Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies

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The success of potent antiretroviral treatment for HIV infection is primarily determined by adherence. We systematically review the evidence of effectiveness of interventions to increase adherence to antiretroviral treatment in sub-Saharan Africa. We identified 27 relevant reports from 26 studies of behavioural, cognitive, biological, structural, and combination interventions done between 2003 and 2010. Despite study diversity and limitations, evidence suggests that treatment supporters, directly observed therapy, mobile-phone text messages, diary cards, and food rations can effectively increase adherence in sub-Saharan Africa. However, some interventions are unlikely to have large or lasting effects, and others are effective only in specific settings. These findings emphasise the need for more research, particularly for randomised controlled trials, to examine the effect of context and specific features of intervention content on effectiveness. Future work should assess intervention targeting and selection of interventions based on behavioural theories relevant to sub-Saharan Africa.

Introduction

Antiretroviral treatment (ART) can substantially reduce morbidity and mortality in people with HIV. However, the clinical effectiveness of ART depends crucially on adherence. Studies done before 2005 showed that the greatest effectiveness could only be achieved if patients took at least 95% of prescribed antiretroviral doses. More recent studies suggest that treatment with some potent ART regimens, such as those based on ritonavir-boosted protease inhibitors and non-nucleoside reverse-transcriptase inhibitors, can achieve viral suppression at lower adherence, and that the adherence needed to prevent viral rebound decreases with duration of suppression. However, only sustained high levels of adherence will ensure that life-extending benefits of ART are maximised and risk of viral resistance is minimised, and low adherence is the most common reason why potential treatment benefits are not achieved or sustained. Poor adherence also substantially increases the health-care costs associated with treatment of HIV in both developing and developed countries. Additionally, high adherence is essential for the reduction of HIV transmission in treatment-as-prevention approaches.

Many national governments in sub-Saharan Africa, with support from international agencies and donors, are striving to provide ART to all people in need. Of the more than 5 million people worldwide who were receiving ART at the end of 2009, almost four-fifths were in sub-Saharan Africa, where ART adherence might be low.

Results of a 2006 meta-analysis of ART adherence investigations showed that, on average, 23% of patients in studies from sub-Saharan Africa did not achieve adequate adherence, with the proportion of non-adherent patients ranging from 2% to 70% across the primary studies included in the analysis. These findings suggest a need to improve adherence substantially in many settings in sub-Saharan Africa. Moreover, most treatment programmes in sub-Saharan Africa have only been enrolling patients for a few years. Experience from developed countries has shown that adherence falls with time on ART, and recent studies suggest similar trends in sub-Saharan Africa.

Interventions to increase ART adherence in sub-Saharan Africa are clearly needed. Most studies of adherence interventions are from developed countries, and many have been previously reviewed. Table 1 provides an overview of categories of interventions to improve ART adherence that have been investigated in the developed world. The evidence from these investigations might, however, have limited relevance to sub-Saharan Africa because the effectiveness of interventions is likely to depend on the context in which they are implemented. For example, adherence interventions in developed countries are usually provided by general nurses, pharmacists, or physicians, while in sub-Saharan Africa health workers specifically trained to care for patients with HIV are commonly responsible for the monitoring and support of ART patients, often with little involvement from physicians.

Further interventions in developed countries might be based on theories of behaviour that are not valid in sub-Saharan Africa, and those that have been specifically tailored to adherence support of specific subpopulations (such as men who have sex with men or injection drug users) might be of little use in the generalised HIV epidemics of sub-Saharan Africa. Resource-intensive interventions directed towards the individual (eg, cognitive behavioural therapy) could be difficult to implement in sub-Saharan Africa because of large numbers of patients, restricted resources, and the public health approach to treatment.

Therefore, evidence from sub-Saharan Africa is important to inform the design and implementation of ART adherence interventions in the region. We present findings from a systematic review of studies investigating the effectiveness of ART adherence interventions in sub-Saharan Africa.

Methods

Search strategy

We systematically searched PubMed for studies that were published before 31 Jan, 2011, and evaluated
interventions to improve ART adherence in sub-Saharan Africa. To identify articles for this Review, we combined two broad search themes with the Boolean operator “and”. The first search theme—ART—combined the Medical Subject Headings (MeSH) terms “antiretroviral therapy, highly active” and “anti-HIV agents”, and the free-text word “antiretroviral”, with the Boolean operator “or”. The second theme—adherence—combined the MeSH term “patient compliance” and the free-text word “adherence”, with “or”. All narrower MeSH terms that are categorised below the selected term in the MeSH hierarchy were included in the PubMed search “((antiretroviral therapy, highly active)[MeSH] OR “anti-HIV agents”[MeSH] OR antiretroviral) AND (“patient compliance”[MeSH] OR adherence))”.

Additionally, we searched the reference lists of all reports included in the final Review and all articles that were excluded because they were review articles, editorials, or commentaries. We further searched the following conference databases: the Conference on Retroviruses and Opportunistic Infections (up to San Francisco, CA, USA, in February 2010),4 the International AIDS Society (up to Cape Town, South Africa, in July, 2009),9 the International Conference on HIV Treatment Adherence (up to Miami, FL, USA, in May, 2010),10 and the mHealth Summit (up to Washington, DC, USA, in November, 2010).11 Furthermore, relevant publications in the grey literature (research reports, working papers, and dissertations)12 were searched by typing of the terms “antiretroviral”, “therapy”, “adherence”, and “intervention” into Google’s internet search engine. Our Review conformed to the PRISMA checklist for systematic reviews.13

### Study selection and eligibility criteria

Three investigators (KC, NC, and AP) independently screened every abstract identified by the PubMed search. The same reviewers used inclusion and exclusion criteria to assess the full eligibility of conference abstracts, grey literature, and non-peer reviewed articles, as well as the studies identified through the screening of abstracts in PubMed. To be included in the final Review, studies could report adherence as the primary or secondary outcome, or simply report adherence measurements in the presence of an intervention. For the purposes of this Review, we restricted the definition of adherence to medication adherence—ie, the extent to which a patient takes a drug in the way intended by the health-care provider. We did not include studies that investigated the related but distinct concepts of adherence to ART appointments14 or retention within ART programmes.15,16

We did not exclude studies on the basis of the type of measurement used to assess ART adherence, but restricted our Review to studies with a control or comparison group (ie, a group that did not receive the intervention). We did not apply any other study-design exclusion criteria; randomised controlled trials, prospective and retrospective cohort studies, and before-and-after studies were acceptable. Ongoing trials without interim analyses were excluded from the final selection. We did not use any language exclusion criteria. Only results from sub-Saharan Africa were included. For multisite studies, data from locations in sub-Saharan Africa were included, unless the data could not be separately extracted. The exclusion criteria were applied in the order shown in the figure. Specifically, the criteria that led to the exclusion of 113 studies during full-text review were applied in the order from top to bottom as shown in the figure. The investigators who selected studies for review were not blinded to study authors, conclusions, or outcomes, because blinding has little effect on systematic review results.11

### Data extraction

Once all potentially relevant full-text articles and abstracts were identified, three of the investigators (TB, KC, and NC) achieved consensus regarding eligibility and extracted data using a standardised extraction form. All measures of adherence were noted, including subjective and objective measures and biological correlates (such as CD4 cell count and viral load). Two investigators independently extracted the data from each study and entered the data into an electronic database. When the two data entries did not match, consensus was reached through data checks and discussion, and if necessary consultation with another investigator (JH) who was not involved in the data extraction.

### Assessment of risk of bias

We followed the PRISMA guidelines to assess the risk of bias in individual studies and across studies.17 As recommended, we assessed the risk separately for

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**Table 1: Categories of interventions to improve ART adherence**

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural</td>
<td>Affect ART adherence through direct behaviour modification</td>
<td>Reminder devices (eg, 7 day pill boxes, alarms, mobile phone text messages or pager messages) Cues for remembering dose times Cash incentives DOT</td>
</tr>
<tr>
<td>Cognitive</td>
<td>Affect ART adherence through teaching, clarification, or instruction</td>
<td>Media education materials (eg, audio, video, or reading materials) Group education Education of individual patients</td>
</tr>
<tr>
<td>Affective</td>
<td>Affect ART adherence through emotional support</td>
<td>Peer support Treatment with antidepressants Counselling</td>
</tr>
<tr>
<td>Biological</td>
<td>Affect ART adherence through improved physical ability to take ART</td>
<td>Food rations Vitamin or micronutrient supplements</td>
</tr>
<tr>
<td>Structural</td>
<td>Affect ART adherence through changes in the delivery structure or through additional service structures</td>
<td>Delivering ART in community centres Income-generating activities for ART patients Community mobilisation</td>
</tr>
<tr>
<td>Combination</td>
<td>Use of a combination of one or more of the above intervention categories</td>
<td>Patient information, behavioural adherence strategies, and peer support</td>
</tr>
</tbody>
</table>

ART=antiretroviral treatment. DOT=directly observed therapy.
different components rather than in an overall scale. For individual randomised controlled trials, we used the method of the Cochrane Collaboration, with checks for selection bias (random generation of sequences for trial allocation and concealment of allocation before and during trial enrolment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (completeness of data for each reported outcome), and reporting bias (completeness of reporting of assessed outcomes). For individual observational studies, we followed the GRADE recommendations. We also compared individual observational studies, with one from Rwanda, one from Tanzania, and one from Kenya, three from Mozambique, three from Nigeria, five from South Africa, four from Kenya, three from Mozambique, three from Uganda, two from Malawi, two from Zambia, one from Rwanda, one from Tanzania, and one from several countries in sub-Saharan Africa. All the records were published in English. A research letter and a conference abstract were from the same study in Uganda; data from both sources were therefore combined to create one record. We extracted information separately—despite overlap of authors, study setting, and enrolled patients—if studies differed in sample size, primary aims, length of follow-up, intervention type, or adherence measures. For example, two of the full-text articles were from the same setting in Malawi, but the first study reported an initial analysis of the overall results of a randomised controlled trial with 3 months of follow-up, and the second included a subsequent subgroup analysis with 9 months of follow-up (webappendix).

Study characteristics
Studies were carried out between 2003 and 2009, and reported between 2004 and 2010; two-thirds were reported in 2009–10 (table 2, webappendix). The median sample size was 433 individuals (IQR 274–620) and the median length of follow-up was 12 months (7–18 months). 12 studies took place exclusively in urban hospital outpatient clinics, five only in rural community-based clinics, and the remaining studies either took place in several settings or did not provide sufficient information for classification (table 2).

Adherence interventions
14 studies used interventions combining behavioural, cognitive, and affective components (table 1). These interventions included treatment supporters that provided both emotional and instrumental adherence support. One intervention incorporated behavioural, cognitive, affective, and biological interventions through combinations of treatment supporters, nutritional support, financial support, psychosocial support, and education sessions. Purely behavioural interventions used directly observed therapy, diary cards, and mobile-phone short message services (text messages) to remind patients to take their ART drugs. Several interventions used directly observed therapy in addition to other adherence support; in table 2, we classified these interventions separately, because the recorded effects can be attributed only to the package of interventions. Purely biological interventions used various food supplements. Structural interventions included several models of delivery, which differed in the type of health worker providing routine adherence support or the type of health-care setting.

Studies of the same intervention category differed in the precise intervention characteristics, length of follow-up, study design, and setting. For example, in studies with directly observed therapy, the frequency of observed therapy varied from every day to every week. In studies with treatment supporters, the person providing the support was a family member or a friend, neighbour, community health worker, or HIV-infected community members. Treatment supporters had different tasks in different studies, including psychosocial support, education about ART, identification of
Table 2: Characteristics of interventions for ART adherence in sub-Saharan Africa

<table>
<thead>
<tr>
<th>Source type</th>
<th>Intervention category</th>
<th>Intervention type</th>
<th>Study period</th>
<th>Study country (city or region)</th>
<th>Health-care setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung et al (2009)⁶⁰</td>
<td>Conference abstract</td>
<td>Behavioural and cognitive</td>
<td>Educational counselling vs alarm device vs combination vs neither</td>
<td>2006–08</td>
<td>Kenya (Nairobi)</td>
</tr>
<tr>
<td>Idako et al (2007)⁶⁷</td>
<td>Journal article</td>
<td>Behavioural</td>
<td>DOT (DAOT, TWOT, and WOT)</td>
<td>2003</td>
<td>Nigeria (Jos)</td>
</tr>
<tr>
<td>Kabore et al (2010)⁶⁷</td>
<td>Journal article</td>
<td>Behavioural, cognitive, affective, biological, and structural</td>
<td>Treatment supporter, nutritional support, financial support, psychological support, and educational counselling</td>
<td>2005–07</td>
<td>Lesotho (Maputsoe), South Africa (Ladysmith), Namibia (Katima Mulilo), and Botswana (Gaborone)</td>
</tr>
<tr>
<td>Mugusi et al (2009)⁶⁴</td>
<td>Journal article</td>
<td>Behavioural, cognitive, and affective</td>
<td>Treatment supporter, calendar with reminders, and educational counselling</td>
<td>2010</td>
<td>Tanzania (Dar es Salaam)</td>
</tr>
<tr>
<td>Nachega et al (2009)⁶⁶</td>
<td>Conference abstract</td>
<td>Behavioural and cognitive</td>
<td>DOT (DAOT) and educational counselling</td>
<td>2005–07</td>
<td>South Africa (Cape Town)</td>
</tr>
<tr>
<td>Nachega et al (2010)⁶⁶</td>
<td>Journal article</td>
<td>Behavioural and cognitive</td>
<td>DOT (DAOT) and educational counselling</td>
<td>2005–07</td>
<td>South Africa (Cape Town)</td>
</tr>
<tr>
<td>Ndekhha et al (2009a)⁶⁹</td>
<td>Journal article</td>
<td>Biological</td>
<td>Lipid paste vs flour supplement</td>
<td>2006–07</td>
<td>Malawi (Blantyre)</td>
</tr>
<tr>
<td>Ndekhha et al (2009b)⁶⁹</td>
<td>Journal article</td>
<td>Biological</td>
<td>Lipid paste vs flour supplement</td>
<td>2006–07</td>
<td>Malawi (Blantyre)</td>
</tr>
<tr>
<td>Pearson et al (2007)⁷⁰</td>
<td>Journal article</td>
<td>Behavioural, cognitive, and affective</td>
<td>Treatment supporter, DOT (DAOT), and education</td>
<td>2004</td>
<td>Mozambique (Beira)</td>
</tr>
<tr>
<td>Sherr et al (2010)⁷⁴</td>
<td>Journal article</td>
<td>Structural</td>
<td>Non-physician provider</td>
<td>2004–07</td>
<td>Mozambique (Central Region)</td>
</tr>
<tr>
<td>Stubbs et al (2009)⁷⁴</td>
<td>Journal article</td>
<td>Behavioural, cognitive, and affective</td>
<td>Treatment supporter</td>
<td>2004–06</td>
<td>Mozambique (Central Region)</td>
</tr>
<tr>
<td>Taiwo et al (2010)⁷⁴</td>
<td>Journal article</td>
<td>Behavioural, cognitive, and affective</td>
<td>Treatment supporter and DOT (DAOT)</td>
<td>2006–08</td>
<td>Nigeria (Jos)</td>
</tr>
</tbody>
</table>

ART=antiretroviral treatment. DOT=directly observed therapy. DAOT=DOT every day. TWOT=DOT every 2 weeks. WOT=DOT every week.

Adherence assessment

Adherence was assessed by subjective and objective measurement instruments (webappendix). Subjective instruments included patient’s recall of the number of

barriers to adherence,⁶⁸ adherence measurement,⁶⁷ adherence reminders to patients to pick up their drugs.⁶⁷,⁷⁵ Directly observed therapy,⁶⁷,⁷⁸ assessment of adverse events,⁶⁷,⁷⁵ and triage to other health-care providers.⁶⁷,⁷⁸
missed doses in the past 3 days, 7 days, or 30 days (11 studies),58–61,63,68–70,71,73,76,80,82 focus groups in which participants were asked if they were able to take their drugs as and when due (one study),73 and health-worker opinions about whether an intervention had improved adherence (two studies).72,74 Objective instruments included pharmacy refill rates (four studies),62,63,66 pill counts in clinics (five studies),41,46,61,79,82 the Medication Event Monitoring System (one study),67 viral-load measurement or CD4 cell count (17 studies),56–61,63,68–70,75,76,78,80,81 and body-mass index (three studies).58,61,78 17 studies used several methods to assess adherence,56–61,63,68–70,75,76,78,80,81

**Intervention outcomes**

16 of the 26 studies showed significantly better adherence in the intervention group than in the comparison group for at least one outcome measurement and one timepoint (webappendix).56,60–63,66–70,73,75,76,80 The interventions tested in the studies with significant effects were structured teaching programmes,79,80 food rations,56 directly observed therapy,41,72 treatment supporters with directly observed therapy,41,46 treatment supporters without directly observed therapy,42,44 non-physician providers,42 different models of ART delivery,41 and mobile-phone text messages.47,70 Two additional studies showed an improvement in adherence, one with treatment supporters and another with case managers;72,74 however, assessments were based on the subjective opinion of health-care providers and the significance of the effect was not reported. The remaining eight studies56–59,61,63,66–68,70,71,73,75,77,78,80 reported non-significant results across all timepoints and adherence measures used.

Ten60,61,66–68,70,71,73,76,79 of 15 randomised controlled trials, six56,62,63,66,67,70,71,82 of seven reports of cohort studies, and three56,72,75 of five before-and-after studies showed improved adherence, according to at least one outcome measure (webappendix). With three exceptions,72,73,76 all studies that found an improvement in adherence did not find an improvement consistently over time41,44 or on self-reported adherence,41 did not assess any biological outcome,41,42,47,72,75,76,80,82 or did not find a significant effect on biological outcomes.56,60–63,79

**Risk of bias**

In most hierarchies of evidence ordered by risk of bias, randomised controlled trials rank above observational studies.91 However, this ranking could be reversed for specific studies, because randomised controlled trials can involve biases, which limit the strength of evidence derived from their results, and observational studies can have characteristics that increase the evidence strength, such as good control of confounding factors or large effect size.73

Five randomised controlled trials used both sequence generation for randomisation and allocation concealment as a safeguard against selection bias,56–60,70 two used only sequence generation97 and one only allocation concealment.98 Only two studies, comparing nutritional interventions, described the masking of study participants and health-care providers to minimise performance bias.56,79 With four exceptions,56,60–62,78 no trial studies reported whether outcome assessors had been blinded to prevent detection bias. However, descriptions of outcome assessments suggested that assessors of self-reported adherence were mostly aware of the trial assignment, while laboratory personnel measuring biological outcomes and analysts were blinded. Finally, all investigators of randomised controlled trials completely reported the results of the outcomes they described in the methods sections. We also compared the reported outcomes of randomised controlled trials with those registered with either Current Controlled Trials or ClinicalTrials.gov and detected no evidence of selective reporting of primary or secondary adherence outcomes.

In all observational studies, appropriate eligibility criteria were defined and applied equally to all participants, and outcome assessment did not differ by intervention assignment. However, only one of the five before-and-after studies used a control group to remove secular time changes in the comparison of adherence before and after the intervention,64 and only three of six cohort studies controlled for different distributions of potential confounding factors between intervention and comparison groups.62,64,65 In the 17 publications that reported loss to follow-up, the loss was always less than 20%—ie, less than the threshold proposed for potentially significant selection bias when individuals are not missing at random.94 In more than half of these studies, loss to follow-up was less than 10%.95,98,99,100–102,104 Most investigations that did not report loss to follow-up were conference abstracts.71,75–78,82

**Discussion**

Several important insights have emerged from this systematic review of interventions to increase ART adherence in sub-Saharan Africa. The reviewed studies investigated six types of adherence-enhancing interventions: text messages and other reminder devices, treatment supporters, directly observed therapy, education and counselling, food supplements, and different health-systems approaches to ART delivery. For each intervention type there is at least one randomised controlled trial36,60–63,66,67,70,71,76 or one observational study36,60–63,66,67,70,71,76 showing effectiveness. However, before policy conclusions can be made, a more detailed examination of the evidence is necessary.

First, the size of an intervention’s effect needs to be considered, not merely the statistical significance. In studies that showed significant effects, the results constituted an improvement of 10% or less in four36,60–63,79,80 10–20% in two,60,62 and an improvement of more than 20% in 12 investigations.36,60–63,66,67,70,71,76,78,80 Although small effect sizes might indicate that investment in the intervention is not worthwhile, such decisions should be made on the basis of economic assessment comparing achievable effects with costs. As yet, such studies have not been done.
Second, improved adherence might not persist over time. Three randomised controlled trials showed a significant intervention effect by some measure of adherence in the first 6 months of the trial, but not in later phases. These results suggest that evidence of effectiveness of adherence-enhancing interventions from studies of short duration might not be generalisable to the long-term. Because ART is lifelong, adherence-enhancing interventions for which effectiveness is limited to a few months would contribute little to overall treatment success. Future studies should thus attempt to assess effectiveness for at least 1 year. Moreover, continuation of some of the studies with significant short-term effects for several more years would be valuable, because long-term effectiveness could be established.

It is important to note, however, that high adherence to ART might be less essential later in treatment than earlier. Lima and colleagues\(^{15}\) reported that the risk of viral rebound caused by imperfect adherence decreases with duration of viral suppression. Therefore, interventions that increase adherence in the first months after ART initiation could improve long-term biological outcomes, even if their effect vanishes over time. While these findings suggest that high adherence might not always be necessary for viral suppression, other results from sub-Saharan Africa indicate that high adherence might not be sufficient for viral suppression in some patients.\(^{19,85}\)

Adherence is merely a means to achieve good health outcomes of ART, rather than a final outcome in its own right. The relation between adherence and ART success is clearly strong; however, better understanding is needed of whether, when, and why near-perfect adherence might not be necessary or sufficient to attain good health outcomes in all patients. Specifically, more evidence is needed about the factors that allow some patients to maintain good virological and immunological outcomes despite imperfect adherence, and about the factors that lead to treatment failure despite near-perfect adherence. We also need to know whether in the two groups of patients in which the close association between adherence and biological measures does not seem to hold, the relation between biological measures and health outcomes (morbidity and mortality) conforms with or deviates from what is observed in the overall population of patients receiving ART.

Third, in examination of the collective evidence on adherence-enhancing interventions in sub-Saharan Africa it is important to consider discrepant findings on intervention effectiveness. For five intervention types shown to be effective in at least one study, other studies did not detect a significant effect (non-text-message reminder devices,\(^{62-68}\) treatment supporters,\(^{44-45}\) directly observed therapy,\(^{72-86}\) education and counselling,\(^{10,77-79}\) and food supplements\(^{81,82}\)). Because of the small number of studies of each intervention type, identification of exact sources of the discrepancies is difficult. One reason for the discrepancies is that for each intervention type, the specific content can differ. For example, non-text-message reminder devices included alarm devices and calendars to support adherence, directly observed therapy ranged from pill taking observed every day to once every week, and treatment-supporter interventions differed in the selection of the supporter and the intensity and content of the support provided.

Further, several factors might limit the ability of some intervention studies to show an effect. For example, the standard of care used in the control group could already produce high adherence in one study, but not in another.\(^{87}\) Ceiling effects can occur when baseline adherence is high, which limits the potential to show improvement. For example, adherence in the study by Roux and colleagues\(^{86}\) was 100% before the intervention and 99% afterwards.

A case in point for discrepant findings is the adherence effect of directly observed therapy. Of studies in sub-Saharan Africa, one high-quality randomised controlled trial\(^{44}\) shows significant adherence improvement with directly observed therapy in both self-reported adherence and biological correlates of adherence. A few other studies suggest that directly observed therapy could improve adherence but this evidence is comparatively weak, because it is based on subjective or objective adherence measures alone, without demonstrated effects on biological correlates.\(^{44,45}\) or because it shows that initial biological effects do not last over time.\(^{7,3}\) In a 2009 meta-analysis\(^{38}\) of randomised controlled trials in developed and developing countries, Ford and colleagues concluded that directly observed therapy did not improve adherence compared with self-administered treatment, but emphasised that “the fact that individual trials found opposing results with respect to benefit of directly observed therapy underscores the importance of considering contextual factors in assessment of adherence interventions”. Conversely, in a 2010 meta-analysis\(^{38}\) of both randomised controlled trials and observational studies, Hart and colleagues found that directly observed therapy “had a significant effect on virological, immunological, and adherence outcomes, although its efficacy was not supported when restricting analysis to randomized controlled trials”. The investigators of this study further noted that “interventions varied widely” and identified features of intervention content that improved the effect on adherence (targeting individuals at high risk of non-adherence; maximising convenience for patients participating in the intervention; and providing adherence support in addition to directly observed therapy, such as other behavioural interventions).\(^{38}\)

Although intervention context and the precise content probably affect intervention effect on adherence, the robustness of conclusions drawn from analyses of study heterogeneity depends crucially on the number of available studies.\(^{38}\) The worldwide evidence is still limited (ten randomised controlled trials in the study by Ford and colleagues,\(^{38}\) and 11 randomised controlled trials and six observational studies in the investigation by Hart and
co-workers”)

Discrepant findings both between and within studies also arise because of differences in outcome measures. Many studies used subjective measures to assess adherence outcomes, including several that did not use any other measure, and a few of the studies that used objective measures did not assess any biological correlates of adherence. Subjective adherence measures are prone to social desirability biases80 and have not correlated well with plasma drug concentrations, CD4 cell counts, or viral loads in several studies.91–93 Health workers (including those involved in the care of the control group in an intervention of directly observed therapy) usually do not have direct knowledge of patients’ pill-taking behaviour and thus might not accurately estimate adherence. Objective measurement instruments, such as pharmacy refill data, pill count or the Medication Events Monitoring System, might not reflect true pill taking if patients discard pills or obtain ART from sources that are not included in the measurement of the refill data, such as friends, family members, or other pharmacies.94 In the absence of a gold-standard measure of adherence, future studies should assess many outcomes. Because adherence affects CD4 cell count and viral load, which in turn will affect morbidity and mortality, the robustness and relevance of a result will increase with the number of distinct outcome measures that show the same result. Conversely, within-study heterogeneity of findings across outcome measures will reduce study robustness and relevance.

Fourth, it is important to consider how far the studies included in this Review differ from those done in other settings. Two important insights gained in two decades of ART adherence research in developed countries are not reflected in the studies in sub-Saharan Africa. Interventions derived from a substantive theory of behaviour change tend to be more effective than are those based on intuition.95–96 However, unlike many studies in developed countries,10 36 37 38 none of the studies in this Review reported a theoretical basis for the investigated intervention. The absence of theoretical foundation might be due to insufficient understanding of how far established theories of behaviour change are applicable to sub-Saharan Africa., even though some models have been investigated in the region (eg, the Information-Motivation-Behavioral Skills model).97–100 Further research on both established and new theories of adherence behaviour is needed in sub-Saharan Africa and could contribute to the design of successful interventions.

Additionally, interventions targeted at patients known to be at risk often have better results than do untargeted interventions.101 Unlike many studies in developed countries,79 102 the studies in this Review did not target sub-populations of patients at high risk of non-adherence, which might have limited their effectiveness. Although some at-risk populations might be uncommon or difficult to identify in sub-Saharan Africa (eg, intravenous drug users or men who have sex with men), other targeting strategies used in developed countries could be feasible, effective, and cost effective in the region. Directly observed therapy, for example, could be appropriate for specific populations,103 such as individuals with depression,104 but not for others, such as individuals who are especially sensitive to stigma.105 A focus on individuals who have had an unsuccessful ART regimen106–107 or on people who have been identified as non-adherent through an adherence screening might also be appropriate in this region.108–111

Fifth, cost is an important consideration for adherence-enhancing interventions in sub-Saharan Africa. A 2010 cost analysis19 12 in South Africa showed that high ART adherence is associated with substantially lower mean monthly direct health-care costs. This finding suggests that effective adherence support could decrease the cost of ART per patient, which would emphasise the importance of adherence-enhancing interventions at a time when the number of individuals requiring ART continues to grow while ART funding might not increase.112 113 Future assessments should include costing studies to test the hypothesis that adherence-enhancing interventions can lead to a net decrease in the cost of ART delivery.

In sum, evidence is emerging that mobile-phone text messages and other reminder devices, treatment supporters, directly observed therapy, education and counselling, food supplements, and different organisations of ART can be effective approaches to increase ART adherence in some settings in sub-Saharan Africa. However, with the exception of text-message reminders, either the evidence is based only on observational studies, which are unlikely to control completely for unmeasured confounding factors, or discrepant findings suggest that intervention effect is strongly affected by context or the precise intervention content. Future research efforts should include randomised controlled trials of interventions to improve adherence in routine ART delivery in sub-Saharan Africa, be based on substantive theories of behaviour, and incorporate costing studies to allow economic assessment of interventions. Additionally, health workers in programmes that have integrated adherence interventions into routine ART delivery should report available evidence on intervention effectiveness.

Sustained, high adherence to ART will be crucial for the long-term success of treatment programmes in sub-Saharan Africa, where most of the people currently receiving and needing ART live and where the options for second-line therapy after first-line failure are often limited. Initial evidence has accrued as to which interventions are likely to substantially improve adherence, but further studies are needed to confirm intervention effects, assess effect duration, identify the modifying effects of the intervention context, and establish intervention cost-effectiveness.
Review

Contributors
TB and M-LN were jointly responsible for the design of the study. KC, NC, and AP did the search of the reported work and data extraction, with support from TB and JH. TB wrote the initial draft of the paper, all authors contributed to the writing of the report.

Conflicts of interest
We declare that we have no conflicts of interest.

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