of any ARV medication; response options included never, during the previous two weeks, during the last month, over a month ago or don't remember. This measure was dichotomized for purposes of analysis (never vs. ever).
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence thresholds used: 100% (perfect adherence score: never missed a dose)

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: no details provided on the assay used • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: demographic, laboratory, and clinical data were collected at enrolment and every 6 months, including HIV-1 RNA viral load, CD4 measures, CDC classification, and antiretroviral medication adherence • All patients received same reference standard: not reported • Missing data: none. At 6 months, data available for 361/387 and 367/387 for index tests 1 and 2; at 12 months, data available for 357/387 and 360/387 for index tests 1 and 2. Missing data < 10% Demographic, laboratory, and clinical data were collected at enrolment and every 6 months, including HIV-1 RNA viral load, CD4 measures, CDC classification, and antiretroviral medication adherence.
Comparative	
Notes	Conflicts of interest: none declared Funding source: supported by NICHD Contracts N01-HD-3-3345 (2002–2007), HHSN267200800001C (2007–2012), and HHSN275201300003C (2012–2017) Trial registry: not reported
Methodological quality	

Duarte 2015 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined			Unclear

Duarte 2015 *(Continued)*

by the reference standard does not match the question?		
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Unclear	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk

Dziva 2017

Study characteristics	
Patient Sampling	• Target population: children aged 6 to 15 years newly diagnosed with HIV infection attending lay worker–delivered treatment support intervention to improve adherence • Recruitment: all children who initiated ART were included. • Inclusion criteria: children aged 6-15 years newly diagnosed with HIV infection • Exclusion criteria: no exclusions reported: all children who initiated ART were included. • Study design: prospective clinical trial

Patient characteristics and setting	• Country: Zimbabwe
	  ◦ World Bank Income classification: low-income
	  ◦ Study setting: community-based (lay worker–delivered treatment support intervention)
	• Study dates: not reported
	• Age of population (years), median (IQR): 11 (9 to 13)
	• Gender (male %): 45
	• Participants included/analysed: 237/166
	• First or second-line regimen: first-line
	  ◦ Type of ART: HIV treatment was provided according to national guidelines.
	  ◦ Time on ART at enrolment: not reported
	  ◦ Time on ART at measurement of viral load and adherence: 48 weeks

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ◦ Validated scale: yes (VAS)
	  ◦ Tool description: participants completed a visual analog scale (VAS) to self-assess their adherence over the past month. The responses were given by either caregivers on behalf of the child, jointly by caregivers and children, or children alone (for older children). The authors noted that the scales routinely used to measure

Dziva 2017 *(Continued)*

	reported nonadherence have been mainly designed for use among adults, and there are no corresponding scales for children. Non-adherent = VAS score < 95% ○ Blinding: no information ○ Threshold prespecified: not reported ○ Adherence threshold used: 95
Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: dual-target COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0.11 • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but both assessed at 48 weeks after initiation of ART • All patients received same reference standard: yes • Missing data: none. Not all children were included in the analysis, as complete adherence and viral load data was only available for 166 children (of 237). Missing data > 10%
Comparative	
Notes	Conflicts of interest: none declared Funding source: Wellcome Trust Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		

Dziva 2017 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Ekstrand 2010

Study characteristics	
Patient Sampling	• Target population: HIV patients, on anti-retroviral medication for at least one month in outpatient Department of Medicine in a Catholic hospital in Bangalore, India • Recruitment: referral from physician needed or Non Governmental Organization • Inclusion criteria: eligibility criteria included being at least 18 years old; capable of communicating in English, Kannada, Tamil, or Telugu; being HIV-infected, on antiretroviral medication for at least one month, and willing to participate in all follow-up visits • Exclusion criteria: not reported • Study design: pospective cohort study

Patient characteristics and setting	• Country: India
	  ○ World Bank Income classification: low-middle-income
	  ○ Study setting: clinic-based (the outpatient Department of Medicine in a Catholic hospital in Bangalore, India)
	• Study dates: not reported (prior to 2008)

Ekstrand 2010 *(Continued)*

- Age of population (years): mean (range): 38 (23 to 74)
- Gender (male %): 69
- Participants included/analysed: 229/202
- First or second-line regimen: not reported
  - Type of ART: virtually all (98%) of the participants were on an NTI-based regimen, with the most common regimens being 3TC/stavudine/NVP (49%), followed by 3TC/AZT/NPV (26%), 3TC/AZT/EFV (8%), and 3TC/stavudine/EFV(7%)
  - Time on ART at enrolment: not reported
  - Time on ART at measurement of viral load and adherence: at least 12 months (mean: 33 months, range: 13 to 145 months)

Index tests	Number of index tests used: 4
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ○ Validated scale: yes
	  ○ Tool description: visual analog scale in last month
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%
	• Test 2. Self-report questionnaire
	  ○ Validated scale: not reported
	  ○ Tool description: self-reported pills missed in previous 1 month
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%
	• Test 3. Self-report questionnaire
	  ○ Validated scale: not reported
	  ○ Tool description: self-reported pills missed in previous 1 week
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%
	• Test 4. Self-report questionnaire
	  ○ Validated scale: not reported
	  ○ Tool description: self-report, % adherence in previous 4 days (detailed dose-by-dose assessment)
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: real Time PCR assay with fluorescein labeled Taqman probe for quantitation of HIV particles • Definition of viral non-suppression: HIV viral load > 100 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: index tests and reference standard were conducted at the same study visits (at 0, 6 and 12 months). Adherence data were self-reported percentages of doses completed in previous 4 days, 1 week and 1 month. • All patients received same reference standard: yes • Missing data: 202 participants who attended study visits at 0 and 12 months were tested. Of 229 enrolled, 11 died and 15 were lost to follow-up, leaving 203. It is unclear what happened to

Ekstrand 2010 *(Continued)*

	one participant. Missing participants > 10%, but reasons were reported and many participants were lost to follow-up because they died.
Comparative	
Notes	Conflicts of interest: none declared Funding source: grant R01MH067513 from the National Institute of Mental Health (NIMH) (Bethesda, MD, USA). (from refID 5045 Ekstrand 2011) Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it prespecified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Ekstrand 2010 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
Could the patient flow have introduced bias?		Low risk	

El-Khatib 2010

Study characteristics	
Patient Sampling	• Target population: adults with HIV, being on ART for at least 12 months • Recruitment: recruited through posters in two outpatient clinics. The following inclusion criteria were applied: at least 18 years old; being on ART for at least 12 months; and consenting to participate in the study • Inclusion criteria: at least 18 years old; being on ART for at least 12 months; and consenting to participate in the study • Exclusion criteria: not reported • Study design: cross-sectional

Patient characteristics and setting	• Country: South Africa
	  ○ World Bank Income classification: upper-middle
	  ○ Study setting: two outpatient clinics at the Chris Hani Baragwanath Hospital, Soweto, Johannesburg
	• Study dates: March to December 2008
	• Age of population (years), median: women: 41, men: 37
	• Gender (male %): 26.87
	• Participants included/analysed: 998/997

El-Khatib 2010 *(Continued)*

- First or second-line regimen: first-line or second-line
  - Type of ART: NNRTI-based (first-line), PI-based (second-line)
  - Time on ART at enrolment: at least 12 months
  - Time on ART at measurement of viral load and adherence: not reported; at least 12 months

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report
	  ○ Validated scale: not reported
	  ○ Tool description: detail about adherence measure: "adherence during the previous weekend which served as a proxy for recent adherence" ...Threshold categories used as cut-off for optimal adherence: "Missed any pills during last weekend"
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 100%
	
	.

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Amplicor HIV-1 Monitor Test, v1.5 (Roche Molecular Diagnostics, Basel, Switzerland) • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this was a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: yes • Missing data: adherence/suppression reported for 997/998. Missing data < 10 %
Comparative	
Notes	Conflicts of interest: none declared Funding source: Swedish International Development Cooperation Agency (Sida) to Z.EK. and NICD and a Karolinska Institutet faculty award (KID) to Z.EK.; African Programme for Training in HIV/TB Research Fogarty Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		

El-Khatib 2010 *(Continued)*

Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Evans 2016

Study characteristics	
Patient Sampling	• Target population: adult, HIV-positive patients on second-line ART, who experienced a single elevated viral load • Recruitment: no details reported • Inclusion criteria: Eligible patients were adult (> 18 years) HIV-positive patients at Themba Lethu who were receiving a second-line ART regimen containing lopinavir/ritonavir or atazanavir/ritonavir and experienced a single elevated viral load (> 400 copies/mL) on second-line ART. • Exclusion criteria: not reported • Study design: cohort study

Patient characteristics and setting	• Country: South Africa
	  ◦ World Bank Income classification: upper-middle-income
	  ◦ Study setting: clinic-based (Themba Lethu Clinic in Johannesburg)
	• Study dates: July 2011 to July 2018
	• Age of population (years), median (IQR): 37.6 (33.6 to 45.3)
	• Gender (male %): 40.8
	• Participants included/analysed:49/49
	• First or second-line regimen: second-line
	  ◦ Type of ART: second-line ART regimen containing LPV/r or atazanavir/ritonavir
	  ◦ Time on ART at enrolment: prior to study eligibility (elevated VL on second-line), median (IQR): 48.8 months (30.4 to 68.8)
	  ◦ Time on ART at measurement of viral load and adherence: 3 or 6 months after an elevated viral load (> 400 copies/mL) on second-line ART

Index tests	Number of index tests used: 1
	
	Types of index tests: electronic monitoring
	
	• Test 1. Electronic monitoring
	  ◦ Validated scale: not applicable
	  ◦ Tool description: patients in the intervention cohort used an electronic adherence monitoring device (EAMD) (WisepillTM)
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 80% (missing ≥ 20%) or taking at least 95% (missing ≥ 5%) of the prescribed medication

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: no details provided on the assay used • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: yes. Viral load testing was not done by the clinic, but by a central lab and therefore those performing the viral load tests were blinded to the study cohorts. Blood samples are sent to the National Health Laboratory Service (NHLS) and viral load and CD4 count results are uploaded directly into TherapyEdge-HIVTM from the NHLS on a daily basis.
Flow and timing	• Time interval between index and reference tests: when participants returned for the follow-up viral load test (3 to 6 months after enrolment), the device was returned and the clinician reviewed the adherence data with the patient. • All patients received same reference standard: not reported • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.

Evans 2016 *(Continued)*

Comparative	
Notes	Conflicts of interest: none declared Funding source: South Africa Mission of the US Agency for International Development (USAID) Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		

Evans 2016 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Farley 2003

Study characteristics	
Patient Sampling	• Target population: caregivers (biologic parent, adoptive parent, foster parent, or other guardian) of perinatally HIV-infected children under the age of 13 years being treated with HAART • Recruitment: caregivers (biologic parent, adoptive parent, foster parent, or other guardian) of perinatally HIV-infected children under the age of 13 years being treated with HAART were invited to participate in a 3-year study of adherence involving periodic interviews and a 6-month baseline period of observation. • Inclusion criteria: caregivers (biologic parent, adoptive parent, foster parent, or other guardian) of perinatally HIV-infected children under the age of 13 years being treated with HAART were invited to participate in a 3-year study of adherence involving periodic interviews and a 6-month baseline period of observation. All children were receiving treatment at the University of Maryland School of Medicine. • Exclusion criteria: children with evidence of significant developmental delays or greater, below the mean on the Test of Nonverbal Intelligence, a severe physical handicap precluding independent ambulation, or those who were receiving all antiretrovirals in liquid formulation were not eligible to participate. • Study design: prospective cohort study

Patient characteristics and setting	• Country: USA
	  ◦ World Bank Income classification: high-income
	  ◦ Study setting: University of Maryland School of Medicine
	• Study dates: recruitment from October 1998 to October 2002
	• Age of population (years), mean: 6.9
	• Gender (male %): 65
	• Participants included/analysed: 31/26

Farley 2003 *(Continued)*

	• First or second-line regimen: not reported
	  ○ Type of ART: defined as treatment with three different antiretroviral agents regardless of drug class
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: not reported; at least 6 months

Index tests	Number of index tests used: 1
	
	Types of index tests: electronic monitoring
	
	• Test 1. Electronic monitoring
	  ○ Validated scale: not applicable
	  ○ Tool description: a Medication Event Monitoring System child-resistant Track Caps was used. A MEMS adherence rate was calculated as follows: medication events or bottle openings/doses prescribed for the interval
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used: 80%
	
	MEMS with a 90% adherence cut-off and data on pharmacy refill adherence assessment and caregiver self-report; however this was not reported in a way that data could be used.

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Roche Amplicor reverse transcribed PCR method • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit details on timing, but both measured at 6 months • All patients received same reference standard: yes • Missing data: 31 caregivers and their children were enrolled; 26 completed the initial 6-month period of the study with greater than 60 days of available adherence monitoring data and were included in this analysis. Of the 5 noncompleters, 1 did not complete the baseline interview and 2 changed to medication formulations precluding MEMS monitoring. Missing data for > 10%
Comparative	
Notes	Conflicts of interest: none declared Funding source: R01 HD36613 and M01 RR165001 Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

Farley 2003 *(Continued)*

Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		

Farley 2003 *(Continued)*

Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Fokam 2017

Study characteristics	
Patient Sampling	• Target population: adolescents living with HIV • Recruitment: consecutive sampling at a referral health facility for care and treatment of HIV-infected children. Children followed up at the study site were all HIV-vertically infected, except for one that was infected through unsafe blood transfusion. • Inclusion criteria: eligibility criteria were: every adolescent living with HIV who: (a) was aware of his HIV status, (b) was registered for ART monitoring at the study site, (c) was receiving ART for at least six months, (d) was capable of responding to the study questionnaire, and (e) had provided a written consent • Exclusion criteria: not reported • Study design: cross-sectional

Patient characteristics and setting	• Country: Cameroon
	  ◦ World Bank Income classification: low-middle-income
	  ◦ Study setting: National Social Insurance Fund Health Centre in Yaounde-Cameroon - a referral health facility for care and treatment of HIV-infected children
	• Study dates: January to May 2016
	• Age of population (years), median (IQR): 13 (11 to 16)
	• Gender (male %): 48
	• Participants included/analysed: 145/145
	• First or second-line regimen: mostly frst-line
	  ◦ Type of ART: 92% were on first-line ART
	  ◦ Time on ART at enrolment: at least 6 months
	  ◦ Time on ART at measurement of viral load and adherence: at least 6 months

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ◦ Validated scale: not reported
	  ◦ Tool description: poor adherence was defined as missing one dose of ART during the past 14 days
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 100%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Abbott Applied Biosystem m2000RT Real Time PCR AB m2000RT • Definition of viral non-suppression: HIV viral load > 50 copies/mL • Blinded to index test: no information

Fokam 2017 *(Continued)*

Flow and timing	• Time interval between index and reference tests: index tests and reference standard were conducted at the same study visits • All patients received same reference standard: yes • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: the authors received no specific funding for this work. Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Fokam 2017 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Gill 2010

Study characteristics	
Patient Sampling	• Target population: adults with HIV receiving ART • Recruitment: this analysis used longitudinal observational data from a three-phase adherence study conducted among HIV-positive patients receiving ART at the Dermatology and STD clinic, Dali Second People's Hospital (DSPH) in Dali, Yunnan Province, China. Patients were eligible for participation if they were aged > 18 years and agreed to all study procedures. Of 97 eligible patients at the clinic, 80 agreed to participate. • Inclusion criteria: patients aged 18 years or older and agreed to all study procedures • Exclusion criteria: not reported • Study design: prospective cohort study

Patient characteristics and setting	• Country: China
	  ◦ World Bank Income classification: low-middle
	  ◦ Study setting: clinic-based (Sexually Transmitted disease clinic in a hospital)
	• Study dates: June 2006 to May 2007
	• Age of population (years), mean (SD): 35.7 (8.1)
	• Gender (male %): 73.9
	• Participants included/analysed: 69/65
	• First or second-line regimen: unclear
	  ◦ Type of ART: twice-daily regimen of nevirapine or efavirenz, plus either zidovudine and lamivudine or lamivudine and stavudine
	  ◦ Time on ART at enrolment: median 8.3 months
	  ◦ Time on ART at measurement of viral load and adherence: median 8.3 months

Index tests	Number of index tests used: 4 Types of index tests: self-report, tablet counts, electronic monitoring

Gill 2010 *(Continued)*

- Test 1. Self-report questionnaire
  - Validated scale: yes (VAS)
  - Tool description: self-report/visual analog scale: indicated by where the patient marked an 'X' on the 0–100% VAS scale
  - Blinding: no information
  - Threshold prespecified: not reported
  - Adherence threshold used: 95%
- Test 2. Tablet counts
  - Validated scale: not applicable
  - Tool description: [Actual number of pills in bottle]/[expected number of pills]
  - Blinding: no information
  - Threshold prespecified: not reported
  - Adherence threshold used: 95%
- Test 3. Electronic moritoring
  - Validated scale: not applicable
  - Tool description: proportion taken: [Actual number of bottle openings]/[expected number of bottle openings]
  - Blinding: no information
  - Threshold prespecified: not reported
  - Adherence threshold used: 95%
- Test 4. Electronic moritoring
  - Validated scale: not applicable
  - Tool description: proportion taken within dose time: [Actual number of bottle openings within ±1 h of the prescribed time]/[expected number of openings]
  - Blinding: no information
  - Threshold prespecified: not reported
  - Adherence threshold used: 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Organon Teknica NucliSens analyzer (BioMerieux, Boxtel, Netherlands) • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: not explicitly reported, but both measured at 6 months • All patients received same reference standard: yes • Missing data: of 69 patients, 65 included in the analysis. Missing data < 10 %
Comparative	
Notes	Conflicts of interest: none declared Funding source: Boston University, USAID, WHO, CDC-GAP/China, NIH Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Gill 2010 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		

Gill 2010 *(Continued)*

Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Haberer 2011

Study characteristics	
Patient Sampling	• Target population: HIV-infected children initiating ART • Recruitment: the study population was drawn from the CHAPAS-1 trial, which was a randomized study of nevirapine (NVP) dose escalation among HIV-infected children initiating ART. All children were treated at the University Teaching Hospital in Lusaka, Zambia. • Inclusion criteria: 1. Aged 3 months to 14 years inclusive; 2. Less than 30 kg in weight; 3. Carers and children where they were appropriate, willing and able to give informed consent; 4. HIV-infected, as determined by: a. Two separate HIV-antibody enzyme-linked immunosorbent assay (ELISA) or rapid tests on the same sample in children > 18 months, b. Two positive proviral DNA tests taken on separate samples in children < 18 months; 5. Previously untreated with antiretrovirals, including any ART given to prevent mother-to-child transmission; 6. Fulfilling one of the World Health Organization (WHO) criteria for initiating treatment: a. WHO paediatric stage 4 or severe stage 3 disease regardless of CD4%, b. CD4 per cent < 15% if > 18 months of age, or < 20% if < 18 months of age, c. WHO paediatric stage 2 disease with consideration of CD4 percentage (< 15% for children > 18 months; < 20% for children < 18 months). (Note current WHO guidelines are under review and the above criteria may be changed, particularly by raising the CD4 percentage cut-off to 25% in children < 18 months; inclusion criteria would be changed accordingly for children to start ART in CHAPAS 1 trial) • Exclusion criteria: 1. Cannot or unwilling to regularly attend the CHAPAS clinic; 2. Severe laboratory abnormalities (contraindicating NVP-based regimen), i.e. serum creatinine > 5 times upper limit of normal (ULN) or aspartate aminotransferase or alanine aminotransferase > 10 times ULN; 3. Active opportunistic infection and/or serious bacterial infection at the time of study entry including tuberculosis (may be enrolled after the acute phase of tuberculosis); 4. Current treatment with any medication known to be contraindicated with any of the drugs prescribed for the patient's ART-therapy in this trial, including rifampicin • Study design: prospective cohort substudy within an RCT

Patient characteristics and setting	• Country: Zambia
	  ◦ World Bank Income classification: low-income
	  ◦ Study setting: clinic-based (outpatients at University Teaching Hospital in Lusaka)
	• Study dates: May 2006 to Dec 2008
	• Age of population (years), median (IQR): 6 (2 to 9)
	• Gender (male %): 55
	• Participants included/analysed: 96/73, 96/72
	• First or second-line regimen: first-line
	  ◦ Type of ART: children randomized to initiate nevirapine (NVP) at full dose used fixed-dose combination (FDC) tablets of stavudine, 3TC, and NVP (Triomune Baby/Junior) twice daily. Children randomized to escalate their dose of NVP used Triomune Baby/Junior once daily for 14 days, together with an FDC of stavudine and 3TC (Lamivir-S) once daily. After 14 days Lamivir-S was stopped and children continued on twice daily Triomune Baby/Junior.
	  ◦ Time on ART at enrolment: treatment-naïve
	  ◦ Time on ART at measurement of viral load and adherence: 48 weeks

Index tests	Number of index tests used: 5

Haberer 2011 *(Continued)*

	Types of index tests: electronic monitoring, tablet counts, self-report
	• Test 1. Electronic monitoring
	  ○ Validated scale: not applicable
	  ○ Tool description: electronic monitoring with MEMS (Medication Event Monitoring System, Aardex, Switzerland) caps
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%; 80%
	• Test 2. Tablet counts
	  ○ Validated scale: not applicable
	  ○ Tool description: home visits pill counts. Unannounced monthly home visits for further pill counts
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence thresholds used: 95%; 80%
	• Test 3. Tablet counts
	  ○ Validated scale: not applicable
	  ○ Tool description: clinic-based pill counts. MEMS data was downloaded at each four-weekly clinic visit
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%; 80%
	• Test 4. Self-report
	  ○ Validated scale: yes (VAS)
	  ○ Tool description: Self-report: visual analogue scale (VAS). Caregivers indicated the child's adherence on a line marked with ''none given'' and ''all given'' at the ends and ''half given'' at the midpoint.
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%, 80%
	• Test 5. Self-report
	  ○ Validated scale: not reported
	  ○ Tool description: Self-report: "last missed dose". Caregiver report of the last missed dose of ART (i.e. caregivers were asked ''When did your child last miss any ART: within the last week, 1–2 weeks, 2–4 weeks, 1–3 months, nothing in 3 months?'')
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%; 80%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Joint Clinical Research Centre Laboratory in Kampala, Uganda (Roche Amplicor Monitor version1.5 ultrasensitive assay) • Definition of viral non-suppression: HIV viral load > 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: viral load measured at 48 weeks, adherence measured over the period and used average over 48 weeks • All patients received same reference standard: yes • Missing data: 96 children were included in the study, but adherence and VL data only available for 72 or 73 children, depending on the adherence test. Missing data for > 10%
Comparative	
Notes	Conflicts of interest: none declared Funding source: CHAPAS-1 is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP 2004.01.H.d2.33011). Cipla Ltd donated the first-line drugs. Drs. Haberer and Bangsberg are support-

Haberer 2011 *(Continued)*

ed by the US National Institute of Mental Health (K23–87228 and K24–87227, respectively) and the Mark and Lisa Schwartz Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Trial registry: ISRCTN 31084535

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			

Haberer 2011 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Hassan 2014

Study characteristics	
Patient Sampling	• Target population: HIV-infected adolescents and adults (≥ 15 years old) who had been on first-line ART for more than six months. • Recruitment: in the first cross-section, all consenting eligible participants were recruited between November 2008 and January 2009. At the same time, a prospective cohort was established in order to describe long-term outcomes of new clients enrolling for HIV care. All available plasma samples from participants recruited in the prospective cohort and meeting our eligibility criteria as at March 2011 were cross-sectionally retrieved.

Hassan 2014 *(Continued)*

	• Inclusion criteria: HIV-infected adolescents and adults (≥ 15 years old) who had been on first-line ART for more than six months • Exclusion criteria: participants with a previous history of ART exposure for prevention of mother-to-child transmission (PMTCT) or for post-exposure prophylaxis (PEP), and those on second-line regimens were excluded from the study. • Study design: cross-sectional

Patient characteristics and setting	• Country: Kenya
	  ○ World Bank Income classification: low-income
	  ○ Study setting: hospital-based, rural setting
	• Study dates: Nov 2008 to March 2011
	• Age of population (years), median (IQR): 36.5 (31.4 to 44.4)
	• Gender (male %): 18.6
	• Participants included/analysed: 232/224
	• First or second-line regimen: first-line
	  ○ Type of ART: first-line regimen, not further specified
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: not reported; at least 6 months

Index tests	Number of index tests used: 1
	
	Types of index tests: pharmacy records
	
	• Test 1. Pharmacy records: Medicine Possession Ratio (MPRs)
	  ○ Validated scale: not applicable
	  ○ Tool description: Medicine Possession Ratios (MPRs) were calculated as proportions of the total number of days between drug pick-ups less the equivalent number of days in possession of ART divided by the time between drug pickups for all visits. A mean MPR for each individual was computed, subtracted from 100% and stratified to satisfactory (≥ 95%) and unsatisfactory (< 95%) adherence according to previously published conventions. Note that the authors therefore retrospectively retrieved pharmacy drug refill data from 12 months (or from the date of ART initiation if follow up period < 12 months) prior to the date of sampling for every individual participant.
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used: 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: viral load quantification was done using an inhouse assay; in brief, a multiplex real time quantitative probe-based assay with an internal control and a series of quantified HIV-1 standards was used to determine virus concentration • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this was a cross-sectional study so likely to be measured simultaneously. Pharmacy drug refill data was retrieved from 12 months (or from the date of ART initiation if follow-up period < 12 months) prior to the date of sampling for every individual participant. • All patients received same reference standard: yes • Missing data: 224 of 232 patients included in the analysis. Missing data < 10 %
Comparative	
Notes	Conflicts of interest: none declared

Hassan 2014 *(Continued)*

Funding source: Wellcome Trust foundation (grant number WT089351MA). ASH and JAB were funded by Wellcome Trust fellowships (WT089351MA and WT083579MA, respectively). SM and HN were employees of the KEMRI/Wellcome Trust research programme while CAO was an employee of the Kenyan Ministry of Health. EJS was funded by the International AIDS Vaccine Initiative while PAC was financially supported by the Health Protection Agency, UK. TFRW was a member of the PharmAccess African studies to Evaluate Resistance (PASER), which received financial support from the Ministry of Foreign Affairs of the Netherlands.

Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		

Hassan 2014 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Jayaweera 2003

Study characteristics	
Patient Sampling	• Target population: adults with HIV, naïve to ARV • Recruitment: no details reported • Inclusion criteria: HIV infection, patients had to be naive to ARV, there were no limits set on HIV-1 RNA or CD4 cell counts. All patients received ritonavir 400 mg and indinavir 400 mg two times a day • Exclusion criteria: not reported • Study design: open-label, non-randomized, single-arm study

Patient characteristics and setting	• Country: USA
	  ◦ World Bank Income classification: high-income
	  ◦ Study setting: hospital-based, Miami city
	• Study dates: not reported
	• Age of population (years): not reported
	• Gender (male %): 58
	• Participants included/analysed: 19/19

Jayaweera 2003 *(Continued)*

	• First or second-line regimen: first-line
	  ○ Type of ART: all patients received ritonavir 400 mg and indinavir 400 mg two times a day
	  ○ Time on ART at enrolment: treatment-naïve
	  ○ Time on ART at measurement of viral load and adherence: 24 weeks

Index tests	Number of index tests used: 1
	
	Types of index tests: composite measure
	
	• Test 1. Self-report questionnaire and pill counts
	  ○ Validated scale: not applicable
	  ○ Tool description: patients were determined to be compliant or non-compliant based on self-report with confirmation based on assessment of pill counts at each study visit. No other details provided
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 100%; ≥ 80%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Amplicor HIV-1 monitor test (Roche, New Jersey, USA) • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: Although the duration of treatment for this study was intended to be 48 weeks, only one of the noncompliant patients has laboratory measurements beyond the week-24 visit. Therefore, statistical analyses have been restricted to data collected during the first 24 weeks of this study. • All patients received same reference standard: yes • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: Abbott Laboratories provided financial support Trial registry: not reported

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	

Jayaweera 2003 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Jiamsakul 2014

Study characteristics	
Patient Sampling	• Target population: HIV-infected people, treatment-experienced switching to second-line ART due to failure

Jiamsakul 2014 *(Continued)*

	• Recruitment: patients were selected from The Therapeutics, Research, Education and AIDS Training in Asia (TREAT Asia) Studies to Evaluate Resistance Monitoring Study (TASER-M). TASER-M began recruitment in 2007 and included 12 clinical sites in Thailand, Hong Kong, Malaysia, Philippines and Indonesia. • Inclusion criteria: patients were either enrolled in TASER-M as treatment-naive or initiating first-line ART (not included in the analysis) or treatment-experienced switching to second-line ART due to failure. • Exclusion criteria: PI-minor mutations from our definition of RAMs as these minor variants may occur as common polymorphisms in HIV-1 non-B subtypes which is predominant in our cohort • Study design: cohort study

Patient characteristics and setting	• Country: Thailand, Hong Kong, Indonesia, Malaysia and Philippines
	  ○ World Bank Income classification: Thailand, Indonesia, Philippines: low-middle; Hong-Kong: high; Malaysia: upper-middle
	  ○ Study setting: 10 sites in Thailand, Hong Kong, Indonesia, Malaysia and Philippines, clinic-based
	• Study dates: not reported (recruitment started in 2007)
	• Age of population (years), median (IQR): 36 (32 to 41)
	• Gender (male %): 66
	• Participants included/analysed: 105/81
	• First or second-line regimen: second-line
	  ○ Type of ART: not reported
	  ○ Time on ART at enrolment: not reported
	  ○ Time on ART at measurement of viral load and adherence: at 12 months from switch to second-line ART (participants on second-line ART)

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ○ Validated scale: yes
	  ○ Tool description: ART adherence was recorded based on the WHO-endorsed self-reported 30-day Visual Analogue Scale (VAS). Adherence level was categorized based on the traditional cut-off point shown to be associated with virological failure: (1) always ≥ 95%, ever < 95% and (3) no assessment (missing)
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used: 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: no details provided on the assay used • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: viral load and adherence was done at 12 months after switching to second-line ART. • All patients received same reference standard: unclear • Missing data: Of 2023 TASER-M participants, 105 participants fit inclusion criteria and were included in the analysis. Viral load and adherence data only available for 81 participants. Missing data > 10%
Comparative	
Notes	Conflicts of interest: none declared

Jiamsakul 2014 *(Continued)*

Funding source: the TREAT Asia Studies to Evaluate Resistance (TASER) is an initiative of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with major support provided by the Dutch Ministry of Foreign Affairs through a partnership with Stichting Aids Fonds, and with additional support from amfAR and the National Institute of Allergy and Infectious Diseases (NIAID) of the U.S. National Institutes of Health (NIH) and the National Cancer Institute (NCI) as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) (grant no. U01AI069907). Queen Elizabeth Hospital and the Integrated Treatment Centre are supported by the Hong Kong Council for AIDS Trust Fund. The Kirby Institute is funded by the Australian Government Department of Health and Ageing and is affiliated with the Faculty of Medicine, UNSW Australia (the University of New South Wales)

Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			

Jiamsakul 2014 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Kitkungvan 2008

Study characteristics	
Patient Sampling	• Target population: adults with HIV, treatment-naïve • Recruitment: analysis only included patients with suppressed VL at 6 months • Inclusion criteria: HIV-drug-naive patients who were ≥ 15 years old, clinically eligible for ART (CD4 count < 200 cells/mL) and subsequently prescribed GPO-VIR. Enrolled patients had confirmed HIV infection and gave written consent to study participation. • Exclusion criteria: patients who did not meet the criteria for ART initiation or began an alternative regimen to GPO-VIR • Study design: prospective observational study

Patient characteristics and setting	• Country: Thailand
	  ○ World Bank Income classification: low-middle
	  ○ Study setting: hospital-based
	• Study dates: April 2003 to 31 March 2007
	• Age of population (years), median (range): 37 (15 to 61)
	• Gender (male %): 64
	• Participants included/analysed: 205/199

Kitkungvan 2008 *(Continued)*

- First or second-line regimen: first-line
  - Type of ART: participants were receiving fixed-dose stavudine, 3TC and NVP
  - Time on ART at enrolment: first-line (treatment-naïve patients)
  - Time on ART at measurement of viral load and adherence: 18 months

Index tests	Number of index tests used: 1
	
	Types of index tests: tablet counts
	
	• Test 1. Tablet counts
	  ○ Validated scale: not applicable
	  ○ Tool description: at each routine medical encounter, the pharmacist calculated the ratio of pills taken divided by the total number of pills prescribed for the interval period. In addition, unannounced home visits including pill counts at participants' residences were conducted randomly by trained adherence counselling educators twice monthly.
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95 to 100%; 75 to 94%; 55 to 74% and 0 to 54%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: no details provided on the assay used • Definition of viral non-suppression: HIV viral load > 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no detailed information about timing, but both happened at 18 months • All patients received same reference standard: unclear • Missing data: 199 of the 205 patients that were included in the study were included in the analysis. Missing data for < 10% participants
Comparative	
Notes	Conflicts of interest: none declared Funding source: this study was supported in part by the Thai American Physician Foundation (to A.A.) and Thammasat University Fund to Infectious Disease and Hospital Epidemiology Research Unit (to A.A.). Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	

Kitkungvan 2008 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	

Labhardt 2012

Study characteristics	
Patient Sampling	• Target population; patients on first-line ART for at least 6 months, aged ≥ 10 years, with viral failure

Labhardt 2012 *(Continued)*

	• Recruitment: all patients aged 16 years or older who started ART with at least three drugs (two NRTIs and one NNRTI) within the two catchment areas between January 2008 and April 2011 were included. • Inclusion criteria: all patients on first-line ART since at least 6 months, aged ≥ 10 years, who fulfilled clinical and/or immunological WHO-criteria for treatment failure and who were followed within the study area • Exclusion criteria: patients taking PI-based ART were excluded from the study. The study only included patients with viral failure. • Study design: cross-sectional

Patient characteristics and setting	• Country: Lesotho
	  ○ World Bank Income classification: low-income
	  ○ Study setting: catchment area of Seboche Hospital in northern Lesotho
	• Study dates: October 2010 and April 2011
	• Age of population (years), median (IQR): 41 (33 to 49)
	• Gender (male %): 51
	• Participants included/analysed: 134/92
	• First or second-line regimen: first-line
	  ○ Type of ART: not reported
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: at least 6 months (most of them 12 months)

Index tests	Number of index tests used: 1
	Types of index tests: self-report
	• Test 1. Self-report
	  ○ Validated scale: yes
	  ○ Tool description: a nurse-clinician assessed the clinical part of the score (adherence measured by a visual analogue scale (VAS)
	  ○ Blinding: no information
	  ○ Threshold prespecified: unclear
	  ○ Adherence threshold used: 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: no details provided on the assay used • Definition of viral non-suppression: HIV viral load > 40 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: the day blood for viral load was drawn, a nurse-clinician assessed the clinical part of the score (adherence measured by a VAS) • All patients received same reference standard: yes • Missing data: only 92 (69%) out of 134 eligible patients could be included in the study, as for the others no viral load result could be obtained.
Comparative	
Notes	Conflicts of interest: none declared Funding source: no funding received Trial registry: not reported
Methodological quality	

Labhardt 2012 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Unclear		

Labhardt 2012 *(Continued)*

Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Landes 2021

Study characteristics	
Patient Sampling	• Target population: post-partum mothers, screened HIV-positive at outpatient clinics in Malawi • Recruitment: this is a nested study of HIV-infected mothers presenting with their 1 to 6 month-old infants at outpatient clinics in Malawi, where they were enrolled for longitudinal follow-up in the NEMAPP study. The subset included in this study, based on regional strata, were enrolled for intensive clinical and laboratory monitoring at 13 health facilities across 8 districts. • Inclusion criteria: 1 to 6 months post-partum mothers, screened HIV-positive at outpatient clinics in Malawi • Exclusion criteria: not reported • Study design: prospective cohort study

Patient characteristics and setting	• Country: Malawi
	  ◦ World Bank Income classification: low-income
	  ◦ Study setting: outpatient clinics in Malawi (13 health facilities across 8 districts)
	• Study dates: October 2014 to March 2016
	• Age of population (years), median (IQR): 29 (24 to 33)
	• Gender (male %): 0 (all female)
	• Participants included/analysed: 1281/441
	• First or second-line regimen: not reported
	  ◦ Type of ART: lifelong ART (i.e. tenofovir/3TC/EFV)
	  ◦ Time on ART at enrolment: not reported
	  ◦ Time on ART at measurement of viral load and adherence: range from 6.1 months to ≥ 24 months

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ◦ Validated scale: not reported
	  ◦ Tool description: self-reported number of days of missed ART in the last month
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 100% (optimal adherence defined as 0–1 days of missed ART)

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Abbott Real-Time HIV-1 Assay, Abbott Laboratories, Chicago, IL • Definition of viral non-suppression: HIV viral load > 40 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: at enrolment, 12 and 24 months • All patients received same reference standard: yes

Landes 2021 *(Continued)*

	• Missing data: of 590 women on ART, 442 with complete VL data at 3 visits were included in further analysis. Missing data > 10%
Comparative	
Notes	Conflicts of interest: not declared Funding source: the President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (CDC) under the terms of cooperative agreement U2GGH000721. CDC staff were involved as co-investigators, assisting in protocol development and approval and manuscript authorship. The authors acknowledge full access to all the data and final responsibility for submission. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies. Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			

Landes 2021 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Mariana 2018

Study characteristics	
Patient Sampling	• Target population: adults infected with HIV, aged > 18 years, ART-naïve on therapy for 12 months • Recruitment: no details reported • Inclusion criteria: adults infected with HIV, aged > 18 years, ART-naive on therapy for 12 months • Exclusion criteria: patients with heart, renal disease and cancer were excluded. • Study design: cross-sectional

Patient characteristics and setting	• Country: Indonesia
	  ◦ World Bank Income classification: lower-middle-income
	  ◦ Study setting: hospital-based (Sulianti Saroso hospital, Jakarta)
	• Study dates: July to October 2017
	• Age of population (years): not reported
	• Gender (male %): 90
	• Participants included/analysed: group 1: 78/78; group 2: 20/20

Mariana 2018 *(Continued)*

	• First or second-line regimen: first-line
	  ○ Type of ART: Group 1 - Fixed dose combination group: first-line treatment with tenovofir and EFV once daily; Group 2 - Free combination group: free combination of ARV
	  ○ Time on ART at enrolment: 12 months
	  ○ Time on ART at measurement of viral load and adherence: 12 months

Index tests	Number of index tests used: 1
	
	Types of index tests: tablet counts
	
	• Test 1. Tablet counts
	  ○ Validated scale: not applicable
	  ○ Tool description: poor adherence was defined as a value of pill consumption < 95% pills. No other details reported
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: no details provided on the assay used • Definition of viral non-suppression: HIV viral load > 40 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this is a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: unclear • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: no funding received NCT record number: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern

Mariana 2018 *(Continued)*

DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		High risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	

Mbengue 2019

Study characteristics	
Patient Sampling	• Target population: HIV-positive adult (≥ 18 years of age) patients who initiated standard first-line ART • Recruitment: secondary analysis of data collected from a prospective observational study • Inclusion criteria: HIV infection, > 18 years, current PI-based second-line ART treatment since at least 6 months and willing to participate and consent signature • Exclusion criteria: patients who transferred in on ART. While pregnant women were eligible to initiate ART, they were not included in the prospective study mainly because they were initiated using different criteria and were managed differently (e.g. transferred out to other facilities for antenatal care).

Mbengue 2019 *(Continued)*

	• Study design: prospective cohort study

Patient characteristics and setting	• Country: South Africa
	  ○ World Bank Income classification: upper-middle-income
	  ○ Study setting: Themba Lethu Clinic (TLC) in Johannesburg, South Africa (clinic visits for study visits)
	• Study dates: treatment initiated between February 2012 and April 2016
	• Age of population (years): not reported
	• Gender (male %): 33.8
	• Participants included/analysed: 357/163
	• First or second-line regimen: first-line
	  ○ Type of ART: standard first-line therapy included tenofovir with 3TC and efavirenz, and in April 2013 TLC introduced a single pill or fixed-dose combination which replaced the multi-pill ART regimen
	  ○ Time on ART at enrollment: 6 months
	  ○ Time on ART at measurement of viral load and adherence: not reported; at least 6 months

Index tests	Number of index tests used: 3
	
	Types of index tests: self-report, composite measure
	
	• Test 1. Self-report VAS
	  ○ Validated scale: yes
	  ○ Tool description: VAS
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 90%
	• Test 2. Self-report questionnaire
	  ○ Validated scale: yes
	  ○ Tool description: tool derived from the Simplified Medication Adherence Questionnaire (SMAQ) tool. For the SMAQ questionnaire, which asks patients about the past 3 months, a patient was considered non-adherent when a positive response to any of the qualitative questions was given, more than two doses over the past week were missed, or he or she had missed taking medicine for more than 2 days over the past 3 months
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used: 100%
	• Test 3. Composite measure
	  ○ Validated scale: not applicable
	  ○ Tool description: a multi-method approach by combining self-report, VAS, PIT and SMAQ and further categorizing overall adherence. When responses to self-report, VAS or pill identification were less than optimal (e.g. answered “yes” to some of the self-report questions, reported < 90% on the VAS, and/or did not know the dose, time and instructions on ART medication), overall adherence was categorized as non-adherent.
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 100%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: not reported • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: during study visits patients met with a counselor to complete an adherence questionnaire and provided blood for additional laboratory testing

Mbengue 2019 *(Continued)*

- All patients received same reference standard: unclear
- Missing data: of 353 patients recruited at baseline data collection, viral load was available for 239 at 6 months. Missing data > 10%

Comparative	
Notes	Conflicts of interest: DE reported grants from Health Economics and Epidemiology Research Office during the conduct of the study. The authors reported no other conflicts of interest in this work. Funding source: the American People and the President's Emergency Plan for AIDS Relief (PEPFAR) through US Agency for International Development (USAID) under the terms of Cooperative Agreements AID-674-A-12-00029 and 72067419CA00004 to HE2RO. The contents are the responsibility of the authors and do not necessarily reflect the views of PEPFAR, USAID or the United States Government. DE was supported by funding from NIH/CFAR/IAS Creative and Novel Ideas in HIV Research (CNIHR) program (sub-award with UAB Center for AIDS Research: P30AI027767) and National Research Foundation (not reported) of South Africa Thuthuka program (post-PhD track 500 TTK1206261680 Grant number 84331). Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	

Mbengue 2019 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

McMahon 2013

Study characteristics	
Patient Sampling	• Target population: adults initiating first-line ART • Recruitment: consecutive initiators of ART were identified during a routine clinic visit after 11-15 months of ART. • Inclusion criteria: adults initiating first-line ART who had not attended or picked up ART within 90 days of their last missed appointment. All baseline clinical and demographic data were abstracted from clinical records and ART dispensing data from pharmacy records. • Exclusion criteria: patients transferred in from other sites or re-initiating ART after a treatment interruption • Study design: prospective cohort study (retrospective data collection)

McMahon 2013 *(Continued)*

Patient characteristics and setting	• Country: India
	  ◦ World Bank Income classification: low-income
	  ◦ Study setting: clinic-based
	• Study dates: Recruitment from October 2009 until October 2015
	• Age of population (years), mean (SD): 38.3 (8.7)
	• Gender (male %): 65
	• Participants included/analysed: 230/170
	• First- or second-line regimen: first-line
	  ◦ Type of ART: not specified. ART was provided for free in this study.
	  ◦ Time on ART at enrolment: treatment-naïve
	  ◦ Time on ART at measurement of viral load and adherence: 12 months

Index tests	Number of index tests used: 5
	
	Types of index tests: self-report, pharmacy records, composite measure
	
	• Test 1. Self-report questionnaire
	  ◦ Validated scale: yes
	  ◦ Tool description: 30 day Self-report (5-point Likert item): "Standardized self-report adherence measures asked about adherence since; initiating ART, or the preceding 30-days". "Adherence questions were originally written in English, translated into Tamil or Telugu and independently backtranslated. Questionnaires were administered in local languages by trained staff experienced in HIV counselling and treatment." Threshold used was binary: '< Excellent' and 'Excellent'
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 100%
	• Test 2. Self-report questionnaire
	  ◦ Validated scale: not reported
	  ◦ Tool description: self-report "Last time missed": "Standardized self-report adherence measures asked about adherence since; initiating ART, or the preceding 30-days". "Adherence questions were originally written in English, translated into Tamil or Telugu and independently backtranslated. Questionnaires were administered in local languages by trained staff experienced in HIV counselling and treatment." Threshold used was binary: '> never' and 'never'
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 100%
	• Test 3. Self-report VAS
	  ◦ Validated scale: yes
	  ◦ Tool description: 30-day VAS: "An additional 30-day self-report measure was the visual analog scale (VAS) where patients indicated on a line marked from 0% to 100% the point that best corresponded to the percentage of pills taken".
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 95%
	• Test 4. Pharmacy records
	  ◦ Validated scale: not applicable
	  ◦ Tool description: medication possession ratio (MPR). This was calculated by dividing the days of ART dispensed by the period of time from ART start to the day of recruitment". "Patients attended monthly for medical review and picked-up ART from a pharmacy staffed by a dedicated pharmacist within the clinic".
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 100 %

McMahon 2013 *(Continued)*

- Test 5. Composite measure
  - Validated scale: not applicable
  - Tool description: combined self-report and MPR: 12-month medication possession ratio (MPR) (days of ART dispensed divided by the period of time from ART start to the day of recruitment) < 100% + suboptimal adherence on either of 2 self-report measures (< excellent adherence in last 30 days, or ever reported missing ART). Threshold used was binary: 'Low adherence' and 'High adherence'.
  - Blinding: no information
  - Threshold prespecified: yes
  - Adherence threshold used: 'high versus low'

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Artus HIV-1 RT-PCR (Qiagen) • Definition of viral non-suppression: HIV viral load > 200 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: baseline characteristics and dichotomous adherence estimates after 12-months ART were compared to 12-month viral load. • All patients received same reference standard: yes • Missing data: 230 were included in the study, after 12 months, 177 were on ART and 174 undertook a viral load. Also, for some of the index tests 170/174 were included; unclear why additional 4 were excluded. Missing data > 10%
Comparative	
Notes	Conflicts of interest: SRL receives payment for lectures (Viiv Healthcare and Janssen), payment for educational presentations (Janssen) and SRL's institution receives grant funding (Merck and Gilead). All other authors, no conflicts. Funding source: JM was supported by a fellowship from Tufts Medical Center Department of Geographic Medicine and Infectious Diseases, and an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship. The study was supported by a Lifespan/Tufts/Brown Center for AIDS Research NIH grant (1P30A142853-12). AM was supported by a Fogarty International Center training grant (5D43TW000237-15). MRJ was supported by an NIH Career Development Award (5K23AI074423-04). SRL is an NHMRC Practitioner Fellow. Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	

McMahon 2013 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between in-	Unclear		

McMahon 2013 *(Continued)*

dex test and reference standard?		
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Messou 2011

Study characteristics	
Patient Sampling	• Target population: HIV-infected adults who started ART • Recruitment: HIV-infected adults who started ART between February 2006 and May 2007 at one of three HIV outpatient clinics in Abidjan and showed up for their six-month visit were eligible for the study. • Inclusion criteria: HIV-infected adults who started ART between February 2006 and May 2007 at one of three HIV outpatient clinics in Abidjan and showed up for their six month visit were eligible for the study. • Exclusion criteria: not reported • Study design: prospective cohort study

Patient characteristics and setting	• Country: Cote d'Ivoire
	  ◦ World Bank Income classification: low-income
	  ◦ Study setting: clinic-based
	• Study dates: February 2006 to May 2007
	• Age of population (years), median (IQR): 36 (30 to 43)
	• Gender (male %): 75
	• Participants included/analysed: 925/1206 at 12 months
	• First- or second-line regimen: first-line
	  ◦ Type of ART: stavudine/AZT + 3TC + NVP/EFV
	  ◦ Time on ART at enrolment: treatment-naïve
	  ◦ Time on ART at measurement of viral load and adherence: 6 and 12 months

Index tests	Number of index tests used: 1
	
	Types of index tests: pharmacy records
	
	• Test 1. Pharmacy records
	  ◦ Validated scale: not applicable
	  ◦ Tool description: the medication possession ratio (MPR) was defined as the number of daily doses of antiretroviral drugs dispensed by the pharmacy to each patient, divided by that patient's total follow-up time in days since ART initiation.
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: > 95%; > 80%; > 65%; > 50%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: ANRS real-time PCR; Biocentric, Bandol, France

Messou 2011 *(Continued)*

	• Definition of viral non-suppression: HIV viral load > 300 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: association between MPR from baseline to month 12 and virologic failure was estimated. • All patients received same reference standard: yes • Missing data: at 6 months, 996/1206 patients included in the analysis. At 12 months, 925/1206 were included in the analysis. Patients were defined as lost to follow-up if: (i) their last contact with study team was less than month 12; (ii) they were not known to be dead or transferred out before month 12; (iii) no further information on their vital status could be obtained within the 6 months following study endpoint (i.e. between month 12 and month 18). Missing data > 10%
Comparative	
Notes	Conflicts of interest: none declared Funding source: Agence Nationale de Recherches sur le SIDA et les hepatitis virales (ANot reportedS 12136, ANot reportedS 12212), National Institute of Allergy and Infectious Diseases (R01 AI058736, K24 AI062476) and Institute of International Education Fulbright (Fellowship CS) Trial registry: Not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	

Messou 2011 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Meya 2009

Study characteristics	
Patient Sampling	• Target population: HIV-1-positive, aged > 18 years, established on first line NNRTI-based ART for ≥ six months • Recruitment: 500 patients were enrolled at a rate of approximately 10 patients per clinic day. Patients were randomly selected from the clinic reception using a list of random numbers. • Inclusion criteria: patients were screened and included in the study if they were HIV-1-positive, aged > 18 years, established on first-line NNRTI-based ART for ≥ six months and did not have viral loads monitored as per routine clinic practice. • Exclusion criteria: patients with acute illness were excluded from the study. • Study design: cross-sectional
Patient characteristics and setting	• Country: Uganda ◦ World Bank Income classification: low-income ◦ Study setting: clinic-based - adult clinic of the Infectious Disease Institute (IDI), Mulago Hospital, Makerere University in Kampala, Uganda

Meya 2009 *(Continued)*

	• Study dates: not reported
	• Age of population (years), median: 38.4
	• Gender (male %): 37
	• Participants included/analysed: 496/496
	• First- or second-line regimen: first-line
	  ○ Type of ART: first-line NTI-based ART
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: not reported; at least 6 months

Index tests	Number of index tests used: 2
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ○ Validated scale: yes
	  ○ Tool description: adherence was measured by self-report, using a modified Adult AIDS Clinical Trials Group adherence questionnaire validated in the setting. Participants were asked to report adherence patterns in the three days prior to enrolment, four weeks prior to enrolment, and since the initiation of ART. A VAS, as well as a question on whether treatment had ever been interrupted for more than two days, was included to assess adherence in the four weeks prior to enrolment and since the initiation of ART; adherence measure use was the question: "Have you missed ART in the last 30 days"; responses were Yes, No.
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 100%
	• Test 1. Self-report VAS
	  ○ Validated scale: yes
	  ○ Tool description: VAS, as well as a question on whether treatment had ever been interrupted for more than two days, was included to assess adherence in the four weeks prior to enrolment and since the initiation of ART; responses were Yes, No.
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 100%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Amplicor HIV-1 Monitor v1.5 – Roche, Switzerland • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information .
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this is a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: yes • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: the Division of Intramural Research of the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, USA. We also acknowledge support from the Career Development Award K23 AI060384 (LAS) Trial registry: not reported

Meya 2009 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the			Low concern

Meya 2009 *(Continued)*

reference standard does not match the question?		
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Mogosetsi 2018

Study characteristics	
Patient Sampling	• Target population: HIV-positive patients, initiating ART • Recruitment: prospective cohort study among patients down referred primarily from the Phedisong 4 clinic, which offers various primary health care services to patients, including ART • Inclusion criteria: age ≥ 18 years, patients initiating ART, patients who were ART-naïve and patients who had undergone the mandatory three adherence counselling classes recommended by the South African Department of Health • Exclusion criteria: not reported • Study design: prospective cohort study

Patient characteristics and setting	• Country: South Africa
	  ◦ World Bank Income classification: upper-middle-income
	  ◦ Study setting: clinic-based
	• Study dates: November 2012 to March 2013
	• Age of population (years), mean (SD): viral suppression group: 37 (9.3); non-suppression group: 35 (8.0)
	• Gender (male %): viral suppression group: 38; non-suppression group: 12
	• Participants included/analysed: 155/98
	• First- or second-line regimen: first-line
	  • Type of ART: PI-based
	  • Time on ART at enrolment: treatment-naïve
	  • Time on ART at measurement of viral load and adherence: 6 months

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ◦ Validated scale: yes (MMAS-4)
	  ◦ Tool description: the adherence of each patient was assessed by means of the Morisky Medication Adherence Scale (MMAS-4). This scale is a generic self-reporting measurement of patient behaviour in taking medication. It consists of four questions with a scoring of 0 for “Yes” and 1 for “No”, with a total range of 0-4

Mogosetsi 2018 *(Continued)*

	points. A score of 0 indicates high adherence, 1-2 medium adherence and 3-4, low adherence. ○ Blinding: no information ○ Threshold prespecified: yes ○ Adherence threshold used: 100%; 95%
Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: m2000 Real Time HIV-1 Viral Load System® supplied by Abbott • Definition of viral non-suppression: HIV viral load > 40 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: data were collected at 6 months. • All patients received same reference standard: yes • Missing data: 98/155 participants included in the analysis at 6 months. Missing were defaulters, deceased, transferred to another health facility, and discontinued participation. Missing data > 10%
Comparative	
Notes	Conflicts of interest: none declared Funding source: no funding received Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		

Mogosetsi 2018 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Moosa 2019

Study characteristics	
Patient Sampling	• Target population: HIV-tuberculosis (TB) co-infected patients receiving tuberculosis treatment • Recruitment: secondary analysis of two studies. The SAPiT study is a three-arm, open-label, randomized controlled trial conducted at the CAPRISA Thekwini HIV-tuberculosis clinic with HIV-tuberculosis co-infected patients receiving tuberculosis treatment. After completion of follow-up in the SAPiT trial, patients were offered enrolment into a prospective observational study, TB Recurrence upon Treatment with HAART (TRuTH), investigating the rate of TB recurrence in HIV-infected adults on ART who had completed pulmonary TB treatment. • Inclusion criteria: SAPiT trial inclusion criteria: To be included, patients had to be independently confirmed at the Department of Medical Microbioloy, Nelson R. Mandela School of Medicine, to have AFB smear positive disease, initiated on the standard tuberculosis treatment regimen at the PCZCDC, have a CD4+ count < 500 cells/mm^3 at screening and have no clinical contraindications to initiation of ART. Female participants were required to agree to use contraception while on efavirenz. • Exclusion criteria: no information on exclusion criteria for the SAPiT and TRuTH studies. In the current paper (secondary analysis), patients who never initiated ART, were lost to follow-up in the SAPiT trial, did not

Moosa 2019 *(Continued)*

	receive ART from the site's research pharmacy, and for whom pill count data was missing for more than 6 consecutive months in either study were excluded. • Study design: three-arm, open-label, randomized controlled trial (the SAPiT study); prospective observational study, (TRuTH study)

Patient characteristics and setting	• Country: South Africa
	  ○ World Bank Income classification: upper-middle-income
	  ○ Study setting: the SAPiT trial (protocol number: CAPRISA 003) was conducted at the CAPRISA eThekwini HIV-tuberculosis clinic. This adjoins one of the largest ambulatory (outpatient) tuberculosis facilities in South Africa, the Prince Cyril Zulu Communicable Disease Centre (PCZCDC) in Durban.The TRuTH study was based in Durban, KwaZulu-Natal, South Africa, an area where it was estimated that 70% of TB patients were HIV co-infected.
	• Study dates: SAPiT trial: June 2005 to July 2008; TRuTH observational study from November 2009 to July 2011 and follow-up was completed in 2014
	• Age of population (years), median (IQR): 34 (29 to 40)
	• Gender (male %): 45.2
	• Participants included/analysed: 270/268 (year 1), 201 (year 2) ,166 (year 3), 243 (year 4), 233 (year 5)
	• First or second-line regimen: first-line
	  ○ Type of ART: study patients were initiated on a once daily, weight-based ART regimen containing EFV or NVP plus 3TC and enteric coated didanosine (ddI) either during or after completion of tuberculosis treatment.
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: different categories: 1 year, 2 years, 3 years, 4 years, 5 years

Index tests	Number of index tests used: 1
	
	Types of index tests: tablet counts
	
	• Test 1. Tablet counts
	  ○ Validated scale: not applicable
	  ○ Tool description: adherence to ART in both studies were determined from pharmacy pill count data. Pill counts were conducted by the study pharmacist at monthly study visits in the SAPiT trial and at monthly or 3-monthly study visits in the TRuTH study. Adherence percentage was calculated using the following formula: (number of pills dispensed at previous visit - number of pills returned/reported remaining/lost at current visit)/number of pills that should have been ingested between visits (daily pill dose x no of days between visits) x 100. Optimal adherence was defined as ≥ 95% of doses taken in the time between the study visits. Pill count data were not available for ART that was dispensed in the CAT programme (time period between exit from SAPiT study and enrolment into TRuTH study). Pill count adherence was not assessed for visits where there was a clinician-initiated treatment interruption or where pill count data were missing.
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: SAPiT trial: Cobas® Amplicor HIV-1 Monitor, version 1.5, Roche; TRUth study: Cobas® Ampliprep-Roche TaqMan • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: pill counts were conducted by the study pharmacist at monthly study visits in the SAPiT trial and at monthly or 3-monthly study visits in the TRuTH study. Viral load done at screening, randomization and 6 monthly thereafter • All patients received same reference standard: yes

Moosa 2019 *(Continued)*

- Missing data: 414 completed SAPiT follow-up; 379 previously enrolled in SAPiT enrolled in TRuTH. Only 270 were included for the retrospective analysis. Data available for n = 268 at year 1, n = 201 at year 2, n = 166 at year 3, n = 243 at year 4, n = 233 at year 5. Missing data > 10% for years 2-5

Comparative	
Notes	Conflicts of interest: none reported Funding source: the research infrastructure for conducting the SAPiT trial, including data management, laboratory and pharmacy cores were established through the Comprehensive International Program of Research on AIDS grant (CIPRA, grant # AI51794). The US President's Emergency Plan for AIDS Relief (PEPfAR) funded the care of all the SAPiT patients; the Global Fund to fight AIDS, Tuberculosis and Malaria funded the cost for drugs used in the SAPiT trial. The TRUTH study was supported by the Howard Hughes Medical Institute, Chevy Chase, MD, USA (grant # 55007065) and the Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA) Cooperative Agreement Number UY2G/ PS001350–02. Patient care was supported by the KwaZulu-Natal Department of Health and the US President's Emergency Plan for AIDS Relief (PEPFAR; Washington DC, USA). KN and TG were supported by the Columbia University-South Africa Fogarty AIDS International Training and Research Program (AITRP) funded by the Fogarty International Center, National Institutes of Health (grant # D43TW00231). No funding was received for this retrospective study. Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		

Moosa 2019 *(Continued)*

If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		

Moosa 2019 *(Continued)*

Could the patient flow have introduced bias?	High risk

Mutwa 2014

Study characteristics	
Patient Sampling	• Target population: HIV-infected cART-naïve children below 15 years of age • Recruitment: children were usually referred from Kigali University Teaching Hospital (which is adjacent to the TRACplus clinic), nearby district hospitals, or health centres providing 'prevention of mother to child HIV transmission services'; a few children were diagnosed at the TRACplus facility itself. All children below the age of 15 years who initiated cART at the TRACplus clinic during the study period were given the opportunity to enrol in the study. • Inclusion criteria: HIV-infected cART-naïve children below 15 years of age who initiated cART • Exclusion criteria: not reported • Study design: prospective cohort study

Patient characteristics and setting	• Country: Rwanda
	  ◦ World Bank Income classification: low-income
	  ◦ Study setting: clinic- and hospital-based (TRACplus clinic, usually reffered from Kigali University Teaching Hospital which is adjacent to the TRACplus clinic), nearby district hospitals, or health centres)
	• Study dates: March 2008 to December 2009
	• Age of population (years), median (IQR): 7.4 (3.2 to 11.5)
	• Gender (male %): 43
	• Participants included/analysed: 123/104
	• First or second-line regimen: first-line
	  ◦ Type of ART: at study initiation in 2007, the 2007 Rwandan ART guidelines (based on the 2006 WHO ART guidelines) were operational, which recommended cART initiation in children and adolescents less than 15 years of age if they were classified as WHO paediatric clinical stage ITT or TV, or had a severe immunodeficiency; children enrolled in the study received cART, cotrimoxazole prophylaxis; they were initiated on a first-line cART regimen consisting of two NRTI (not reported TTs) and a nonnucleoside reverse TI. A cART regimen was defined as NVP-based, efavirenz-based or PI-based. From 2009 (revised Rwandian Guidelines) children known to have been exposed to nevirapine in the context of PMTCT were initiated on a first-line regimen with two TIs and a Pl.
	  ◦ Time on ART at enrolment: treatment-naïve
	  ◦ Time on ART at measurement of viral load and adherence: 6 months

Index tests	Number of index tests used: 1
	
	Types of index tests: composite measure
	
	• Test 1.Composite measure
	  ◦ Validated scale: not applicable
	  ◦ Tool description: self-report and pill count, and assessment was conducted at every clinic and pharmacy follow-up visit. The caregivers were asked questions by face-to-face interviewing using a structured questionnaire. They were asked how many doses of the prescribed medication the child had missed during the previous 30 days and at what time points this occurred, and reasons for non-adherence. Children were classified as non-adherent if having taken < 95% of the medication prescribed in the last 30 days. In addition, study nurses and pharmacy staff counted pill dispensed and returned, unused, assuming all the other pills were used.
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported

Mutwa 2014 *(Continued)*

	○ Adherence threshold used: 95%
Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Roche Cobas AmpliPrcp/Cobas TaqMan HIV-I, Roche Molecular Systems, France • Definition of viral non-suppression: HIV viral load > 40 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: viral load measured at enrolment and at months 3, 6, 12 and adherence measured at evey follow-up visit • All patients received same reference standard: yes • Missing data: 104/123 were included in the 12-month analysis. Missing data for > 10% of participants
Comparative	
Notes	Conflicts of interest: none declared Funding source: Infectious Disease Network for Treatment and Research in Africa Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		

Mutwa 2014 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Navarro 2014

Study characteristics	
Patient Sampling	• Target population: adult HIV-1-infected patients who were treatment-experienced and had poor adherence to HAART • Recruitment: all consecutive adult HIV-1-infected patients attending the HIV unit of University Hospital Vall d'Hebron in Barcelona • Inclusion criteria: All consecutive adult HIV-1-infected patients who were treatment-experienced and had poor adherence to HAART were included in an adherence programme since its introduc-

Navarro 2014 *(Continued)*

	tion in 2009. Treatment-experienced patients were defined as those who had received one or more previous HAART regimens. Patients could be receiving HAART or not at the time of entering the programme, and all of them had a detectable viral load. Patients were considered poor adherents if they had more than two consecutive detectable viral loads and admitted to having missed some doses between visits. Patients were included in the adherence program for 48 weeks. • Exclusion criteria: not reported • Study design: prospective cohort study

Patient characteristics and setting	• Country: Spain
	  ○ World Bank Income classification: high-income
	  ○ Study setting: hospital-based
	• Study dates: not reported
	• Age of population (years), median (IQR): 42.7 (36.9 to 47.2)
	• Gender (male %): 51.5
	• Participants included/analysed: 136/93
	• First or second-line regimen: unclear
	  ○ Type of ART: present HAART regimen (treatment prescribed at the entry in the adherence programme) mainly based on a ritonavir-boosted PI regimen (n = 99, 72.8%); NNRTI and other drugs such as INSTI-integrase strand transfer inhibitors
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: 48 weeks

Index tests	Number of index tests used: 2
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ○ Validated scale: yes
	  ○ Tool description: Simplified Medication Adherence Questionnaire (SMAQ), a validated questionnaire that assesses not only the adherence to HAART or not (yes or no), but also the percentage of compliance (< 30%, 30–60%, 60–90%, or > 90%). Patients are asked to answer the following questions: (1) "Do you ever forget to take your medicine?", (2) "Are you careless at times about taking your medicines?", (3) "If sometimes you feel worse, do you stop taking your medicine?", (4) "Taking into account only the last week, how often have you not taken your medicines?", (5) "Did you not take any of your medicines over the past weekend?", (6) "Over the past 3 months, how many days have you not taken any medicine at all?" The first five questions were used to asses the categorical variable adherence (yes or no) questionnaire and report their adherence to treatment over time (weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96)
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used: > 90%; > 60%
	• Test 2. Pharmacy records or secondary database analysis
	  ○ Validated scale: yes
	  ○ Tool description: based on a drug dispensing record at the pharmacy, the number of bottle refills divided by the number of months of follow-up, assuming that every bottle has enough pills for 1 month of treatment
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used: > 90%; > 60%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: not reported • Definition of viral non-suppression: HIV viral load > 50 copies/mL • Blinded to index test: no information

Navarro 2014 *(Continued)*

Flow and timing	• Time interval between index and reference tests: no explicit information on timing, just that both adherence and viral load were assessed at 48 weeks • All patients received same reference standard: not reported • Missing data: participants who had an undetectable viral load but who had not yet reached week 48 of follow-up at the moment of the analysis were not included in the analysis. 6 patients (4.4%) were lost to follow-up with a viral load > 50 copies/mL, and 7 patients had not yet reached week 48 of follow-up at the time of the analysis. Other patients had missing data as well, reasons not reported.
Comparative	
Notes	Conflicts of interest: no competing financial interests exist. Funding source: partially funded by the RD12/0017/0003 project as part of the Plan Nacional I +D+ i, Investigation Cientifica, Desarrollo e Innovación, and co-financed by ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER) Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Navarro 2014 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Nelson 2010

Study characteristics	
Patient Sampling	• Target population: HIV-1-infected treatment-naive patients from ARTEMIS phase III trial aimed at comparing the efficacy and safety of once-daily darunavir/ritonavir (800/100 mg) versus lopinavir/ritonavir (800/200 mg total daily dose), each with a fixed-dose background tenofovir and emtricitabine regimen • Recruitment: participants were randomly enrolled in routine clinical practice. • Inclusion criteria: ARTEMIS inclusion criteria included treatment-naive HIV-1-infected patients aged at least 18 years, with plasma HIV-1 RNA at least 5000 copies/mL. Patients coinfected with hepatitis B and/or C virus were allowed entry if their condition was clinically stable and they were not expected to require treatment during the trial.

Nelson 2010 *(Continued)*

	• Exclusion criteria: active AIDS-defining illness; any clinically significant disease; clinical or laboratory evidence of significantly decreased hepatic function or decompensation; acute viral hepatitis at screening or calculated creatinine clearance less than 70 mL/min. Individuals with primary HIV infection or those pregnant or breastfeeding were also excluded. Patients with grade 3 or 4 laboratory abnormalities (division of AIDS grading table) were not eligible with some exceptions (diabetes or asymptomatic glucose, triglyceride or cholesterol elevations) unless clinical assessment identified health risks. • Study design: a randomized, phase III, open-label multicentre trial

Patient characteristics and setting	• Country: 26 countries
	  ○ World Bank Income classification: all
	  ○ Study setting: clinic-based
	• Study dates: September 2005 to May 2008
	• Age of population (years), mean (SD): DRV/r: 36 (9); LPV/r: 35 (9)
	• Gender (male %): DRV/r: 70; LPV/r: 70
	• Participants included/analysed: 689/646
	• First or second-line regimen: unclear
	  ○ Type of ART: DRV/r; LPV/r; DRV/r + LPV/r
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: 96 weeks

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ○ Validated scale: not applicable
	  ○ Tool description: patients were asked to complete a modified medication adherence self-report inventory (M-MASRI) questionnaire and report their adherence to treatment over time (weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96)
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: > 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: VircoTYPE HIV-1 assays (Virco BVBA; Mechelen, Belgium) • Definition of viral non-suppression: HIV viral load > 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, just that both adherence and viral load were assessed at 96 weeks • All patients received same reference standard: not reported • Missing data: almost all eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: M. N. has received research grants and travel bursaries and served as an advisor to Johnson & Johnson/Tibotec/Janssen-Cilag. P.-M. G. has received grants and/or fees for conferences from BMS, Gilead, GSK, Tibotec and MSD, in the previous 12 months. R. D., V. S. and L. L. are employees of Tibotec. E. S. is an employee of Johnson & Johnson Pharmaceutical Services.

Nelson 2010 *(Continued)*

LLC. L. C. was an employee of Tibotec at the time of the study.

M. N., P.M. G. and L. C. do not own stock in any revelant companies.

R. D. has been granted restricted stock units in J&J.

E. S. and L. L. own stock options in J&J.

V. S. owns stock and stock options in J&J.

Jackie Phillipson (Gardiner-Caldwell Communications) provided assistance n drafting the manuscript and collating author contributions.

Funding source: Tibotec BVBA

Trial registry: NCT00258557

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			

Nelson 2010 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	

Oette 2006

Study characteristics	
Patient Sampling	• Target population: adults on stable HAART for more than 3 months • Recruitment: participants were randomly enrolled in routine clinical practice. • Inclusion criteria: unselected cohort that underwent therapeutic drug monitoring while on stable HAART for more than 3 months • Exclusion criteria: not reported • Study design: prospective cohort study

Patient characteristics and setting	• Country: Germany (not explicity reported)
	  ◦ World Bank Income classification: high-income
	  ◦ Study setting: clinic-based (university outpatient unit specialized for infectious diseases)
	• Study dates: 2002-2004
	• Age of population (years), mean (SD): 44.3 (10.4)
	• Gender (male %): 76.7
	• Participants included/analysed: 210/208

Oette 2006 *(Continued)*

- First- or second-line regimen: unclear
  - Type of ART: patients were treated with the following quantifiable antiretroviral drugs, used as a single or boosted agent: ritonavir-boosted amprenavir (n = 10), ritonavir-boosted atazanavir (n = 30), efavirenz (n = 24), ritonavir-boosted lopinavir (n = 78), nelfinavir (n = 17), NVP (n = 23), ritonavirboosted saquinavir (n = 4). The following combinations of compounds were applied: efavirenz and ritonavir-boosted lopinavir (n = 4), nevirapine and ritonavir-boosted amprenavir (n = 2), nevirapine and ritonavir-boosted lopinavir (n = 8), ritonavir-boosted lopinavir and amprenavir (n = 3), ritonavir boosted lopinavir and saquinavir (n = 7), ritonavir-boosted saquinavir and atazanavir (n = 1)
  - Time on ART at enrolment: at least 6 months
  - Time on ART at measurement of viral load and adherence: 24 weeks

Index tests	Number of index tests used: 2
	
	Types of index tests: self-reports
	
	• Test 1. Self-report on self-efficacy question
	  ◦ Validated scale: not applicable
	  ◦ Tool description: self-efficacy evaluating the belief of the patients to be able to be compliant with the prescribed combination scheme (yes; no)
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: sufficient; low
	• Test 2. Self-report on medication intake question
	  ◦ Validated scale: not applicable
	  ◦ Tool description:correctness of medication intake was assessed by the question of having forgotten a drug dose within the last 2 days, 14 days, last weekend or never.
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: always; not always

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: not reported • Definition of viral non-suppression: HIV viral load > 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but both measures were taken at 24 weeks. • All patients received same reference standard: not reported • Missing data: almost all eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: the laboratory costs were financed, in part, by the companies Abbott, Boehringer-Ingelheim, GlaxoSmithKline and Hoffmann La Roche. Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Oette 2006 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		

Oette 2006 *(Continued)*

Did all patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Okonji 2012

Study characteristics	
Patient Sampling	• Target population: pregnant/lactating women (32–34 weeks gestation to 24 weeks postpartum) • Recruitment: not reported • Inclusion criteria: participants were enrolled into this substudy, if they had adherence, viral load, and CD4 data in at least 3 time points during the intervention period and agreement to exclusively breastfeed up to 24 weeks postpartum. • Exclusion criteria: not reported • Study design: phase IIb open-label clinical trial

Patient characteristics and setting	• Country: Kenya
	  ◦ World Bank Income classification: low-income
	  ◦ Study setting: clinic-based (outpatients)
	• Study dates: July 2003 to November 2007
	• Age of population (years), median (IQR): 24 (15 to 43)
	• Gender (male %): 0 (all women)
	• Participants included/analysed: 500/434
	• First- or second-line regimen:
	  ◦ Type of ART: initially enrolled participants were initiated on NVP/lamivudine/zidovudine (3TC/ZDV) regardless of baseline CD4+ cell counts.
	  ◦ Time on ART at enrolment: at least 6 months
	  ◦ Time on ART at measurement of viral load and adherence: > 24 weeks

Index tests	Number of index tests used: 1
	
	Types of index tests: table counts
	
	• Test 1. Table counts
	  ◦ Validated scale: not applicable
	  ◦ Tool description: adherence was calculated as the percent of pills dispensed that were actually taken. Drug calendar and self-report data were used only to further probe adherence issues among participants. Through pill count, adherence was calculated by trained pharmacy staff over a given period, by subtracting the number of pills returned during every scheduled visit from the number dispensed. Participants were also given a simple user-friendly drug calendar to mark date, day, and time (times in day were described in pictorial forms, i.e. sunrise, sunset, etc.) when the pills were taken. Participants returned the drug calendars to the pharmacy technician for review during clinic visits. Last, self-report through standard questionnaires administered during routine study visits were used to assess adherence. Participants were asked the number of doses they missed in the past 3 days and within a specified recall period (within the last one month).
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: no

Okonji 2012 *(Continued)*

	○ Adherence threshold used: ≥ 95%
Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: amplicor version 1.5 monitor test standard (Roche Diagnostics Systems, Branchburg, New Jersey) • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit details on timing, just that both adherence and VL were tested at baseline, 14, and 24 weeks • All patients received same reference standard: yes • Missing data: yes; different numbers for adherence and viral load presented based on excluding different groups from analysis
Comparative	
Notes	Conflicts of interest: none declared Funding source: the Division of HIV/AIDS Prevention, Surveillance and Epidemiology, National Center for STD, HIV and TB Prevention, Atlanta, GA and by the Kenya Medical Research Institute (KEMRI) through a cooperative agreement with the US Centers for Disease Control and Prevention (KEMRI Protocol number 691/CDC Protocol number 3677) Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		

Okonji 2012 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Orrell 2003

Study characteristics	
Patient Sampling	• Target population: participants from the Cape Town AIDS Cohort (CTAC), a group of HIV-positive individuals presenting to University of Cape Town HIV clinics which serve largely indigent populations • Recruitment: not reported • Inclusion criteria: all antiretroviral naive patients who commenced ART on any established study by December 2000 were eligible for adherence monitoring. • Exclusion criteria: not reported

Orrell 2003 *(Continued)*

	• Study design: prospective cohort study

Patient characteristics and setting	• Country: South Africa
	  ◦ World Bank Income classification: upper-middle-income
	  ◦ Study setting: clinic-based (University of Cape Town HIV clinics)
	• Study dates: January 1996 to May 2001
	• Age of population (years), mean (SD): 33.4 (8.7)
	• Gender (male %): 57
	• Participants included/analysed: 289/278
	• First- or second-line regimen: unclear
	  ◦ Type of ART: all participants were antiretroviral-naive and provided written consent to participate in multicentre phase III clinical trials of combination ART. They were assigned to one of six multicentre phase III studies. Participants in two studies in 1996 were given dual therapy with an additional third concurrent, placebo-controlled and double-blinded drug (placebo versus a non-nuceoside reverse transcriptase inhibitor regimen). In the other four studies, participants were given triple therapy regimens.
	  ◦ Time on ART at enrolment: not reported; at least 6 months
	  ◦ Time on ART at measurement of viral load and adherence: 48 weeks

Index tests	Number of index tests used: 1
	
	Types of index tests: composite measure
	
	• Test 1. Composite measure: tablet counts + pharmacy records
	  ◦ Validated scale: not applicable
	  ◦ Tool description: adherence to therapy was assessed using clinic-based pill counts and pharmacy refill data over a period of 48 weeks. Patients were instructed to return all medication bottles and unused pills at each study visit, but were not told that the returns were to be counted. All tablets of each antiretroviral medication were counted prior to dispensing and upon return. Adherence to therapy was calculated using the formula: (sum of tablets dispensed – sum of tablets returned)/(total tablets prescribed over the 48-week study interval).
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: no
	  ◦ Adherence threshold used: > 95%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: not reported • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, just that both were measured at 48 weeks • All patients received same reference standard: not reported • Missing data: almost all eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: M. B. was partially funded by a grant from the BMS ‘Secure-The-Future’ fund. D. B. received funding from The Doris Duke Charitable Foundation. Trial registry: not reported

Orrell 2003 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear

Orrell 2003 *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Unclear	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk

Orrell 2017

Study characteristics	
Patient Sampling	• Target population: participants of an RCT at The Hannan Crusaid Treatment Centre in Gugulethu, Cape Town • Recruitment: entry into the study was offered consecutively to all eligible participants presenting to the clinic. • Inclusion criteria: participants were eligible for the parent study if they had their own mobile phone, signed an informed consent, and had either a baseline CD4 count below 350 cells/µL or a stage 3 or 4 AIDs-defining illness in keeping with the national HIV guidelines for starting ART. All patients on the parent study with viral load data available at week 16 or week 48 were included in this substudy. • Exclusion criteria: not reported • Study design: cohort (substudy of an RCT)

Patient characteristics and setting	• Country: South Africa
	  ◦ World Bank Income classification: upper-middle-income
	  ◦ Study setting: clinic-based (public sector urban ART outpatient clinic)
	• Study dates: July 2012 to April 2014
	• Age of population (years), mean (SD): 34.5 (9.1)
	• Gender (male %): 34.8
	• Participants included/analysed: 230/180
	• First- or second-line regimen: first-line
	  ◦ Type of ART: first-line treatment at the time of the study included tenofovir, lamivudine, and efavirenz, given as 3 separate tablets once a day. Toward the end of the study period in October 2013, a fixed-dose combination became available, but priority was given to naive patients entering care and few of the study participants were switched to the fixed-dose combination during the study. Zidovudine, stavudine, nevirapine, and lopinavir in combination with ritonavir were available as alternative agents.
	  ◦ Time on ART at enrolment: at least 6 months
	  ◦ Time on ART at measurement of viral load and adherence: 48 weeks (treatment-naive patients with 96 weeks follow-up in the trial)

Index tests	Number of index tests used: 4 Types of index tests: self-report; table count; pharmacy records or secondary database analysis; electronic monitoring (MEMS)

Orrell 2017 *(Continued)*

- Test 1. Self-report questionnaire
  - Validated scale: not applicable
  - Tool description: study staff who were not part of the clinical team asked each participant: "Did you swallow your pills yesterday/2 days ago/3 days ago?"
  - Blinding: no information
  - Threshold prespecified: yes
  - Adherence threshold used: 100%
- Test 2. Tablets count
  - Validated scale: not applicable
  - Tool description: not reported
  - Blinding: no information
  - Threshold prespecified: no
  - Adherence threshold used: ≥ 95%
- Test 3. Pharmacy records or secondary database analysis
  - Validated scale: not applicable
  - Tool description:
    - Pharmacy refill: gaps method (PR-gaps). This measure used pharmacy-dispensing quantities and refill visit dates to determine the number off medication-free days (days when the participant could not have had medication in hand) in each dispensing period. The number of medication-free days were subtracted from the number of days in the period, and the result divided by the number of days in the period (up to week 16 or up to week 48) to give an adherence percentage.
    - Pharmacy refill: average method (PR-average). An electronic dispensing system (iDART) was used at the site to record the date of ART dispensed and the quantity given to each participant. Obvious errors, such as date and dispensing duplications were removed. A cumulative PR-average measure was obtained at week 16 and week 48 visits by dividing the number of days of EFV, NPV or LPV/r tablets each patient received between study randomisation date and the visit date, by the number of days they were in care over the same period.
  - Blinding: no information
  - Threshold prespecified: no
  - Adherence threshold used: ≥ 95%
- Test 4. Electronic monitoring (MEMS)
  - Validated scale: not applicable
  - Tool description: Wisepill (electronic adherence monitoring)
  - Blinding: no information
  - Threshold prespecified: no
  - Adherence threshold used: ≥ 80%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: HIV-1 RNA 3.0 assay®, Bayer Healthcare, Leverkusen, Germany) • Definition of viral non-suppression: HIV viral load > 40 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing. All available adherence data were used from each individual who had an HIV-RNA drawn around week 48 (weeks 32–64) in a per-protocol analysis from the time they entered care until the date of the respective viral load. • All patients received the same reference standard: yes • Missing data: 180/230 patients retained at 48 weeks
Comparative	
Notes	Conflicts of interest: none declared Funding source: the Discovery Foundation supported CO through an Academic Fellowship Award in 2013 and EDCTP awarded CO a senior fellowship from 2012 to 2014: TA.2011.40200.015.

Orrell 2017 *(Continued)*

Trial registry: PACTR201311000641402

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Orrell 2017 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Ortega 2004

Study characteristics	
Patient Sampling	• Target population: patients attending outpatient services and receiving HAART • Recruitment: all patients attending outpatient services at the Hospitals of León and Bierzo, Spain • Inclusion criteria: patients treated with HAART with two NRTI and a PI not boosted with ritonavir • Exclusion criteria: not reported • Study design: cross-sectional

Patient characteristics and setting	• Country: Spain
	  ◦ World Bank Income classification: high-income
	  ◦ Study setting: hospital-based (outpatient service)
	• Study dates: January to June 2000
	• Age of population (years), mean (SD): 38 (7)
	• Gender (male %): 72
	• Participants included/analysed: 136/136
	• First or second-line regimen: unclear
	  ◦ Type of ART: HAART with two NRTI and a PI not boosted with ritonavir
	  ◦ Time on ART at enrolment: at least 6 months
	  ◦ Time on ART at measurement of viral load and adherence: not reported; at least 6 months

Index tests	Number of index tests used: 2

Ortega 2004 *(Continued)*

	Types of index tests: composite (self-report + pharmacy records)
	• Test 1. Composite measure (self-report interview + pharmacy refill records)
	  ○ Validated scale: not reported
	  ○ Tool description: patients provided information about the doses taken during the 4 days preceding the interview, and the delay in collecting drugs in the last 3 months was also registered.
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used:
	  ■ ≥ 10% forgotten doses
	  ■ ≥ 9 days delay
	• Test 2. Composite measure (self-reported interview + pharmacy refill records + other: plasmatic concentration of PIs)
	  ○ Validated scale: not reported
	  ○ Tool description: patients provided information about the doses taken during the 4 days preceding the interview, and the delay in collecting drugs in the last 3 months was also registered. In addition, plasmatic concentration of protease inhibitor were measured.
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used:
	  ■ ≥ 10% forgotten doses
	  ■ ≥ 9 days delay
	  ■ ≥ 50 ng/mL for indinavir, ≥ 1000 ng/mL for ritonavir, ≥ 250 ng/mL for saquinavir; ≥ 500 ng/mL for nelfinavir

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: not reported • Definition of viral non-suppression: HIV viral load ≥ 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this was a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: not reported • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: Wellcome Foundation and the Biomedical Research Institute (INBIOMED) of the University of León, Spain Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Ortega 2004 *(Continued)*

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		

Ortega 2004 *(Continued)*

Could the patient flow have introduced bias?	Low risk

Paolillo 2017

Study characteristics	
Patient Sampling	• Target population: HIV-infected adults enrolled in NIH-funded research studies at the University of California, San Diego, HIV Neurobehavioral Research Program (HNRP) from 2003 to 2015 • Recruitment: not reported • Inclusion criteria: participant's baseline visit at the HNRP who were receiving ART at the time of the visit and reported drinking alcohol in the previous 30 days • Exclusion criteria: non-drinkers • Study design: cohort (participant's baseline visit at the HNRP)

Patient characteristics and setting	• Country: USA
	  ◦ World Bank Income classification: high-income
	  ◦ Study setting: clinic-based (outpatient research program)
	• Study dates: 2003 to 2015
	• Age of population (years), mean (SD): 42.2 (8.6)
	• Gender (male %): 85.6
	• Participants included/analysed: 535/535
	• First- or second-line regimen: unclear
	  ◦ Type of ART: NRTI plus PI; NRTI plus NNRTI. Other less common ART regimen types included other combinations of the six ART drug classes.
	  ◦ Time on ART at enrolment: at least 6 months
	  ◦ Time on ART at measurement of viral load and adherence: median duration of exposure to ART was 63 months (IQR: 28 to 105)

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ◦ Validated scale: not applicable
	  ◦ Tool description: self-report AIDS Clinical Trial Group (ACTG), a questionnaire indicating any missed ART doses in the previous 4 days
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: yes
	  ◦ Adherence threshold used: 100%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: not reported • Definition of viral non-suppression: HIV viral load ≥ 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: not explicit, but seemed that both measures were taken on the same day • All patients received same reference standard: not reported • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.

Paolillo 2017 *(Continued)*

Comparative	
Notes	Conflicts of interest: none declared Funding source: Emily W. Paolillo is supported by an Institutional Ruth L. Kirschstein National Research Service Award (NRSA) T32 grant funded by the NIAAA within the National Institutes of Health (Award T32 AA013525). Data for this study was collected as part of five larger ongoing studies: 1) The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) is supported by awards N01 MH22005, HHSN271201000036C, and HHSN271201000030C from NIH; 2) the California NeuroAIDS Tissue Network (CNTN) is supported by awards U01MH083506, R24MH59745 from NIMH; 3) the HIV Neurobehavioral Research Center (not reported) is supported by Center award P30MH062512 from NIMH; 4) the Translational Methamphetamine AIDS Research Center (TMARC) is supported by Center award P50DA026306 from the National Institute on Drug Abuse (NIDA); and 5) a NIDA grant award P01DA1206507 Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			

Paolillo 2017 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	

Parienti 2010

Study characteristics	
Patient Sampling	• Target population: HIV-infected patients treated with ritonavir-boosted PI from two multicentre cohort studies (Etude et Surveillance par Pilulier électronique de l'Observance et de l'Incidence de la Réplication virale-ESPOIR and RE-search in Access to Care in the Homeless-REACH) • Recruitment: The ESPOIR cohort selected consecutive patients receiving or starting twice-a-day LPV/r–based regimens and monitored adherence in several outpatient clinics in France. The REACH cohort selected HIV-positive homeless and marginally housed individuals in San Francisco, California. • Inclusion criteria: not reported • Exclusion criteria: not reported • Study design: analysis of data from prospective cohort studies

Patient characteristics and setting	• Country: France, USA
	  ○ World Bank Income classification: high-income
	  ○ Study setting: hospital- and community-based (the ESPOIR cohort: several outpatient clinics in France; the REACH cohort: HIV-positive homeless and marginally housed individuals in San Francisco)
	• Study dates: December 2006 to December 2008
	• Age of population (years), mean (SD): 43.9 (7.5)
	• Gender (male %): 82
	• Participants included/analysed: 72/72

Parienti 2010 *(Continued)*

	• First- or second-line regimen: not reported
	  ○ Type of ART: The ESPOIR cohort: twice-a-day lopinavir-ritonavir–based regimens; REACH cohort: ritonavir-boosted PI
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: at least 24 months as cohort followed for this time

Index tests	Number of index tests used: 1
	
	Types of index tests: composite measure
	
	• Test 1. Composite measure (electronic monitoring ± tablet counts, lopinavir plasma levels)
	  ○ Validated scale: not reported
	  ○ Tool description: 6 caps of the Medication Event Monitoring System (MEMS) which measures patterns of missed doses with a time/date record of pill bottle opening behaviour. Average per cent dose adherence was defined as the number of MEMS events (pill bottle openings), divided by the number of prescribed doses, multiplied by 100. In addition, adherence was confirmed by measuring lopinavir plasma levels in the ESPOIR cohort and by having monthly unannounced pill counts in the REACH cohort.
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes; (1) number of days without a dose, defined as drug discontinuation for > 24 hours and < 48 hours, (2) number of treatment interruptions lasting ≥ 48 hours, and (3) the duration of the longest treatment interruption (in days)
	  ○ Adherence threshold used: > 95%; > 80%; > 70%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: not reported • Definition of viral non-suppression: HIV viral load > 50 copies/mL and > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: not reported • All patients received same reference standard: not reported • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: J.-J.P. reported that he has received travel grants, honoraria for presentation at workshops, and consultancy honoraria from Abbott, Boehringer Ingelheim, and Bristol-Myers Squibb. Y.Y. reported that he has received travel grants, honoraria for presentation at workshops, and consultancy honoraria from Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Merck, Pfizer, Roche, and Tibotec. All other authors: no conflicts declared Funding source: The ESPOIR cohort was supported by an Abbott Laboratories unrestricted grant (to Caen Côte de Nacre University hospital). The REACH cohort was supported by the National Institute of Mental Health (grant RO-54907) and the National Institute on Alcohol Abuse and Alcoholism (grant K-24 015287). Trial registry: not reported
Methodological quality	

Parienti 2010 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined			Unclear

Parienti 2010 *(Continued)*

by the reference standard does not match the question?		
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Unclear	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk

Parker 2017

Study characteristics	
Patient Sampling	• Target population: adults from AIDS Clinical Trials Group (ACTG) A5202, which randomized ART-naive, HIV-infected participants to receive placebo-controlled abacavir–lamivudine or TDF–emtricitabine with open-label ATV/r or EFV • Recruitment: not reported • Inclusion criteria: age ≥ 18 years, HIV type 1 infected, had 7 days or less of ART prior to enrolment, informed consent obtained • Exclusion criteria: significant drug or alcohol abuse thought likely to impact adherence • Study design: open-label RCT

Patient characteristics and setting	• Country: USA
	  ○ World Bank Income classification: high-income
	  ○ Study setting: not reported
	• Study dates: 2005 to 2009
	• Age of population (years), median (IQR): 38 (31 to 45)
	• Gender (male %): 83
	• Participants included/analysed: 1649/1857
	• First- or second-line regimen: unclear
	  ○ Type of ART: ATV/r or EFV
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: at least 6 months as RCT with 24 weeks follow-up time

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report single question
	  ○ Validated scale: not applicable
	  ○ Tool description: 6 potential responses to the question “When was the last time you missed any of your medications?” to assess adherence (never skip medications, more than 3 months ago, 1–3 months ago,

Parker 2017 *(Continued)*

2–4 weeks ago, 1–2 weeks ago, and within the past week). Participants who did not provide a self-report form were considered to be not adherent for that report.

- Never Skip Medications (3 categories): 1. Adherent (reported never or missing their last dose more than 1 month ago on both the week 8 and week 24 reports); 2. Not adherent (reported missing their last dose within the past month on the available week 8 and week 24 reports or missing both reports); 3. Inconsistent (reported adherence on either the week 8 or week 24 report and either not adherent on the other report or missing the other report)
- Missed pill more than 3 months ago or never skip medications (3 categories): 1. Adherent (reported never or missing their last dose more than 1 month ago on both the week 8 and week 24 reports); 2. Not adherent (reported missing their last dose within the past month on the available week 8 and week 24 reports or missing both reports); 3. Inconsistent (reported adherence on either the week 8 or week 24 report and either not adherent on the other report or missing the other report)
- Missed pill 1-3 months ago, more than 3 months ago or never skip medications (3 categories): 1. Adherent (reported never or missing their last dose more than 1 month ago on both the week 8 and week 24 reports); 2. Not adherent (reported missing their last dose within the past month on the available week 8 and week 24 reports or missing both reports); 3. Inconsistent (reported adherence on either the week 8 or week 24 report and either not adherent on the other report or missing the other report)
- Missed pill 2-4 weeks ago, 1-3 months ago, more than 3 months ago or never skip medications (3 categories): 1. Adherent (reported never or missing their last dose more than 1 month ago on both the week 8 and week 24 reports); 2. Not adherent (reported missing their last dose within the past month on the available week 8 and week 24 reports or missing both reports); 3. Inconsistent (reported adherence on either the week 8 or week 24 report and either not adherent on the other report or missing the other report)
- Missed pill 1-2 weeks ago, 2-4 weeks ago, 1-3 months ago, more than 3 months ago or never skip medications (3 categories): 1. Adherent (reported never or missing their last dose more than 1 month ago on both the week 8 and week 24 reports); 2. Not adherent (reported missing their last dose within the past month on the available week 8 and week 24 reports or missing both reports); 3. Inconsistent (reported adherence on either the week 8 or week 24 report and either not adherent on the other report or missing the other report)

- Blinding: not reported
- Threshold prespecified: not reported
- Adherence threshold used: adherent or inconsistent, non-adherent

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Roche Amplicor Monitor Assay Version 1.5 • Definition of viral non-suppression: HIV viral load > 200 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: viral load measured at 24 weeks; adherence behavior through week 24 • All patients received same reference standard: yes • Missing data: 89% continued on study after the week-24 visit.
Comparative	
Notes	Conflicts of interest: A. C. C reported research grants to her institution from Bristol-Myers Squibb, Merck & Co., and Roche Molecular Systems; Data Safety and Monitoring Board membership for Merck & Co.–sponsored clinical trials; and has developed educational presentation for International Antiviral Society-USA. E. S. D. is a consultant/advisor for Bristol Myers Squibb, Gilead, Janssen, Merck, Teva, and ViiV and has received research support from Gilead, Merck, and ViiV. All other authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors considered relevant to the content of the manuscript have been disclosed.

Parker 2017 *(Continued)*

Funding source: National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH; AI042006, AI068636, AI069481 and UM1AI068634) and the Harvard University Center for AIDS Research, an NIH-funded program (P30 AI060354)

Trial registry: AIDS Clinical Trials Group A5202

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			

Parker 2017 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Pasquau 2018

Study characteristics	
Patient Sampling	• Target population: adults with a positive HIV-1 antibody and/or PCR test, receiving any triple treatment containing a boosted PI • Recruitment: not reported • Inclusion criteria: patients infected with HIV-1, documented with a positive HIV-1 antibodies test and/or positive PCR confirmed for HIV-1 RNA, with an undetectable VL within the last six months and on triple antiretroviral therapy with any boosted PI. For women with childbearing potential, negative urine pregnancy test during the screening visit • Exclusion criteria: pregnancy or nursing, acute hepatitis, documented resistance to LPV/r or failure on a PI therapy, concomitant therapy with drugs contraindicated for use with LPV/r, known history of drug addiction or chronic alcohol consumption, current active opportunistic infection or documented infec-

Pasquau 2018 *(Continued)*

	tion within 4 weeks of screening, renal disease with creatinine clearance < 60 mL/min, concomitant use of nephrotoxic or immunosuppressor drugs including corticosteroids, interleukin-2 or chemotherapy, prior medical history of psychiatric disorders such as depressive syndrome, schizophrenia or psychotic disease • Study design: open-label RCT

Patient characteristics and setting	• Country: Spain
	  ○ World Bank Income classification: high-income
	  ○ Study setting: hospital-based
	• Study dates: January 2010 to December 2011
	• Age of population (years), mean (SD): monotherapy group 44.5 (8); triple therapy group 45.2 (9)
	• Gender (male %): monotherapy group: 71.4; triple therapy group: 71.8
	• Participants included/analysed: 225/197
	• First- or second-line regimen: unclear
	  ○ Type of ART: LPV/r in monotherapy or continuing combined antiretroviral triple treatment with a boosted PI
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: at least 6 months as RCT with 24 weeks follow-up time

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ○ Validated scale: yes (GEEMA adherence questionnaire)
	  ○ Tool description: this questionnaire included six individual questions. Four of the questions were qualitative ("Do you ever forget to take your medicine?", "Are you careless at times about taking your medicine?", "Sometimes if you feel worse, do you stop taking your medicine?" and "Did you not take any of your medicine over the past weekend?"); the other two questions ("Thinking about the last week. How often have you not taken your medicine?" and "Since the last visit how many days have you not taken any medicine at all?") were independently quantified and analysed.
	  ○ Blinding: no reported
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used: 100% (overall GEMMA quetionnaire)

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: not reported • Definition of viral non-suppression: HIV viral load > 200 copies/mL and > 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: 24 weeks • All patients received same reference standard: not reported • Missing data: 197 out of 225 study participants were included in the analysis.
Comparative	
Notes	Conflicts of interest: J. Pasquau has received financial grants and/or honoraria from Janssen-Cilaq, Bristol-Myers-Squibb, AbbVie, Merck Sharp& Dohme, ViiV&Gilead as speaker for fees and/or as Advisor fees. M.l. Montes has served as a speaker for Jannsen, BMS, ViiV, AbVie, a consultant for Janssen, BMS and Abbie. J. Vergas has received research grants and/or honoraria for advisories and/or conferences from Boehringer Ingelheim, GSK, ViiV, BMS, Abbott, Gildead, Janssen, Roche Farma and Merck.

Pasquau 2018 *(Continued)*

J. Hernandez Quero has received financial grants and or honoraria from Jannsen-Cilaq, Bristol-Myers-Squibb, Abbvie, Merck Sharp & Dohme, ViiV & Gilead as speaker fees and/or as a Advisor fees.

F. Orihuela has received payment for training sessions from AbbVie, Boehring Ingelheim, Bristol-Myers Squibb, Gilead Scieneces, Janssen, Merck-Sharp & Dohme and ViiV Healthcare.

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Funding source: AbbVie Spain (ACA-SPAI-08-16). The study was sponsored by the Spciedad Andaluza de Enfermedades Infecciosas (SAEI). AbbVie had a role in the study design, preparation of the final report and manuscript writing.

Trial registry: NCT 01166477; EudraCT number 2009-014430-25

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		

Pasquau 2018 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Phillips 2019

Study characteristics	

Phillips 2019 *(Continued)*

Patient Sampling	• Target population: women who were enrolled in the MCH-ART study at the Midwife-Obstetric Unit, Gugulethu Community Health Centre, Cape Town • Recruitment: not reported • Inclusion criteria: the first 150 women between 36 and 60 months postpartum who agreed to participate and had blood drawn for ARV assays • Exclusion criteria: women who were pregnant or had switched to second-line ART • Study design: cross-sectional

Patient characteristics and setting	• Country: South Africa
	  ◦ World Bank Income classification: upper-middle-income
	  ◦ Study setting: community health centre
	• Study dates: March 2013 to March 2017 (MCH-ART parent study)
	• Age of population (years), mean: 33
	• Gender (male %): 0 (all women)
	• Participants included/analysed: 137/137
	• First- or second-line regimen: first-line
	  ◦ Type of ART: first-line regimen of TDF (300 mg), emtricitabine (200 mg) or lamivudine 300 mg (XTC), and EFV 600 mg, provided as a once-daily fixed-dose combination
	  ◦ Time on ART at enrolment: at least 6 months
	  ◦ Time on ART at measurement of viral load and adherence: median (IQR): 3.9 years (3.7 to 4.0)

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ◦ Validated scale: not applicable
	  ◦ Tool description: medication adherence in the past 30 days was measured using a simple, 3-item scale.
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: not reported
	  ◦ Adherence threshold used: 100%; 80%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 assay; Roche Diagnostics, Branchburg, New Jersey • Definition of viral non-suppression: HIV viral load > 400 copies/mL and > 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: adherence measured and blood drawn for viral load testing both at the same day (study visit) • All patients received same reference standard: yes • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: The President's Emergency Plan for AIDS Relief (PPFAR) through the National Institute of Child Health and Human Development (NICHD), grant number 1R01HD074558 and 1R01HD080465. The University of Cape Town (UCT) Clinical PK Laboratory is supported by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health under award numbers UM1 AI068634, UM1 AI068636, and UM1 AI106701. Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) at UCT

Phillips 2019 *(Continued)*

was provided by the National Institute of Allergy and Infectious Diseases (U01 AI068632), The Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Institute of Mental Health grant AI068632. Ms Phillips receives partial funding from the South African Department of Science and Technology/National Research Foundation (DST - not reported), Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, Stellenbosch, South Africa. Dr Orrell is partially supported through DAIDS grants (1R01AI122300–01, 1R34MH108393-01 and 2UM1AI0695-08).

Trial registry: NCT01933477 (parent study)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowl-	Unclear		

Phillips 2019 *(Continued)*

edge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Pulido 2009

Study characteristics	
Patient Sampling	• Target population: all patients enrolled in the OK and OK04 clinical trials randomized to receive LPV/r monotherapy • Recruitment: likely consecutive • Inclusion criteria: all patients enrolled in the OK and OK04 clinical trials randomized to receive LPV/r monotherapy ... Briefly, patients included in both trials did not have a history of virological failure while receiving a protease inhibitor, were receiving two NRTIs and LPV/r for ≥ 1 month prior to randomization and had serum HIV-1 RNA < 50 copies/mL for ≥ 6 months prior to randomization. • Exclusion criteria: pregnancy, presence of serum hepatitis B surface antigen in patients treated with lamivudine, emtricitabine or tenofovir disoproxil fumarate, need for treatment with agents known to have potential major interactions with LPV/r and major psychiatric diseases as assessed by the investigator • Study design: two arms from two RCTs

Patient characteristics and setting	• Country: Spain
	  ○ World Bank Income classification: high-income
	  ○ Study setting: clinic-based
	• Study dates: OK 04 trial: December 2004 to June 2006; OK pilot trial: May 2003 to August 2004
	• Age of population (years), median (range): OK pilot: 42 (25-54); OK 04: 41 (28-78)
	• Gender (male %): OK pilot: 81; OK 04: 76
	• Participants included/analysed: 121/121

Pulido 2009 *(Continued)*

- First- or second-line regimen: unclear
  - Type of ART: LPV/r monotherapy
  - Time on ART at enrolment: ≥ 6 month
  - Time on ART at measurement of viral load and adherence: at least 6 months; suppressed: median (IQR) 23 (15-32) months and non-suppressed: median (IQR): 26 (13-34) months on LPV/r

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ○ Validated scale: yes (GEEMA adherence questionnaire)
	  ○ Tool description: this questionnaire included six individual questions. Four of the questions were qualitative ("Do you ever forget to take your medicine?", "Are you careless at times about taking your medicine?", "Sometimes if you feel worse, do you stop taking your medicine?" and "Did you not take any of your medicine over the past weekend?"); the other two questions ("Thinking about the last week. How often have you not taken your medicine?" and "Since the last visit how many days have you not taken any medicine at all?") were independently quantified and analysed. A missed dose on ≥ 2 visits in the week prior to study visit was considered as non-adherence.
	  ○ Blinding: no information
	  ○ Threshold prespecified: yes
	  ○ Adherence threshold used: 100%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: automatized RNA extraction in an Cobas AmpliPrep instrument followed by quantification using the Cobas TaqMan HIV1 in a TaqMan 48 analyzer (Roche Molecular Systems, Inc., Branchburg, New Jersey, USA) • Definition of viral non-suppression: HIV viral load > 50 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: up to one week • All patients received same reference standard: yes • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: FP is the recipient of a BAE grant from the Instituto de Salud Carlos III, Spanish Ministry of Health. JRA is an investigator from the Programa de Intensificación de la Actividad Investigadora, National Health System (I3SNS) 2008 INT07/147. FP and JRA have received consulting and lecture fees from Abbott Laboratories, Bristol–Myers Squibb, Gilead Sciences, GlaxoSmith-Kline and Roche. RD has received grant support and lecture fees from Abbott Laboratories. MJP-E was an occasional speaker and advisor for Abbott Labora-tories, Bristol–Myers Squibb, Boeringher–Ingelheim, Gilead, GlaxoSmithKline, Roche and Tibotec. J Portilla has received lecture fees from Abbott Laboratories, Bristol–Myers Squibb, GlaxoSmithKline, Roche, Schering–Plough and Boehringer–Ingelheim. BC has served as a consultant on advisory boards, speakers' bureaus and in the conduct of clinical trials with Roche, Boehringer–Ingelheim, Abbott Laboratories, Bristol–Myers Squibb, GlaxoSmithKline, Gilead, Tibotec, Merck, Janssen, Pfizer, Siemens, Monogram Biosciences and Panacos. The other authors declared no competing interests.

Pulido 2009 *(Continued)*

Funding source: Abbott Laboratories and the Fundación de Investigación Médica Mutua Madrileña

Trial registry: NCT00114933

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Pulido 2009 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Sangeda 2014

Study characteristics	
Patient Sampling	• Target population: adults with HIV starting ART or being on ART at a clinic • Recruitment: convenient sample • Inclusion criteria: HIV-infected adult patients either starting ART or being on ART who attended an HIV/AIDS Care and Treatment Centre at Amana District Hospital in Dar es Salaam, Tanzania, in 2010 • Exclusion criteria: < 18 years, pregnancy, having opportunistic infections, or malignancy • Study design: prospective cohort study

Patient characteristics and setting	• Country: Tanzania
	  ○ World Bank Income classification: low-income
	  ○ Study setting: clinic-based
	• Study dates: May to July 2010
	• Age of population (years), median (IQR): 39 (34 to 47)
	• Gender (male %): 36.2
	• Participants included/analysed: 220/162
	• First- or second-line regimen: not reported
	  ○ Type of ART: not reported
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: median (IQR): 37 months (30 to 48)

Index tests	Number of index tests used: 3 Types of index tests: self-report, tablet counts, and pharmacy records or secondary database analysis

Sangeda 2014 *(Continued)*

- Test 1. Self-report tool
  - Validated scale: yes
  - Tool description: two major sections: 1) a VAS which probed the percentage of doses taken in the previous month, and 2) two questions from the Swiss HIV Cohort Study Adherence Questionnaire (SHCS-AQ) regarding frequency of missed doses and if a patient ever missed two consecutive doses (drug holiday) in the previous month
  - Blinding: no information
  - Threshold prespecified: yes
  - Adherence threshold used:
    - VAS: 90%; 95%; 100%
    - Two questions: 100%
- Test 2. Tablet count
  - Validated scale: not applicable
  - Tool description: at each visit, pills remaining in bottles were counted and the proportion of these pills to the dispensed pills during the previous visit was calculated based on the dose and the number of days dispensed. The pill count adherence percent was obtained by dividing the number of pills consumed by the total number of pills at the beginning of the given interval and multiplied by 100.
  - Blinding: no information
  - Threshold preespecified: not reported
  - Adherence threshold used: 50%; 55%; 60%; 65%; 70%; 75%; 80%; 85%; 90%; 95%; 100%
- Test 3. Pharmacy records or secondary database analysis
  - Validated scale: not applicable
  - Tool description: Refill adherence was not calculated on a monthly basis to reduce an error of a few additional pills left over at the end of each refill period, but on the cumulative sum of the days that a patient was late for ARV pick-up appointments in each month over the year, divided by the total number of days over all periods between pick-up periods in the year of study, resulting in the percentage of time the patient was without medication over the whole year. Refill adherence was 100% if all pills during the scheduled refill period had been picked up on time. Refill percent values above 100 for patients who refilled earlier than scheduled were rounded to 100 percent.
  - Blinding: no information
  - Threshold preespecified: yes
  - Adherence threshold used: 50%; 55%; 60%; 65%; 70%; 75%; 80%; 85%; 90%; 95%; 100%

Adherence measurements were taken at four time points during a one-year follow-up, including at recruitment (zero), one, two, and 12 months after recruitment. Overall adherence for each method was the mean of the measurements taken at the four time points and this mean was considered in subsequent analyses. For self-report measures and tablet counts, the 12-month visit adherence measure was used; for pharmacy refill, only the overall measure was used.

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: not reported • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: for self-report measures and tablet count, the adherence and viral load measures were at the same visit. For pharmacy refill, an overall measure of adherence during the whole time period was used. • All patients received same reference standard: no • Missing data: of 220 patients followed for a year, 58 were not included in analysis. Missing data > 10%
Comparative	
Notes	Conflicts of interest: none declared

Sangeda 2014 *(Continued)*

Funding source: The Belgian Technical Cooperation; the Fonds voor Wetenschappelijk Onderzoek Vlaanderen; MRC grant in association with University of Manchester's Health Research Centre; authors' respective institutions; Sida, under Muhimbili University of Health and Allied Sciences (MUHAS) small grants scheme

Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted	Unclear		

Sangeda 2014 *(Continued)*

without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Segeral 2010

Study characteristics	
Patient Sampling	• Target population: adults with HIV/AIDS receiving HAART for at least six months • Recruitment: likely consecutive (survey) • Inclusion criteria: HAART prescribed according to WHO recommendations (WHO stages III and IV, irrespective of the CD4 cell count, or asymptomatic patients with CD4 cell counts ≤ 200/µL) both to ARV-naive patients and to patients having previously ARV paid for themselves; all patients who had at least one adherence assessment were included in the analysis. • Exclusion criteria: not reported • Study design: cross-sectional

Patient characteristics and setting	• Country: Cambodia
	  ○ World Bank Income classification: low-income
	  ○ Study setting: outpatient clinic
	• Study dates: not reported
	• Age of population (years), median (IQR): 35 (31 to 41)
	• Gender (male %): 58
	• Participants included/analysed: 341/259
	• First- or second-line regimen: first-line NNRTI-based regimens
	  ○ Type of ART: HAART combination was (AZT or d4T)/3TC/EFV initially, but was then switched to (AZT or d4T)/3TC/NVP after July 2004, owing to EFV supply problems
	  ○ Time on ART at enrolment: at least 6 months
	  ○ Time on ART at measurement of viral load and adherence: not reported; at least 6 months

Segeral 2010 *(Continued)*

Index tests	Number of index tests used: 3
	
	Types of index tests: self-report, visual analog scale, drug plasma concentration
	
	• Test 1. Self-report questionnaire
	  ◦ Validated scale: not reported
	  ◦ Tool description: the questionnaire consisted of three questions focussing on recent drug intake: (i) "Did you miss any HAART doses during the last four days?," (ii) "Were you late for any of your intakes by more than two hours during the last four days?," and (iii) "Did you miss any HAART doses last week-end?"
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: yes
	  ◦ Adherence threshold used: 100%
	• Test 2. A visual analog scale
	  ◦ Validated scale: yes
	  ◦ Tool description: patients were asked to answer the question: "In general, would you say you take your treatment?
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: "never" (score 1) and "always" (score 10). Any answer different from 10 was considered to represent nonadherence.
	  ◦ Adherence threshold used: score 9, score 10
	• Test 3. Composite measure (self-report questionnaire + drug plasma concentration)
	  ◦ Validated scale: not reported
	  ◦ Tool description: the questionnaire consisted of three questions focussing on recent drug intake: (i) "Did you miss any HAART doses during the last four days?," (ii) "Were you late for any of your intakes by more than two hours during the last four days?," and (iii) "Did you miss any HAART doses last week-end?" Patients were asked to come to the clinic in the morning without having taken their daily dose of NVP, and 12 hours after their last dose of EFV. EFV and NVP plasma concentrations measured by using high-performance liquid chromatography; concentrations below 1000 ng/mL and 3000 ng/mL, respectively, were considered non-adherence.
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: yes
	  ◦ Adherence threshold used: 100%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: ANS second-generation (G2) real-time RT-PCR • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this was a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: yes • Missing data: patients who did not have adherence measurements were excluded from analysis; 13 patients (3.8%) died, 14 (4.1%) were lost to follow-up, 9 (2.6%) were directed to other centres, 12 were on an LPV/r-containing regimen, 8 were on a triple NRTI combination, and 25 could not be evaluated.
Comparative	
Notes	Conflicts of interest: none declared Funding source: ESTHER programme Trial registry: not reported
Methodological quality	

Segeral 2010 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined			Low concern

Segeral 2010 *(Continued)*

by the reference standard does not match the question?		
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Segeral 2018

Study characteristics	
Patient Sampling	• Target population: adults with HIV on PI-based second-line ART regimen for at least 6 months • Recruitment: likely consecutive; patients were exhaustively enrolled if they were HIV-infected adults • Inclusion criteria: HIV infection, > 18 years, current PI-based second-line ART treatment since at least 6 months and willing to participate and consent to signature • Exclusion criteria: ongoing PI-based second-line regimen for less than 6 months at time of study intake • Study design: cross-sectional

Patient characteristics and setting	• Country: Cambodia
	  ◦ World Bank Income classification: low-income
	  ◦ Study setting: 13 representative ART sites (6 in Phnom Penh and 7 in provinces)
	• Study dates: recruitment from February 2013 to April 2014
	• Age of population (years), median (IQR): 42 (37 to 48)
	• Gender (male %): 61.8
	• Participants included/analysed: 1348/1317
	• First- or second-line regimen: second-line
	  ◦ Type of ART: PI-based second-line regimen
	  ◦ Time on ART at enrolment: at least 6 months
	  ◦ Time on ART at measurement of viral load and adherence: not reported; at least 6 months

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ◦ Validated scale: yes (14-item validated scale)
	  ◦ Tool description: patients provided information about the doses taken during the 4 days preceding the survey, about whether they respected the dose schedule during the previous 4 days and 4 weeks, and whether treatment interruption had occurred

Segeral 2018 *(Continued)*

	for at least two consecutive days within the previous 4 weeks. The algorithm proposed by (Carrieri 2001). was used to calculate the adherence score corresponding to the 4 days preceding the survey, by comparing the number of pills taken with those prescribed. ◦ Blinding: no information ◦ Threshold prespecified: yes ◦ Adherence threshold used: 100%; ≥ 80%
Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: G2 Generic HIV-1 VL ANRS kit (Biocentric, Bandol, France) conducted at National Center for HIV/AIDS, Dermatology and STD (NCHADS) laboratory • Definition of viral non-suppression: HIV viral load > 250 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this was a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: yes • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: French National Agency for Research on AIDS and Viral Hepatitis (ANRS) Trial registry: NCT01801618

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		

Segeral 2018 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Spire 2008

Study characteristics	
Patient Sampling	• Target population: HIV-infected adults receiving ART at a hospital • Recruitment: not reported • Inclusion criteria: patients who had been receiving ART for 24 (± 2 months) as part of HIV program run by Médecins sans Frontières, in collaboration wth the Ministry of Health of Cambodia, at the Infectious Disease department in Khmero-Sovietic Friendship hospital in Phnom Penh • Exclusion criteria: not willing to participate • Study design: cross-sectional

Patient characteristics and setting	• Country: Cambodia
	  ○ World Bank Income classification: low-income
	  ○ Study setting: hospital-based
	• Study dates: December 2004 to December 2005
	• Age of population (years), median (IQR): 36 (32 to 40)

Spire 2008 *(Continued)*

- Gender (male %): 57.5
- Participants included/analysed: 346/346
- First- or second-line regimen: first-line
  - Type of ART: ARV treatment-naïve at ART initiation (95.4%). A total of 280 patients were receiving a first-line ART regimen associating d4T, 3TC (lamivudine) and EFV while 56 were receiving d4T, 3TC and NVP and the remaining 10 another first-line regimen
  - Time on ART at enrolment: 24 ± 2 months
  - Time on ART at measurement of viral load and adherence: 24 months

Index tests	Number of index tests used: 1
	
	Types of index tests: composite
	
	• Test. Composite measure (self-report questionnaire + two VAS; range 1-6)
	  ◦ Validated scale: yes
	  ◦ Tool description: a face-to-face interview based on a standardized questionnaire translated into Khmer was administered by an external member of staff. This questionnaire included several questions about patient's adherence to ART in the 4 days or the 4 weeks prior to the interview. Five questions regarding adherence to HAART were included in all self-administered questionnaires according to the methodology established by the AIDS Clinical Trial Group. Adherence to ART was assessed using a dichotomous score already validated in previous studies. Patients were first asked to list for each drug included in their HAART regimen the number of pills taken all of their prescribed doses in the 4 days before the visit. In addition, two visual analog scales measuring adherence in general and in the last 4 weeks were completed. Patients who reported scores < 5 were reclassified as non-adherent.
	  ◦ Blinding: no information
	  ◦ Threshold prespecified: yes
	  ◦ Adherence threshold used: 100%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: real-time PCR technology which allows quantification of HIV-1 non-B subtypes including those circulating in Asia performed at HIV/hepatitis laboratoty of Necker Enfants Malades Hospital, Paris • Definition of viral non-suppression: HIV viral load > 40 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: both measures taken at 24 months after initiation of ART, but this was a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: yes • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: not reported Funding source: Médecins sans Frontières and Sidact Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Spire 2008 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it prespecified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			

Spire 2008 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Tabb 2018

Study characteristics	
Patient Sampling	• Target population: HIV-positive young people who attended a monthly youth-focused HIV clinic • Recruitment: not reported • Inclusion criteria: HIV-positive young people who knew their HIV status attending a youth-focussed HIV clinic called 'Teen Club' (at either Kilimanjaro Christian Medical Centre or Mawenzi Regional Referral Hospital in Moshi) to receive education on topics such as stigma, adherence, and sexual reproductive health • Exclusion criteria: not reported • Study design: cross-sectional

Patient characteristics and setting	• Country: Tanzania
	  ◦ World Bank Income classification: low-income
	  ◦ Study setting: youth-focussed HIV clinic
	• Study dates: December 2013-December 2014 (Kilimanjaro); February to July 2015 (Moshi)
	• Age of population (years), median (IQR): 16 (14 to 18)
	• Gender (male %): almost 50%
	• Participants included/analysed: 227/227
	• First- or second-line regimen: both first- and second-line regimens
	  ◦ Type of ART: first-line regimens included two NRTI and a NNRTI of either NVP or EFV; second-line regimens included two NRTIs and a RTV-boosted PI of either LPV or ATV
	  ◦ Time on ART at enrolment: at least 6 months
	  ◦ Time on ART at measurement of viral load and adherence: not reported; at least 6 months

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report questionnaire
	  ◦ Validated scale: not reported
	  ◦ Tool description: a structured questionnaire was administered by trained, native Swahili-speaking, female research assistants which included queries on self-reported adherence by asking dichotomously, "Have you missed any doses of your medication in the last two weeks, yes or no?" and categorically, "Think about the past week (7 days); on average, how often did you miss a dose of medication?" Response options included, "(1) once a day; (2) more than once a week, but not every day; (3) once a week; or (4) I don't miss my medicine." Inadequate adherence by self-report was defined as reporting any missed ART doses on either of the survey items.
	  ◦ Blinding: no information

Tabb 2018 *(Continued)*

	○ Threshold prespecified: not reported ○ Adherence threshold used: 100%
Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: HIV-1 real-time PCR; the Abbott m2000, Abbott laboratories, Illinois, USA • Definition of viral non-suppression: HIV viral load > 400 copies/mL • Blinded to index test: no information
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this was a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: yes • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: the current work was supported by Duke University Center for AIDS Research, an NIH-funded program; International Research Scientist Development Award funded by the Fogarty International Center and the National Institute of Mental Health; the Global Health Fellows Program of the National Institutes of Health funded by the Fogarty International Center and the National Institute of Mental Health; the Infectious Diseases Society of America Medical Scholars Program. The National Institute of Allergy and Infectious Diseases at the National Institutes of Health funded analyses of hair samples. Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		

Tabb 2018 *(Continued)*

If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Zoufaly 2013

Study characteristics	
Patient Sampling	• Target population: HIV-1 infected children on ART at the HIV service • Recruitment: all children who attended for routine follow-up and drug refill from September 2010 to August 2011 • Inclusion criteria: HIV-1-infected paediatric patients on ART attending Bamenda Regional Hospital with informed consent obtained by parents or legal guardians

Zoufaly 2013 *(Continued)*

	• Exclusion criteria: no plasma was available, > 18 years at enrolment, caregivers or children did not consent for participation in the study • Study design: cross-sectional

Patient characteristics and setting	• Country: Cameroon
	  ○ World Bank Income classification: lower-middle-income
	  ○ Study setting: hospital-based
	• Study dates: September 2010 to August 2011
	• Age of population (years), median (IQR): 8.8 (6.1 to 11.4)
	• Gender (male %): 52.8
	• Participants included/analysed: 230/174
	• First- or second-line regimen: unclear
	  ○ Type of ART: ART containing two NVP in all children < 2 years irrespective of CD4+ T-cell count and thereafter according to absolute CD4+ T-cell count level. LPV/r was used when children were recently exposed to NVP in prevention of mother-to-child transmission regimens or in second-line regimens. EFV was used in case of non-tolerance of NVP.
	  ○ Time on ART at enrolment: median 3.4 years
	  ○ Time on ART at measurement of viral load and adherence: not reported; at least 6 months

Index tests	Number of index tests used: 1
	
	Types of index tests: self-report
	
	• Test 1. Self-report number of daily doses taken
	  ○ Validated scale: not applicable
	  ○ Tool description: adherence reported by the child or caregiver was categorized according to the number of full daily doses taken in the previous 28 days, and recorded by a trained study nurse.
	  ○ Blinding: no information
	  ○ Threshold prespecified: not reported
	  ○ Adherence threshold used: 95%; 75%

Target condition and reference standard(s)	Target condition: viral non-suppression • Reference standard: HIV-1 real-time PCR; Abbott laboratories, Illinois, USA • Definition of viral non-suppression: HIV viral load > 200 copies/mL • Blinded to index test: yes
Flow and timing	• Time interval between index and reference tests: no explicit information on timing, but this was a cross-sectional study so likely to be measured simultaneously • All patients received same reference standard: yes • Missing data: none. All eligible participants with viral load test and adherence measures were included in the main analysis.
Comparative	
Notes	Conflicts of interest: none declared Funding source: partly funded by ESTHER Germany Trial registry: not reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns

Zoufaly 2013 *(Continued)*

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Index test)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Zoufaly 2013 *(Continued)*

Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

3TC: lamivudine
ACTG: AIDS Clinical Trials Group
AFB: Acid Fast Bacilli
AIDS: acquired immunodeficiency syndrome
ANRS: National Agency for AIDS Research
ART: antiretroviral therapy
ARV: antiretroviral
ATV: atazanavir
AZT: zidovudine
CD4: cluster of differentiation 4
CDC: centres for disease control and prevention
CTAC: community training and assistance centre
d4T: stavudine
ddI: didanosine
DNA: deoxyribonucleic acid
DRV/r: darunavir/ritonavir
EAMD: electronic adherence monitoring device
EFV: efavirenz
ELISA: enzyme-linked immunosorbent assay
FDC: fixed drug combination
FTC: emtricitabine
G2: second generation
GEEMA: Grupo Español para el Estudio Multifactorial de la Adherencia
GPO: Government Pharmaceutical Organization
HAART: highly active antiretroviral therapy
HIV: Human immunodeficiency virus
HNRP:HIV Neurobehavioral Research Program
iDART: intelligent dispensing of ART
IQR: interquartile range
INSTI: integrase strand transfer inhibitors
ITT: intention-to-treat
LPV: lopinavir
LPV/r: ritonavir-boosted lopinavir
MCH-ART: Maternal Child Health ART
MEMS: medication event monitoring system
MMAS(-4): Morisky medication adherence scale 4
M-MASRI: modified medication adherence self-report inventory
MPR: medication possession ratio
NA: not applicable
NCT: National Clinical Trial
NHLS: national health laboratory services
NIAID: national institute of allergy and infectious diseases
NVP: nevirapine
NNRTI: nonnucleoside reverse transcriptase
NRTI: nucleoside reverse transcriptase inhibitors
NTI: non-structured treatment interruption
NtRTI: nucleoside reverse transcriptase inhibitor
PACTG: pediatric AIDS clinical trials group
PCR: Polymerase chain reaction
PCZCDC: Prince Cyril Zulu Communicable Diseases Centre
PEP: post-exposure prophylaxis
PI: protease inhibitor
PIT: pills identification test
PMTCT: prevention of mother to child transmissions

RAM:resistance-associated mutations
RCT: randomised control trial
REACH:Reversing the Epidemic in Africa with Choices in HIV Prevention
RNA: ribonucleic acid
RPV: ripivirine
RTV: ritonavir
Rx: treatment
SHCS-AQ: Swiss HIV cohort study adherence questionnaire
SMAQ: simplified medication adherence questionnaire
STD: standard
TB: tuberculosis
TDF: tenofovir disoproxil fumarate
TRuTH: TB recurrence upon treatment with HAART
ULN: upper limit of normal
VAS: visual analogue scale
VL: viral load
WHO: World Health Organization
ZDV: zidovudine

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 ART regimen in a person who has not yet had documented virological suppression on this regimen.
EACS 2017	Confirmed (< 1 month) HIV viral load > 50 copies/mL 6 months after starting therapy (initiation or modification) in people on ART. Depending on the HIV viral load 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.

ART: antiretroviral therapy

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 infection medicines; point-of-care laboratories

Table 2. Health service nomenclature *(Continued)*

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

CD4: cluster of differentiation

Table 3. Excluded studies: duplicate reference

Excluded studies: duplicate reference (N = 37)
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5. Barfod 2005a Barfod TS, Gerstoft J, Rodkjaer L, Pedersen C, Nielsen H, Møller A, et al. Patients' answers to simple questions about treatment satisfaction and adherence and depression are associated with failure of HAART: a cross-sectional survey [corrected] [published erratum appears in AIDS Patient Care & STDS 2005 Aug;19(8):544]. AIDS Patient Care & STDs 2005;19(5):317-25
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8. Bien-Gund 2021a

Table 3. Excluded studies: duplicate reference *(Continued)*

Bien-Gund CH, Ho JI, Bair EF, Marcus N, Choi RJ, Szep Z, et al. Financial incentives and real-time adherence monitoring to promote daily adherence to HIV treatment and viral suppression among people living with HIV: a pilot study. Journal of Acquired Immune Deficiency Syndromes 2021;87(1):688-92
9. Brittain 2018a Brittain K, Remien RH, Mellins CA, Phillips TK, Zerbe A, Abrams EJ, et al. Determinants of suboptimal adherence and elevated HIV viral load in pregnant women already on antiretroviral therapy when entering antenatal care in Cape Town, South Africa. AIDS Care 2018;30(12):1517-23
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11. Chabikuli 2010a Chabikuli NO, Datonye DO, Nachega J, Ansong D. Adherence to antiretroviral therapy, virologic failure and workload at the Rustenberg Provincial Hospital. South African Family Practice 2010;52(4):350-5
12. Cruz 2014a Cruz MLS, Cardoso CAA, Darmont MQ, Souza E, Andrade SD, D'Al Fabbro MM, et al. Viral suppression and adherence among HIV-infected children and adolescents on antiretroviral therapy: results of a multicenter study. [Supressão viral e adesão entre crianças e adolescentes vivendo com HIV na terapia antirretroviral: resultados de um estudo multicêntrico]. Jornal de Pediatria 2014;90(6):563-71
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Table 3. Excluded studies: duplicate reference *(Continued)*

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Table 4. Excluded studies: wrong reference standard

Excluded studies: wrong reference standard (N = 104)
Abouyannis 2011
Abouyannis M, Menten J, Kiragga A, Lynen L, Robertson G, Castelnuovo B, et al. Development and validation of systems for rational use of viral load testing in adults receiving first-line ART in sub-Saharan Africa. AIDS 2011;25(13):1627-35
ACTRN12618001882213 2018
Evaluation of an antiretroviral therapy adherence intervention by pharmacist among HIV infected patients [A randomized controlled study to evaluate the effect of pharmacist led educational intervention on antiretroviral therapy adherence among human immunodeficiency virus infected patients]. anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376259&isReview=true? (first received 20 Nov 2018)
Ahoua 2009
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Table 4. Excluded studies: wrong reference standard *(Continued)*

Ahoua 2011
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Alcoba 2003
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Apornpong 2021
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Table 5. Excluded studies: wrong index test *(Continued)*

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Young J, Smith C, Teira R, Reiss P, Jarrin Vera I, Crane H, et al. Antiretroviral pill count and clinical outcomes in treatment-naive patients with HIV infection. HIV Medicine 2018;19(2):132-42

Table 6. Excluded studies: not possible to extract data for 2x2 table

Excluded studies: not possible to extract data for 2x2 table (N = 468)
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Ahmed 2007
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Aids Alert 2007
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Almeida-Brasil CC, Moodie EEM, Cardoso TS, Nascimento ED, Ceccato M. Comparison of the predictive performance of adherence measures for virologic failure detection in people living with HIV: a systematic review and pairwise meta-analysis. AIDS Care 2019;31(6):647-59
Alsan 2016
Alsan M, Beshears J, Nguyen M, Choi J, Armstrong W, Madrian B, et al. A commitment contract for virologic suppression in poorly adherent HIV+ individuals. AIDS 2016;24(E-1):449
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Amirkhanian 2018
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Arrabal-Duran P, Rodriguez-Gonzalez CG, Chamorro-de-Vega E, Gijon-Vidaurreta P, Herranz-Alonso A, Sanjurjo-Saez M. Switching to a rilpivirine/emtricitabine/tenofovir single-tablet regimen in RNA-suppressed patients infected with human immunodeficiency virus 1: effectiveness, safety and costs at 96 weeks. International Journal of Clinical Practice 2017;71(8):e12968
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Ba S, Raugi DN, Smith RA, Sall F, Faye K, Hawes SE, et al. A trial of a single-tablet regimen of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate for the initial treatment of human immunodeficiency virus type 2 infection in a resource-limited setting: 48-week results from Senegal, West Africa. Clinical Infectious Diseases 2018;67(10):1588-94
Bagwell 2018
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Ballif 2009
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Bardon 2020
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Bien-Gund 2021
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Brown LK, Whiteley L, Mena L, Craker L, Arnold T. 3.62 Enhancing health among youth living with HIV using an Iphone game. Journal of the American Academy of Child and Adolescent Psychiatry 2018;57(10):S202
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Camargo 2012
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Carrico 2014
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Castagna 2014
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Chendi 2019
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Cluver 2021
Cluver L, Shenderovich Y, Toska E, Rudgard WE, Zhou S, Orkin M, et al. Clinic and care: associations with adolescent antiretroviral therapy adherence in a prospective cohort in South Africa. AIDS (London, England) 2021;35(8):1263-71
Codina 2004
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Cohen 2013
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Collazos 2010
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Collier 2005
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Costa 2018
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Coyle 2019
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Craker 2019
Craker L, Tarantino N, Whiteley L, Brown L. Measuring antiretroviral adherence among young people living with HIV: observations from a real-time monitoring device versus self-report. AIDS Behavior 2019;23(8):2138-45
Crauwels 2019
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Crockett 2020
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Cunningham 2019
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Deering 2009
Deering KN, Shannon K, Sinclair H, Parsad D, Gilbert E, Tyndall MW. Piloting a peer-driven intervention model to increase access and adherence to antiretroviral therapy and HIV care among street-entrenched HIV-positive women in Vancouver. AIDS Patient Care and STDs 2009;23(8):603-9
DeJesus 2008
DeJesus E, Ruane P, McDonald C, Garcia F, Sharma S, Corales R, et al. Impact of switching virologically suppressed, HIV-1-infected patients from twice-daily fixed-dose zidovudine/lamivudine to once-daily fixed-dose tenofovir disoproxil fumarate/emtricitabine. HIV Clinical Trials 2008;9(2):103-14
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De Lazzari E, Lonca M, Rojas J, Gonzalez-Cordon A, Blanch J, Inciarte A, et al. A 24-week pilot study of dual maintenance therapy with raltegravir and lamivudine. Aids 2019;33(12):1891-6
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NCT03109743. Group clinical visit adherence intervention for HIV+ women of color. clinicaltrials.gov/ct2/show/NCT03109743 (first received 12 April 2017)
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NCT03198962. Use of amphetamine-type stimulants & its relationship with HIV incidence and antiretroviral adherence among MSM and TG. clinicaltrials.gov/ct2/show/NCT03198962 (first received 26 June 2017)
NCT03200054 2017
NCT03200054. Postpartum adherence clubs for antiretroviral therapy. clinicaltrials.gov/ct2/show/NCT03200054 (first received 27 June 2017)
NCT03218592 2017
NCT03218592. ENLIGHTEN: establishing novel antiretroviral imaging for hair to elucidate non-adherence. clinicaltrials.gov/ct2/show/NCT03218592 (first received 14 July 2017)
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Table 7. Excluded studies: viral load and adherence not measured at the same time

Excluded studies: viral load and adherence not measured at the same time (N = 62)
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Anigilaje 2014
Anigilaje EA, Dabit OJ, Tyovenda RK, Emebolu AJ, Agbedeh AA, Olutola A, et al. Effects of leisure activities and psychosocial support on medication adherence and clinic attendance among children on antiretroviral therapy. HIV/AIDS (Auckland, N.Z.) 2014;6:127-37
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Arrivillaga 2009

Table 7. Excluded studies: viral load and adherence not measured at the same time *(Continued)*

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Bangsberg 2010
Bangsberg DR, Ragland K, Monk A, Deeks SG. A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV plus homeless and marginally housed people. Aids 2010;24(18):2835-40
Barfod 2005
Barfod TS, Gerstoft J, Rodkjaer L, Pedersen C, Nielsen H, Moller A, et al. Patients' answers to simple questions about treatment satisfaction and adherence and depression are associated with failure of HAART: a cross-sectional survey. AIDS Patient Care and STDs 2005;19(5):317-25
Beckwith 2018
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Burack 2010
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Campbell 2010

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Table 7. Excluded studies: viral load and adherence not measured at the same time *(Continued)*

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Simoni 2014

Table 7. Excluded studies: viral load and adherence not measured at the same time *(Continued)*

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Table 8. Excluded studies: wrong patient population

Excluded studies: wrong patient population (N = 31)
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Table 8. Excluded studies: wrong patient population *(Continued)*

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Goldman 2008
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Table 8. Excluded studies: wrong patient population *(Continued)*

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Shah 2007
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Excluded studies: viral load obtained from medical records (N = 158)
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Belzer 2014
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Bienczak 2017
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Bisson 2008

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Blumenthal 2014	
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Boarts 2006	
Boarts JM, Sledjeski EM, Bogart LM, Delahanty DL. The differential impact of PTSD and depression on HIV disease markers and adherence to HAART in people living with HIV. AIDS and Behavior 2006;10(3):253-61	
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Bonn-Miller MO, Oser ML, Bucossi MM, Trafton JA. Cannabis use and HIV antiretroviral therapy adherence and HIV-related symptoms. Journal of Behavioral Medicine 2014;37(1):1-10	
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Chaiyachati 2011	
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Cooper 2021	
Cooper RL, Brown LL, Tabatabai M, Haas DW, Shepherd BE, Myers HF, et al. The effects of perceived stress and cortisol concentration on antiretroviral adherence when mediated by psychological flexibility among Southern black men living with HIV. AIDS and Behavior 2021;25(2):645-52	
Crane 2017	
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Cruz 2014	
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Table 9. Excluded studies: viral load obtained from medical records *(Continued)*

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Farley 2008	
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Fox 2018	
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Gutierrez 2012	

Table 9. Excluded studies: viral load obtained from medical records *(Continued)*

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Kacanek 2015	
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Kagee 2012	
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Kalichman 2016	

Table 9. Excluded studies: viral load obtained from medical records *(Continued)*

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Table 10. Ongoing studies

Ongoing studies
1. ACTRN12613000265774. The SMART study: can a smartphone application improve adherence to antiretroviral therapy? [In patients with HIV infection can a smartphone application designed to enhance patients' understanding of their illness (compared to a reminder device), increase rates of adherence to antiretroviral therapy?]. anzctr.org.au/Trial/Registration/TrialReview.aspx?id=363542&isReview=true (first received 27 February 2013)
2. Arbune M, Potârnichie OM, Păsărin L, Mârţu S. Ethical dilemma related to therapeutic nonadherence of HIV youth. Revista Română de Bioetică 2014;12(1):72-9
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6. CTRI/2013/06/003777. A study to assess whether an information technology (IT) system with a cell phone interface, will improve treatment effectiveness in HIV-1 subjects [A randomized, controlled trial to assess the impact of TAMA (Health IT System) on treatment effectiveness in HIV-1 infected subjects initiated on first-line antiretroviral therapy. - projectUNITE]. trialsearch.who.int/?TrialID=CTRI/2013/06/003777 (first received 24 June 2013)
7. CTRI/2018/01/011169. Assessment of adverse drug reactions, drug-drug interactions and medication adherence outcomes among elderly HIV seropositive patients in comparison with young HIV seropositive patients undergoing highly active antiretroviral therapy. ctri.nic.in/Clinicaltrials/advsearch.php (first received 5 January 2018)
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15. IRCT20100601004076N23. MHealth for antiretroviral adherence [The acceptability and effectiveness of a mobile-health intervention to improve adherence to treatment and medication for people living with HIV]. who.int/trialsearch/Trial2.aspx?TrialID=IRCT20100601004076N23 (first received 9 March 2019)

Table 10. Ongoing studies *(Continued)*

16. ISRCTN35514212. Evaluating the impact of an intervention providing support with ART [Applying the Medical Research Council guidance to evaluate an intervention to support uptake and adherence to antiretroviral therapy for HIV]. doi.org/10.1186/ISRCTN35514212 (first received 21 February 2014)

17. ISRCTN69078957. Children with human immunodeficiency virus (HIV) in Africa - pharmacokinetics and acceptability/adherence of simple antiretroviral regimens (CHAPAS-3 trial) [A randomised trial to compare the toxicity and pharmacokinetics of three fixed-dose combination based antiretroviral regimens for treatment of human immunodeficiency virus (HIV) infected children in Africa]. doi.org/10.1186/ISRCTN69078957 (first received 15 April 2010)

18. ISRCTN78797542. Randomised controlled trial on Highly Active AntiRetroviral Therapy (HAART), social networks, and adherence in Mozambique [A randomized control trial of peer-delivered modified directly observed therapy for HAART in Mozambique]. doi.org/10.1186/ISRCTN78797542 (first received 31 January 2006)

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27. NCT00051805. Promoting adherence to anti-HIV drug regimens [Promoting adherence to antiretroviral regimens]. clinicaltrials.gov/ct2/show/NCT00051805 (first received 17 January 2003)

28. NCT00134602. Pediatric impact: promoting adherence to medications among HIV-infected children [An intervention to promote adherence to antiretroviral medications among HIV-infected children 5-12 years of age]. clinicaltrials.gov/ct2/show/NCT00134602 (first received 25 August 2005)

29. NCT00135382. Study switching HIV-1 infected patients with an undetectable viral load on a first protease inhibitor-based regimen to an efavirenz-based regimen [A Phase 3 study switching HIV-1 infected patients with an undetectable viral load on a first protease inhibitor-based regimen to an efavirenz-based regimen]. clinicaltrials.gov/ct2/show/NCT00135382 (first received 26 August 2005)

30. NCT00160849. Lopinavir/r monotherapy as maintenance therapy after long term viral suppression [Study on the feasibility of antiretroviral therapy with a single agent - lopinavir/r - in patients treated with HAART and with viral load below 80 copies/ml]. clinicaltrials.gov/ct2/show/NCT00160849 (first received 12 September 2005)

31. NCT00194545. Effect of medication diaries on adherence to highly active antiretroviral drugs among HIV-1 infected Kenyan children [Effect of medication diaries on adherence to highly active antiretroviral drugs among HIV-1 infected Kenyan children]. clinicaltrials.gov/ct2/show/NCT00194545 (first 19 September 2005)

Table 10. Ongoing studies *(Continued)*

32. NCT00196612. Once daily antiretroviral therapy in HIV infected adults treated with HAART [Phase II randomized trial comparing efficacy and safety of the maintenance of a HAART association protease inhibitor containing versus a once daily antiretroviral triple association, in HIV adult patients with undetectable viral load ANRS 099 ALIZE]. clinicaltrials.gov/ct2/show/NCT00196612 (first received 20 September 2005)
33. NCT00199979. Zidovudine/lamivudine + nevirapine twice daily, versus tenofovir + lamivudine + nevirapine once daily in ARV-naive patients [Multicenter, randomized, open-label trial, assessing the efficacy of zidovudine, lamivudine and nevirapine combination administered twice daily, versus the association of tenofovir, lamivudine and nevirapine, once daily, in antiretroviral naive HIV-1 infected patients]. clinicaltrials.gov/ct2/show/NCT00199979 (first received 20 September 2005)
34. NCT00203853. Evaluation of an intervention on adherence to Highly Active Antiretroviral Therapy (HAART) in HIV infected adults [Evaluation of an intervention (consisting of an electronic reminder device, pillboxes, and monthly telephone calls) on adherence to Highly Active Antiretroviral Therapy (HAART) in HIV infected adults]. clinicaltrials.gov/ct2/show/NCT00203853 (first received 20 September 2005)
35. NCT00224445. Boosted atazanavir and truvada given once-daily - BATON study [Boosted atazanavir and truvada given once-daily (BATON Study): a Phase 4 study of safety, efficacy & adherence in HIV infected, antiretroviral naïve subjects treated with a simple once-daily regimen]. clinicaltrials.gov/ct2/show/NCT00224445 (first received 23 September 2005)
36. NCT00234962. Study of adherence effects and clinical outcomes of kaletra based HIV antiviral therapy [Factors associated with adherence in a cohort of HIV positive subjects on a first time PI containing HAART regimen: observational study of the impact of adherence on viral load for a HAART regimen containing kaletra vs other selected PI containing HAART]. clinicaltrials.gov/ct2/show/NCT00234962 (first received 10 October 2005)
37. NCT00273780. Highly Active Antiretroviral Therapy (HAART) adherence interventions [HAART adherence interventions in Africa: an RCT]. clinicaltrials.gov/ct2/show/NCT00273780 (first received 9 January 2006)
38. NCT00324688. Safety study of once a day ART and opiate substitute [Open-label multicenter study to assess the efficacy, the tolerability and the adherence of a once daily (QD) taken antiretroviral therapy (ART) containing the NtRTI tenofovir DF 300 mg in combination with the best suitable once a day regimen being 1 NRTI plus 1 PI or 1 NRTI plus 1 NNRTI in HIV-1-infected IVDU- patients with opiate substitution being either antiretroviral-naive or with suppressed viral load and without a history of virological failure]. clinicaltrials.gov/ct2/show/NCT00324688 (first received 11 May 2006)
39. NCT00339092. Modified directly observed therapy for improving antiretroviral therapy adherence in people with HIV [A RCT of HIV adherence case management and modified directly observed therapy]. clinicaltrials.gov/ct2/show/NCT00339092 (first received 20 June 2006)
40. NCT00408642. An enhanced adherence support programme for Highly Active Antiretroviral Therapy (HAART) [An enhanced adherence support programme for HAART]. clinicaltrials.gov/ct2/show/NCT00408642 (first received 7 December 2006)
41. NCT00602758. Effectiveness of enhanced counseling and observed therapy on antiretroviral adherence in people with HIV [ART adherence: enhanced counseling and observed therapy]. clinicaltrials.gov/ct2/show/NCT00602758 (first received 28 January 2008)
42. NCT00716040. Social-psychological intervention to improve adherence to HAART [Effectiveness of a social-psychological intervention to improve adherence to antiretroviral drug regimens for AIDS: a randomized controlled trial]. clinicaltrials.com/hiv-infections/NCT00716040/ (first received March 2008)
43. NCT00799864. A study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of rilpivirine (TMC278) in human immunodeficiency virus infected adolescents and children aged greater than or equal to 6 years [A Phase II, open label, single arm trial to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of rilpivirine (TMC278) in antiretroviral naive HIV-1 infected adolescents and children aged >= 6 to <18 years]. clinicaltrials.gov/ct2/show/NCT00799864 (first received 1 December 2008)
44. NCT00821366. Effective AIDS treatment and support in the free state (FEATS) [Effective AIDS treatment and support in the free state (FEATS): adherence and nutritional support for effective and sustainable antiretroviral treatment in resource constrained settings]. clinicaltrials.gov/ct2/show/NCT00821366 (first received 13 January 2009)

Table 10. Ongoing studies *(Continued)*

45. NCT00959361. Evaluation of effectiveness of pharmaceutical care on the adherence of HIV-positive patients to antiretroviral therapy [Evaluation of effectiveness of pharmaceutical care on the adherence of HIV-positive patients to antiretroviral therapy - randomized clinical trial]. clinicaltrials.gov/ct2/show/NCT00959361 (first received 14 August 2009)

46. NCT01006005. Adherence-suppression-resistance relationships for atripla compared to historical antiretroviral regimens. clinicaltrials.gov/ct2/show/NCT01006005 (first received 1 November 2009)

47. NCT01049568. Cell phone reminders intervention [A pilot study using cell phone interactions to improve medication adherence in adolescents who have previously failed antiretroviral therapy due to non-adherence]. clinicaltrials.gov/ct2/show/NCT01049568 (first received 14 January 2010)

48. NCT01061762. Adherence intervention for people with low-literacy [HIV treatment adherence intervention for people with poor literacy skills]. clinicaltrials.gov/ct2/show/NCT01061762 (first received 3 February 2010)

49. NCT01122186. Intervention targeting medication adherence and methamphetamine use in HIV positive men (ACE). clinicaltrials.gov/ct2/show/NCT01122186 (first received 13 May 2010)

50. NCT01347437. Improving antiretroviral medication adherence among HIV-infected youth [Improving antiretroviral medication adherence among HIV-infected youth: Phase II]. clinicaltrials.gov/ct2/show/NCT01347437 (first received 4 May 2011)

51. NCT01505660. Randomized controlled trial using patient reported outcomes and care managers to improve HIV medication adherence in routine clinical care. clinicaltrials.gov/ct2/show/NCT01505660 (first received 6 January 2012)

52. NCT01559805. Intervention to improve engagement in care among newly diagnosed HIV-positive men [Efficacy trial of a brief health enhancement intervention for newly diagnosed men]. clinicaltrials.gov/ct2/show/NCT01559805 (first received 21 March 2012)

53. NCT01641367. A5288/MULTI-OCTAVE: management using latest technologies to optimize combination therapy after viral failure [Management using the latest technologies in resource-limited settings to optimize combination therapy after viral failure (MULTI-OCTAVE)]. clinicaltrials.gov/ct2/show/NCT01641367 (first received 16 July 2012)

54. NCT01760759. Antiretroviral therapy adherence and secondary prevention of human immunodeficiency virus. clinicaltrials.gov/ct2/show/NCT01760759 (first received 4 January 2013)

55. NCT01772992. CVCTPlus: a couples-based approach to linkage to care and ARV adherence. clinicaltrials.gov/ct2/show/NCT01772992 (first received 21 January 2013)

56. NCT02001064. Care4Today v2.0 application for improving adherence to HIV medications [Pilot study of Care4Today v.2.0 application for improving adherence to HIV medications]. clinicaltrials.gov/ct2/show/NCT02001064 (first received 4 December 2013)

57. NCT02044484. HIV clinic-based intervention to improve ART adherence and prevent HIV transmission. clinicaltrials.gov/ct2/show/NCT02044484 (first received 24 January 2014)

58. NCT02119390. Medication adherence in human immunodeficiency virus (HIV) [Targeting enhanced adherence to medication: a pilot study in adolescents and young adults with human immunodeficiency virus (HIV)]. clinicaltrials.gov/ct2/show/NCT02119390 (first received 21 April 2014)

59. NCT02167828. Increasing social support to improve HIV care engagement and adherence in St. Petersburg, Russia [Increasing social support to improve HIV care engagement and adherence]. clinicaltrials.gov/ct2/show/NCT02167828 (first received 19 June 2014)

60. NCT02206906. Incentives to promote medication adherence among HIV-infected youth [Investigation of incentives to promote medication adherence among HIV-infected youth on antiretroviral therapy]. clinicaltrials.gov/ct2/show/NCT02206906 (first received 1 August 2014)

61. NCT02249962. Option B+: study on safety, viral suppression, and survival on second line ART [Option B+: ART safety and durability during first and subsequent pregnancies]. clinicaltrials.gov/ct2/show/NCT02249962 (first received 26 September 2014)

62. NCT02269917. Study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) regimen versus boosted protease inhibitor (bPI) along with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) regimen in virological-

Table 10. Ongoing studies *(Continued)*

ly-suppressed, HIV-1 infected participants [A Phase 3, randomized, active-controlled, open-label study to evaluate the efficacy, safety and tolerability of switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects]. clinicaltrials.gov/ct2/show/NCT02269917 (first received 21 October 2014)

63. NCT02329782. Supporting treatment adherence readiness through training (START) [Controlled evaluation of the adherence readiness program for ART adherence]. clinicaltrials.gov/ct2/show/NCT02329782 (first received 1 January 2015)

64. NCT02354053. Evaluation of switching from current cART to triumeq with adherence support will enhance HIV control in vulnerable populations (TRIIADD) [A phase IV, multicentre randomized prospective open label study to evaluate whether switching from current cART to triumeq in addition to adherence support will enhance virologic control and adherence in vulnerable populations relative to adherence support alone]. clinicaltrials.gov/ct2/show/NCT02354053 (first received 3 February 2015)

65. NCT02383108. Strategy for maintenance of HIV suppression with once daily integrate inhibitor+darunavir/ritonavir in children (SMILE) [A two-arm, phase 2/3 multicentre, open-label, randomised study evaluating safety and antiviral effect of current standard antiretroviral therapy compared to once daily integrase inhibitor administered with darunavir/ritonavir (DRV/r) in HIV-1 infected, virologically suppressed paediatric participants]. clinicaltrials.gov/ct2/show/NCT02383108 (first received 9 March 2015)

66. NCT02396394. Improving ART retention and adherence in Uganda: the WiseMama study. clinicaltrials.gov/ct2/show/NCT02396394 (first received 24 March 2015)

67. NCT02464423. Improving adherence among HIV+ Rwandan youth: a TI-CBTe indigenous leader model. clinicaltrials.gov/ct2/show/NCT02464423 (first received 8 June 2015)

68. NCT02491177. Mother and infant visit adherence and treatment engagement study (MOTIVATE!) [Maximizing adherence and retention for women and infants in the context of option B+]. clinicaltrials.gov/ct2/show/NCT02491177 (first received 7 July 2015)

69. NCT02659761. Triumeq as an integrase single tablet regimen in people with HIV who inject drugs [A prospective, single arm, open-label 96 week observational trial of the tolerability, adherence and efficacy of a dolutegravir/abacavir/lamivudine single tablet regimen in HIV-1 antibody positive people living with HIV with a history of injection drug use switching from existing ART or starting treatment after discontinuation of ART]. clinicaltrials.gov/ct2/show/NCT02659761 (first received 20 January 2016)

70. NCT02676128. Mobile health application to improve HIV medication adherence. clinicaltrials.gov/ct2/show/NCT02676128 (first received 8 February 2016)

71. NCT02677675. Effectiveness of mobile phone technology on adherence and treatment outcomes among HIV positive patients on ART [Effectiveness of mobile phone technology in improving adherence and treatment outcomes among HIV positive patients on antiretroviral therapy (ART) in Malaysia]. clinicaltrials.gov/ct2/show/NCT02677675 (first received 9 February 2016)

72. NCT02704208. A technology-delivered peer-to-peer support ART adherence intervention for substance-using HIV+ adults. clinicaltrials.gov/ct2/show/NCT02704208 (first received 9 March 2016)

73. NCT02761746. Motivational enhancement system for adherence (MESA) for youth starting ART. clinicaltrials.gov/ct2/show/NCT02761746 (first received 4 May 2016)

74. NCT02777229. Efficacy and safety of a dolutegravir-based regimen for the initial management of HIV infected adults in resource-limited settings (NAMSAL) [A phase III randomized, open label trial to evaluate dolutegravir versus efavirenz 400 mg, both combined with tenofovir disoproxil fumarate + lamivudine for the initial management of HIV infected adults in resource-limited settings]. clinicaltrials.gov/ct2/show/NCT02777229 (first received 19 May 2016)

75. NCT02782130. Epic allies HIV ART adherence intervention [Epic allies: a gaming mobile phone application to improve engagement in care, antiretroviral uptake, and adherence among young men who have sex with men (YMSM) and trans women who have sex with men]. clinicaltrials.gov/ct2/show/NCT02782130 (first received 25 May 2016)

76. NCT02797093. Impact of ART adherence on HIV persistence and inflammation. clinicaltrials.gov/ct2/show/NCT02797093 (first received 13 June 2016)

Table 10. Ongoing studies *(Continued)*

77. NCT02797262. Measuring and monitoring adherence to ART with pill ingestible sensor system. clinicaltrials.gov/ct2/show/NCT02797262 (first received 13 June 2016)

78. NCT02800655. Digital health feedback system for longitudinal measurement of medication adherence during anti-retroviral (ARV) therapy [A prospective single arm open label intervention study using the DHFS with HIV infected participants initiating or continuing HIV treatment]. clinicaltrials.gov/ct2/show/NCT02800655 (first received 15 June 2016)

79. NCT02878642. Adherence to dolutegravir and outcome (DOLUTECAPS) [Cohort study to assess electronic-caps defined adherence patterns - virological outcome relationship amongst HIV-1 infected subjects receiving dolutegravir-based antiretroviral therapy)]. clinicaltrials.gov/ct2/show/NCT02878642 (first received 25 August 2016)

80. NCT02888288. Integrating mental health into a HIV clinic to improve outcomes among Tanzanian youth. clinicaltrials.gov/ct2/show/NCT02888288 (first received 5 September 2016)

81. NCT02907697. Adherence intervention for HIV-infected drug users. clinicaltrials.gov/ct2/show/NCT02907697 (first received 20 September 2016)

82. NCT02987530. National multicenter trial evaluating two treatments in patients with primary human immunodeficiency virus (HIV-1) infection (OPTIPRIM-2) [Phase III multicenter randomized trial evaluating in patients at the time of the primary HIV-1 infection, the impact on the viral reservoir of a combination including tenofovir/emtricitabine and dolutegravir or tenofovir/emtricitabine and darunavir/cobicistat]. clinicaltrials.gov/ct2/show/NCT02987530 (first received 9 December 2016)

83. NCT03076359. Traditional healers as adherence partners for persons living with HIV in rural Mozambique [Traditional healers as adherence partners for PLHIV in rural Mozambique]. clinicaltrials.gov/ct2/show/NCT03076359 (first received 10 March 2017)

84. NCT03086655. Tel-me-box: testing new, real-time strategies for monitoring HIV medication adherence in India [Tel-me-box: validating and testing a novel, low-cost, real-time monitoring device with hair level analysis among adherence-challenged patients]. clinicaltrials.gov/ct2/show/NCT03086655 (first received 22 March 2017)

85. NCT03088241. "Switch Either Near Suppression Or THOusand" (SESOTHO) [Switch to second-line versus WHO-guided standard of care for unsuppressed patients on first-line ART with viremia below 1000 copies/mL - a multicenter, parallel-group, open-label, randomized clinical study in rural Lesotho]. clinicaltrials.gov/ct2/show/NCT03088241 (first received 23 March 2017)

86. NCT03092115. Youth mHealth adherence intervention for HIV+ YMSM [Feasibility testing of a novel mHealth intervention to improve adherence to antiretroviral therapy among HIV+ men who have sex with men (MSM) youth]. clinicaltrials.gov/ct2/show/NCT03092115 (first received 27 March 2017)

87. NCT03092531. Positive steps to enhance problem solving skills [Adaptive intervention strategies trial for strengthening adherence to antiretroviral HIV treatment among youth]. clinicaltrials.gov/ct2/show/NCT03092531 (first received 28 March 2017)

88. NCT03127397. Contribution of "praise messages" to HIV treatment retention and adherence among female sex workers in Ethiopia. clinicaltrials.gov/ct2/show/NCT03127397 (first received 25 April 2017)

89. NCT03149757. Connecting youth and young adults to optimize ART adherence: youTHrive efficacy trial [Connecting youth and young adults to optimize art adherence: testing the efficacy of the youth thrive intervention]. clinicaltrials.gov/ct2/show/NCT03149757 (first received 11 May 2017)

90. NCT03195452. QDISS Stud: QD isentress as switch strategy in virologically suppressed HIV-1 infected-patient. clinicaltrials.gov/ct2/show/NCT03195452 (first received 22 June 2017)

91. NCT03198962. Use of amphetamine-type stimulants & its relationship with HIV incidence and antiretroviral adherence among MSM and TG [Use of amphetamine-type stimulants and its relationship with HIV incidence and antiretroviral adherence among Thai men who have sex with men and transgender women]. clinicaltrials.gov/ct2/show/NCT03198962 (first received 26 June 2017)

92. NCT03199027. Timing of referral to adherence clubs for antiretroviral therapy [Timing of referral to adherence clubs for antiretroviral therapy - a randomised controlled trial]. clinicaltrials.gov/ct2/show/NCT03199027 (first received 26 June 2017)

Table 10. Ongoing studies *(Continued)*

93. NCT03205566. Time to protection and adherence requirements of raltegravir with or without lamivudine in protection from HIV infection. clinicaltrials.gov/ct2/show/NCT03205566 (first received 2 July 2017)
94. NCT03256422. Antiretroviral treatment taken 4 days per week versus continuous therapy 7/7 days per week in HIV-1 infected patients [Randomized, open-label and multicentric trial evaluating the non-inferiority of antiretroviral treatment taken 4 consecutive days per week versus continuous therapy 7/7 days per week in HIV-1 infected patients with controlled viral load under antiretroviral therapy]. clinicaltrials.gov/ct2/show/NCT03256422 (first received 22 August 2017)
95. NCT03292432. Triggered escalating real-time adherence (TERA) intervention [Triggered escalating real-time adherence intervention to promote rapid HIV viral suppression among youth living with HIV failing antiretroviral therapy: the TERA study]. clinicaltrials.gov/ct2/show/NCT03292432 (first received 25 September 2017)
96. NCT03331978. A randomized controlled trial of an antiretroviral treatment adherence intervention for HIV+ African Americans. clinicaltrials.gov/ct2/show/NCT03331978 (first received 6 November 2017)
97. NCT03387397. Assessing differential adherence to medications and quality of life among people living with HIV and comorbidities. clinicaltrials.gov/ct2/show/NCT03387397 (accessed 2 January 2018)
98. NCT03394391. The effectiveness of SMS in improving antiretroviral medication adherence among adolescents living with HIV in Nigeria (STARTA) [A single-blind, randomized, parallel design study to assess the effectiveness of SMS reminders in improving art adherence among adolescents living with HIV in Nigeria (STARTA Trial-Adolescents)]. clinicaltrials.gov/ct2/show/NCT03394391 (first received 9 January 2018)
99. NCT03397576. Adherence through home education and nursing assessment, Indonesia (ATHENA-I) [A randomized controlled trial of a medication adherence intervention (ATHENA-I) to increase adherence to antiretroviral therapy among HIV-infected prisoners in Indonesia]. clinicaltrials.gov/ct2/show/NCT03397576 (first received 12 January 2018)
100. NCT03493568. Switch from dual regimens based on dolutegravir plus a reverse transcriptase inhibitor to E/C/F/TAF in virologically suppressed, HIV-1 infected patients (Be-OnE) [Open label, randomized (1:1) clinical trial to evaluate switching from dual regimens based on dolutegravir plus a reverse transcriptase inhibitor to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in virologically suppressed, HIV-1 infected patients (Be-OnE Study)]. clinicaltrials.gov/ct2/show/NCT03493568 (first received 10 April 2018)
101. NCT03535337. Adherence interventions for HIV youth via text & cell phone - sequential multiple assignment randomized trial (SMART) [Adaptive antiretroviral therapy adherence interventions for youth living with HIV through text messaging and cell phone support embedded within the sequential multiple assignment randomized trial (SMART) design]. clinicaltrials.gov/ct2/show/NCT03535337 (first received 24 May 2018)
102. NCT03555396. Couples ART adherence intervention for PWID in Kazakhstan [A couple-based antiretroviral therapy adherence intervention for people who inject drugs]. clinicaltrials.gov/ct2/show/NCT03555396 (first received 13 June 2018)
103. NCT03580668. Effectiveness, safety, adherence, and health-related quality of life in HIV-1 infected adults receiving bictegravir/emtricitabine/tenofovir alafenamide (BIC-STaR) [Multi-center, Canadian, non-interventional, cohort study of the effectiveness, safety, adherence, and health-related quality of life in HIV-1 infected adult patients receiving bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF)]. clinicaltrials.gov/ct2/show/NCT03580668 (first received 9 July 2018)
104. NCT03600103. Technology based community health nursing to improve combination anti-retroviral therapy (cART) adherence and virologic suppression in youth living with HIV [Technology based community health nursing to improve cART adherence and virologic suppression in youth living with HIV (TECH-N 2 CHECK-IN): a regional multi-site study]. clinicaltrials.gov/ct2/show/NCT03600103 (first received 26 July 2018)
105. NCT03618511. Interventions to improve HIV antiretroviral therapy adherence [Interventions to improve HIV antiretroviral therapy adherence in Sofala Province Mozambique]. clinicaltrials.gov/ct2/show/NCT03618511 (first received 7 August 2018)
106. NCT03665532. Youth engagement study: intervention to increase HIV treatment engagement and adherence for young people living with HIV [Unified intervention to impact HIV care continuum]. clinicaltrials.gov/ct2/show/NCT03665532 (first received 11 September 2018)

Table 10. Ongoing studies *(Continued)*

107. NCT03760458. The pharmacokinetics, safety, and tolerability of abacavir/dolutegravir/lamivudine dispersible and immediate release tablets in HIV-1-infected children less than 12 years of age [Phase I/II study of the pharmacokinetics, safety, and tolerability of abacavir/dolutegravir/lamivudine dispersible and immediate release tablets in HIV-1-infected children less than 12 years of age]. clinicaltrials.gov/ct2/show/NCT03760458 (first received 30 November 2018)

108. NCT03823261. Effects of a nurse-delivered cognitive behaviour therapy on adherence and depressive symptoms in HIV infected persons of South Korea. clinicaltrials.gov/ct2/show/NCT03823261 (first received 30 January 2019)

109. NCT03858478. Initiation of first-line antiretroviral treatment with tenofovir alafenamide - emtricitabine - bictegravir at the first clinical contact in France: trial IMEA 055 - FAST. clinicaltrials.gov/ct2/show/NCT03858478 (first received 28 February 2019)

110. NCT03978793. MyTPill: a novel strategy to monitor antiretroviral adherence among HIV+ prescription opioid users (MyTPill). clinicaltrials.gov/ct2/show/NCT03978793 (first received 7 June 2019)

111. NCT03991013. Tenofovir/lamivudine/dolutegravir combination as second line ART: a randomised controlled trial (ARTIST) [Anti-Retroviral Therapy In Second-line: Investigating Tenofovir-lamivudine-dolutegravir (ARTIST): a randomised controlled trial]. clinicaltrials.gov/ct2/show/NCT03991013 (first received 19 June 2019)

112. NCT03999411. Smartphone intervention for smoking cessation and adherence to anti-retroviral therapy (ART) among people living with human immunodeficiency virus (HIV) [A novel smartphone-based intervention to support smoking cessation and adherence to antiretroviral therapy among people living with HIV: a pilot randomized clinical trial]. clinicaltrials.gov/ct2/show/NCT03999411 (first received 26 June 2019)

113. NCT04009057. Effectiveness, safety, adherence, and health-related quality of life in HIV-1 infected adults receiving bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) [Multi-center, Israeli, non-interventional, cohort study of the effectiveness, safety, adherence, and health-related quality of life in HIV-1 infected adult patients receiving bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF)]. clinicaltrials.gov/ct2/show/NCT04009057 (first received 5 July 2019)

114. NCT04012931. A study of switching to RPV plus other ARVs in HIV-1-infected children (aged 2 to <12 years) who are virologically suppressed [A phase 2, open-label, single-arm, multicenter study to evaluate the pharmacokinetics, safety, tolerability, and efficacy of switching to RPV plus other ARVs in HIV-1-infected children (aged 2 to <12 years) who are virologically suppressed]. clinicaltrials.gov/ct2/show/NCT04012931 (first received 9 July 2019)

115. NCT04024488. Group-based intervention to improve mental health and adherence among youth living with HIV in low resource settings [IMPAACT 2016 - evaluating a group-based intervention to improve mental health and antiretroviral therapy (ART) adherence among youth living with HIV in low resource settings]. clinicaltrials.gov/ct2/show/NCT04024488 (first received 18 July 2019)

116. NCT04035759. Positive affect promotion to empower optimal adherence to HIV therapy (Project APPEAL). clinicaltrials.gov/ct2/show/NCT04035759 (first received 29 July 2019)

117. NCT04054466. Nursing counseling to the change of behavior of alcohol consumption in patients in HAART [Effectiveness of the nursing counseling to the change of behavior of alcohol consumption in patients receiving HAART]. clinicaltrials.gov/ct2/show/NCT04054466 (first received 13 August 2019)

118. NCT04077047. ALWH: social networks, adherence and retention [Understanding and developing a network-based social support intervention to improve retention in HIV care and antiretroviral therapy adherence for adolescents living with HIV]. clinicaltrials.gov/ct2/show/NCT04077047 (first received 4 September 2019)

119. NCT04132674. Switching to a fixed dose combination of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in HIV-1 infected marginalized populations who are virologically suppressed. clinicaltrials.gov/ct2/show/NCT04132674 (first received 21 October 2019)

120. NCT04222270. Caregiver peer support and ART adherence among children (CaPS) [The impact of structured caregiver peer support (CaPS) on ART adherence and viral suppression among children living with HIV in Nigeria]. clinicaltrials.gov/ct2/show/NCT04222270 (first received 9 January 2020)

121. NTR176. The AIMS study [Theory- and evidence-based intervention to improve adherence to antiretroviral therapy among HIV-infected patients: the AIMS study]. trialsearch.who.int/Trial2.aspx?TrialID=NTR176 (first received 1 September 2005)

Table 10. Ongoing studies *(Continued)*

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123. PACTR201006000222401. Children with human immunodeficiency virus (HIV) in Africa, pharmacokinetics and acceptability/adherence of simple antiretroviral regimen (CHAPAS-3) [A randomised trial to compare toxicity and pharmacokinetics of three fixed-dose combination based antiretroviral regimens for treatment of human immunodeficiency virus (HIV) infected children in Africa]. pactr.samrc.ac.za/Search.aspx (first received 15 June 2010)

124. PACTR201311000641402. The TAP study [A randomised controlled Trial to explore Adherence-failure relationships in a South African antiretroviral delivery site using an electronic adherence device and sparse Pharmacokinetic sampling]. pactr.samrc.ac.za/Search.aspx (first received 11 September 2013)

125. PACTR201405000815100. Effectiveness of an alcohol-focused intervention in improving adherence to antiretroviral therapy (ART) and HIV treatment outcomes. pactr.samrc.ac.za/Search.aspx (first received 22 April 2014)

126. PACTR201508000950148. Cell phone ringtones and antiretroviral therapy in Yaounde [Cell phone ringtones for improving adherence to antiretroviral therapy in Yaounde, Cameroon]. pactr.samrc.ac.za/Search.aspx (first received 29 November 2014)

127. PACTR201611001858240. Kadoma cellphone study [Does a weekly short message service reminder improve adherence to antiretroviral therapy? A randomized control trial among HIV clients seeking care at Rimuka integrated HIV and TB clinic Kadoma (Zimbabwe)]. pactr.samrc.ac.za/Search.aspx (first received 10 November 2016)

128. PACTR201712002844286. REMIND [Effect of reminder cues and tailored feedback on adherence to antiretroviral drug treatment among people living with HIV in the Kilimanjaro region, Tanzania]. pactr.samrc.ac.za/Search.aspx (first received 7 December 2017)

129. PACTR201802003035922. The HIV/TB co-infection mobile phone SMS trial [Rentention in care and adherence to treatment in HIV/TB co-infection]. pactr.samrc.ac.za/Search.aspx (first received 1 February 2018)

130. PACTR201806003040425. Adolescent retention and adherence trial [Conditional economic incentive and motivational interviewing to improve adolescents retention and adherence to antiretroviral therapy and HIV care in Anambra State, South East Nigeria: a cluster randomized trial]. pactr.samrc.ac.za/Search.aspx (first received 2 February 2018)

131. PACTR201810631281009. Exploring 6-month dispensing intervals for adherence clubs - a cluster randomized study. pactr.samrc.ac.za/Search.aspx (first received 10 October 2018)

132. PACTR201811482580522. Effect of patient education on adherence to antiretroviral therapy and its clinical outcomes among human immunodeficiency virus patients in Jos university teaching hospital, Nigeria. pactr.samrc.ac.za/Search.aspx (first received 14 November 2018)

133. PACTR201811878799717. Mobile phone SMS for adherence support for hypertension in South African adults in care for HIV infection [MObile Phone text messages to support Hypertension treatment ADherence in adults attending HIV treatment centres in the Western Cape Province of South Africa: a pilot study – the MOPHADHIV trial]. pactr.samrc.ac.za/Search.aspx (first received 20 November 2018)

134. PACTR201904582515723. The HIV/AIDS mobile phone and home visit trial [Retention and adherence among adolescents living with HIV: an overview of the Centre region of Cameroon]. pactr.samrc.ac.za/Search.aspx (first received 26 April 2019)

135. PACTR201904781300573. VISEND [Virological impact of switching from efavirenz and nevirapine-based first-Line ART regimens to dolutegravir]. trialsearch.who.int/Trial2.aspx?TrialID=PACTR201904781300573 (first received 4 April 2019)

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145. U1111-1184-0639. A valiation of efficacy of trial-based cognitive therapy in the adherence to drug treatment in HIV-infected patients [Controlled trial comparing the efficacy of Trial-Based Cognitive Therapy (TBCT) and standard treatment about the adherence to the treatment of patients with HIV/AIDS with antiretroviral therapy failure assisted in Salvador, Bahia]. ensaiosclinicos.gov.br/rg/RBR-8qqzk8 (first received 24 August 2016)
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147. UMIN000031442. Effect of cognitive behavior therapy for antiretroviral therapy adherence and depression among people living with HIV and depressive symptoms: a randomized controlled trial. center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000034137 (first received 23 February 2018)
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HISTORY

Protocol first published: Issue 7, 2018

CONTRIBUTIONS OF AUTHORS

Rhodine Smith supported protocol development, assessed studies for inclusion, extracted data, conducted quality assessments, and drafted the review.

Gemma Villanueva assessed studies for inclusion, extracted data, conducted quality assessments, analysed the data, interpreted the analyses, and drafted the review.

Katrin Probyn assessed studies for inclusion, extracted data, conducted quality assessments, and drafted the review.

Yanina Sguassero assessed studies for inclusion, extracted data, conducted quality assessments, and drafted the review.

Nathan Ford supported protocol development, assessed studies for inclusion, and contributed to the draft manuscript.

Catherine Orrell supported protocol development, assessed studies for inclusion, and contributed to the draft manuscript.

Karen Cohen supported protocol development, assessed studies for inclusion, and contributed to the draft manuscript.

Marty Chaplin contributed to the statistical analyses and contributed to the draft manuscript.

Mariska MG Leeflang supported protocol development, assessed studies for inclusion, interpreted the analyses, and drafted the review.

Paul Hine wrote the protocol, assessed studies for inclusion, interpreted the analyses, and drafted the review.

All authors revised the draft, and agreed with its submission and publication.

DECLARATIONS OF INTEREST

Rhodine Smith has no known conflicts of interest.

Gemma Villanueva is employed by Cochrane Response, an evidence services unit operated by the Cochrane Collaboration, and has no known conflicts of interest. Cochrane Response was contracted by the CIDG to write this review.

Katrin Probyn is employed by Cochrane Response, an evidence services unit operated by the Cochrane Collaboration, and has no known conflicts of interest. Cochrane Response was contracted by the CIDG to write this review.

Yanina Sguassero is employed by Cochrane Response, an evidence services unit operated by the Cochrane Collaboration, and has no known conflicts of interest. Cochrane Response was contracted by the CIDG to write this review.

Nathan Ford has no known conflicts of interest.

Catherine Orrell was study author on the TAP study (2012-2014) and the META study (2014-2017), and has no known conflicts of interest.

Karen Cohen has no known conflicts of interest.

Marty Chaplin has no known conflicts of interest.

Mariska MG Leeflang has no known conflicts of interest.

Paul Hine has no known conflicts of interest.

The author team has 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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Internal sources

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External sources

- Foreign, Commonwealth, and Development Office (FCDO), UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We amended the title from 'Measures of antiretroviral adherence for detecting viral non-suppression in people living with HIV' (Hine 2018), to 'Accuracy of measures for antiretroviral adherence in people living with HIV'.

We added the website ClinicalTrials.gov to our search strategy after discussion with the CIDG Information Specialists.

We had planned to screen conference abstracts and contact authors in our protocol but, due to the large numbers of studies in the initial searches, we did not complete this.

At the time the protocol was drafted, we did not plan to GRADE the certainty of the evidence. We finally agreed to use the GRADE approach as it is now the recommended approach to summarize the findings from diagnostic test accuracy reviews.

There were minor changes made to the QUADAS-2 tool; these were captured and highlighted in Appendix 4.

INDEX TERMS

Medical Subject Headings (MeSH)

*Anti-Retroviral Agents [therapeutic use]; *HIV Infections [complications] [drug therapy]; Reference Standards; Sensitivity and Specificity; Viral Load

MeSH check words

Adult; Child; Humans