

Research in context

Evidence before this study

The 2013 WHO consolidated guidelines on the use of antiretroviral therapy for the treatment and prevention of HIV infection promoted the use of text messaging to improve adherence to therapy. Before we did our systematic literature search, we searched MEDLINE and Embase to find systematic reviews published up to June 1, 2016, that assessed the full spectrum of interventions to improve adherence, using the search string "(HIV or antiretroviral therapy) AND (adherence) AND (systematic review or meta-analysis)". Previous systematic reviews have been restricted to pairs of interventions; the only network meta-analysis that explored adherence interventions for antiretroviral therapy was limited to studies in Africa. Low rates of adherence have been reported too in high-income settings, so there is a need to explore the evidence at the global setting.

Added value of this study

This was the first network meta-analysis to consider all adherence interventions within a single global analysis.

We show that adherence interventions have small effects and that they are not easily statistically distinguishable from one another. These results support the benefits of text messaging, counselling, and supporters, and they further support the additive effect of behavioural and cognitive interventions. Novel to this study, time of outcome measurement with respect to the intervention (ie, whether adherence was assessed while the intervention was still active rather than previously completed) was an effect modifier, suggesting that the effects of interventions wane over time.

Implications to all available evidence

With the recent scale-up of antiretroviral therapy programmes and increasing number of people living with HIV, steps to improve and maintain consistent long-term adherence to antiretroviral therapy are crucial. WHO's recent guidelines used the findings of this comprehensive network meta-analysis, and HIV programmes could consider adopting or adapting these interventions according to resource availability and programme outcomes.

meta-analysis approach,¹² aiming to establish the effectiveness of interventions on adherence and, when reported, achievement of viral suppression.

Methods

Search strategy and selection criteria

We used the PRISMA extension to network meta-analysis to design and report the trial¹³ and the protocol for this study is available from the authors on request. We searched the Cochrane Central Register of Controlled Trials, Embase, and MEDLINE for English-language reports published up to July 16, 2015 (search terms in appendix pp 3–4). Interventions targeting enhanced adherence to antiretroviral therapy only (ie, not an antiretroviral therapy regimen) were not eligible. As such, most studies published before 1996 were excluded. In addition to the database searches, we searched for conference abstracts published from Jan 1, 2013, to July 16, 2015, on Embase, the International AIDS Conference (AIDS), the Conference on Retroviruses and Opportunistic Infections (CROI), and the International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention. We hand searched the bibliographies of published systematic reviews. We included randomised controlled trials of any intervention to improve adherence to antiretroviral therapy relative to the standard of care in people living with HIV; the outcomes of interest were treatment adherence and viral suppression. We used no restrictions for treatment experience or previous antiretroviral therapy failures. We excluded studies that used real-time monitoring of patients for adherence assessment.

JJHP and JIF reviewed all abstracts and proceedings identified in the searches. The same two investigators

independently reviewed abstracts for full-text review. If any discrepancies occurred between the studies selected by the two investigators, a third investigator (SK) provided arbitration.

We assessed risk of bias in the included randomised controlled trials using the Cochrane risk-of-bias tool.¹⁴ To assess the overall strength of evidence, we used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system for network meta-analyses.¹⁵ As in pairwise meta-analyses, we applied the GRADE system to direct evidence (ie, data with head-to-head comparisons). When only indirect evidence was available, we used the network meta-analysis estimate and evaluated the shortest indirect pathway with the largest number of trials. For each outcome, the strength of evidence began as high-quality evidence and was rated down when limitations were present due to risk of bias, inconsistency, indirectness, imprecision, or reporting bias.

Using a standardised data sheet in Microsoft Excel 2013, two investigators independently extracted data for study characteristics, interventions used, patient characteristics at baseline, and outcomes for the study populations of interest for the final list of selected eligible studies. Any discrepancies observed between the data extracted by the two extractors were resolved by consensus between JJHP and JIF through discussion.

To improve interpretability and thereby support decision making, we grouped treatment arms using the following categories: standard of care, enhanced standard of care, telephone, SMS, behavioural skills training or medication adherence training, multimedia, cognitive behavioural therapy, supporter, incentives, and device

See Online for appendix

reminder interventions (panel). Recognising heterogeneity across the term standard of care, we defined enhanced standard of care as interventions that provided more support than the usual standard of care (most commonly adherence counselling).

The primary outcome was adherence to antiretroviral therapy, defined as the proportion of patients in each trial arm meeting the trial-defined adherence criteria. The secondary outcome was proportion of patients achieving viral suppression, also as defined by the trial. We preferentially extracted results for intention-to-treat analyses. All outcomes were extracted for the end of the study period.

Data analysis

We did our analyses within the Bayesian framework with hierarchical models. All outcomes were dichotomised and were analysed by last observed timepoint. We used a logistic regression model with the logit link function and a binomial likelihood. Because heterogeneity was anticipated, we considered both fixed-effects and random-effects models. Model selection was done with the deviance information criterion (DIC), which penalises for model complexity and leverage plots. The model with the best fit was chosen as the primary analysis model. Estimates of comparative treatment effect from the network meta-analyses were represented as odds ratios (ORs) with associated 95% credible intervals (95% CrI).

We used meta-regression to account for populations at risk of poor adherence and time discrepancies between the outcome and intervention, and to determine whether these were effect modifiers.¹⁶ We defined populations considered at risk of poor adherence according to published data and included people who inject drugs, other substance users (including those who use alcohol and non-injecting drugs), people with mental health disorders (including severe depression), and people known to be non-adherent at study entry.¹⁷ The time-discrepancy variable pertained to whether adherence or viral suppression was measured during the adherence intervention or after the intervention was withdrawn. Both of these covariates were modelled as a dichotomised variable.

As a sensitivity analysis, we analysed by three periods of follow-up (12 weeks, 24 weeks, and 48 weeks) and with only the per-protocol population results. We did all analyses with R version 3.1.2 and OpenBugs version 3.23 (OpenBUGS Project Management Group).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. SK and EJM had full access to all of the data in the study. SK was responsible for the integrity of the data, accuracy of the data analysis, and the final decision to submit for publication.

Panel: Definitions (node) used for categorisation of interventions in the network meta-analysis

Standard of care (SOC)

Instructions by the health-care provider at treatment initiation regarding how to take ART medication and the importance of adhering to it

Enhanced standard of care (eSOC)

Interventions that provided more support than the usual care; the most common type included adherence counselling; other examples included short sessions on education and motivations

Telephone

Interventions that use scripted serial telephone calls or that use calls to support patients. Call frequencies varied from every 2 weeks to 2 months with regular intervals; however, in some cases daily and weekly calls were used at initial stages

Short message service (SMS)

Text messages sent to patients' mobile phones (their own or provided by the study); includes one-way or two-way messages, long and short messages, and at various frequencies (daily, weekly, less than weekly)

Behavioural skills training or medication adherence training (BST/MAT)

Interventions that provide educational training on how to adhere to ART, including interventions that involved module-based learning as well as those designed to improve life skills, behaviours, knowledge, and attitudes.

Multimedia

Interventions that involved materials available online or through the use of a computer or tablet

Cognitive behavioural therapy (CBT)

Includes CBT and cognitive behavioural stress management, as well as interventions that involved counselling with individuals with trained professionals and included interventions that used motivational interviewing

Supporter

Interventions that involved the use of an individual (chosen by clinics or patients) to support treatment adherence, included peer-based support, home visits, treatment assistants, and medication managers and also included directly observed therapy and modified directly observed therapy

Incentives

Included conditional or unconditional cash transfers, financial incentives, or the use of vouchers to support adherence

Device reminder

Interventions that involved the use calendars, alarms, pagers, or disease management assistance system devices

ART=antiretroviral therapy.

Results

85 trials met the inclusion criteria (figure 1, appendix pp 26–63),^{18–102} including all trials in our previous smaller network meta-analysis.¹⁰ Trials were of moderate quality, with low risk of bias (appendix pp 5–25). Adherence was most commonly self-reported (45 papers; 53%); seven papers (8%) did not report adherence measures (appendix p 65). The most common definitions used for adherence were higher than 95% and 100% adherence.

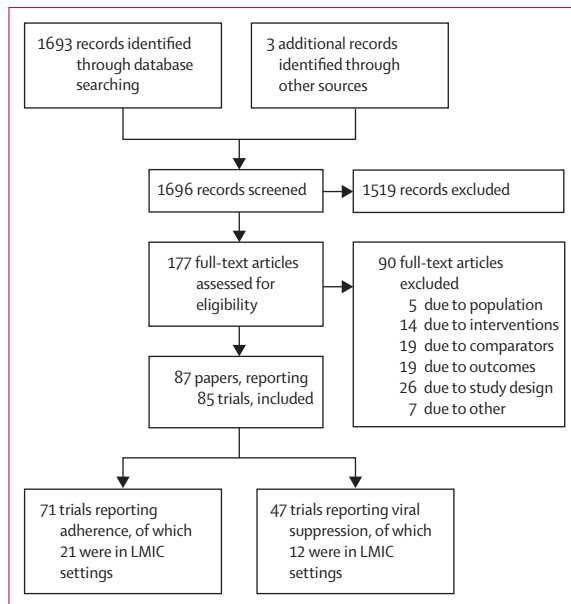


Figure 1: Study selection
LMIC=low-income and middle-income countries.

The most common definitions used for viral suppression were HIV-1 RNA concentrations lower than 400 copies per mL and HIV-1 RNA concentrations lower than 50 copies per mL (appendix p 66). Notable outlying definitions of suppression included HIV-1 RNA lower than 5000 copies per mL²⁷ and a 1.0 log reduction in viral load at 3 months (appendix pp 41–54).⁶⁶ Our exploratory analysis suggested that the choice of thresholds used to define adherence and viral suppression was not an effect modifier, and we therefore pooled data for adherence and viral suppression across studies despite varying definitions.

Our global network included 71 trials (11582 patients, randomised to 151 intervention arms) that reported antiretroviral therapy adherence and 47 trials (7355 patients, randomised to 97 intervention arms) that reported viral suppression (appendix pp 67–69). Of trials done in LMICs (the LMIC network), 21 trials reported antiretroviral therapy adherence (5943 patients, randomised to 50 intervention arms) and 12 trials (3485 patients, randomised to 24 intervention arms) reported viral suppression. The nine categories of interventions formed a network of 19 interventions (nodes) with single interventions or combinations of interventions (figure 2). The network diagrams for the global network and LMIC network are online (appendix pp 73–75, 77).

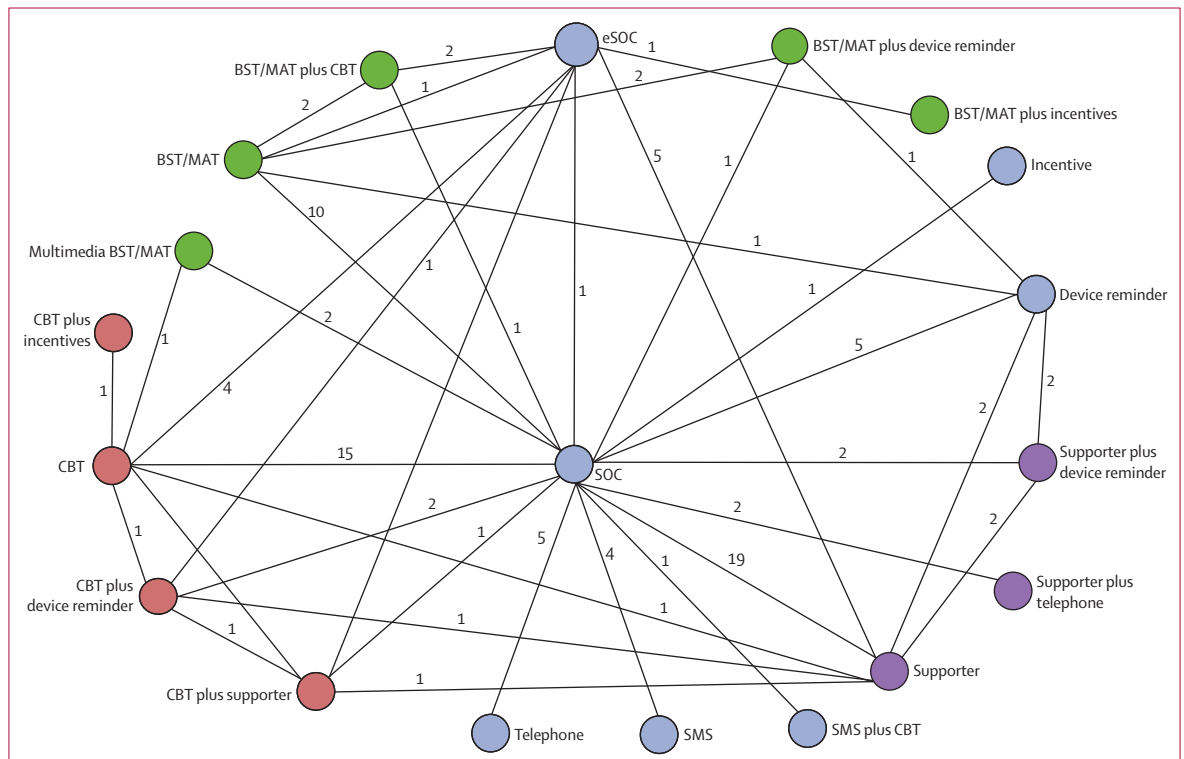


Figure 2: Network of the comparisons between interventions
Each node (circle) represents an intervention, each line represents a direct comparison between interventions, and each number on the lines represents the number of trials with the comparison in question. Green circles show BST/MAT (educational) based interventions, red circles show counselling based interventions, purple circles show supporter based interventions, and blue circles show all other interventions. BST/MAT=behavioural skills training or medication adherence training. CBT=cognitive behavioural therapy. eSOC=enhanced standard of care. SMS=short message services (text messaging). SOC=standard of care.

For the global network analysis, the time discrepancy was an effect modifier for both antiretroviral therapy adherence (coefficient estimate on the log-odds scale -0.43 , 95% CrI -0.75 to -0.11) and viral suppression (-0.48 , -0.84 to -0.12), suggesting that the effects of interventions wane over time. Adjusting for at-risk population led to worst fit for the global network. For the LMIC network analysis, we used unadjusted random-effects models because adjusting for neither population at risk of poor adherence nor the time discrepancy improved the model fit. Moreover, the waning effect could not be detected due to a smaller number of eligible trials.

The results of the pairwise meta-analysis and the network meta-analysis were similar in the global network (figures 3, 4, 5). For antiretroviral therapy adherence, SMS interventions were superior in improving, relative to standard of care, the proportion of patients crossing a study-defined adherence threshold (OR 1.48, 95% CrI 1.00–2.19). Enhanced standard of care had similar effects on adherence as standard of care (1.05, 0.72–1.55). Supporter plus telephone interventions performed better than all interventions, except for cognitive behavioural therapy plus incentives (2.80, 0.41–17.46) and cognitive behavioural therapy plus device reminder (1.12, 0.48–2.62; for details of cognitive behavioural therapy interventions see appendix pp 70–71). However, the supporter plus telephone node only connected with the standard of care node through two trials of high-risk populations (intravenous drug users⁹⁸ and patients with major depression¹⁰⁰), and this limited connection probably influenced the results (figure 2). Multiple interventions showed generally superior adherence to single interventions, indicating additive effects (figure 3). For viral suppression, only cognitive behaviour therapy (OR 1.46, 95% CrI 1.05–2.12) and supporter interventions (1.28, 1.01–1.71) were superior to standard of care in the global network, but their comparative efficacies were slight (figures 4, 5).

The results for adherence were mostly similar between the global network and the LMIC network, and the results of pairwise meta-analysis, where direct evidence was available, were similar to the network meta-analysis in the LMIC network (appendix pp 13–24). SMS interventions improved adherence compared with standard of care (OR 1.49, 95% CrI 1.04–2.09). Supporter plus telephone interventions showed superior efficacies compared with most other interventions (appendix p 76), except for cognitive behaviour therapy plus supporter and SMS plus cognitive behaviour therapy (there was no cognitive behaviour therapy plus incentives node in the LMIC network); however, again because only two trials connected it to standard of care, the observed effects are questionable. Interventions of supporters and SMS plus cognitive behaviour therapy (which were not distinguishable from standard of care in the global network) showed superior efficacies in the LMIC network (appendix p 76). Furthermore, telephone interventions were inferior in

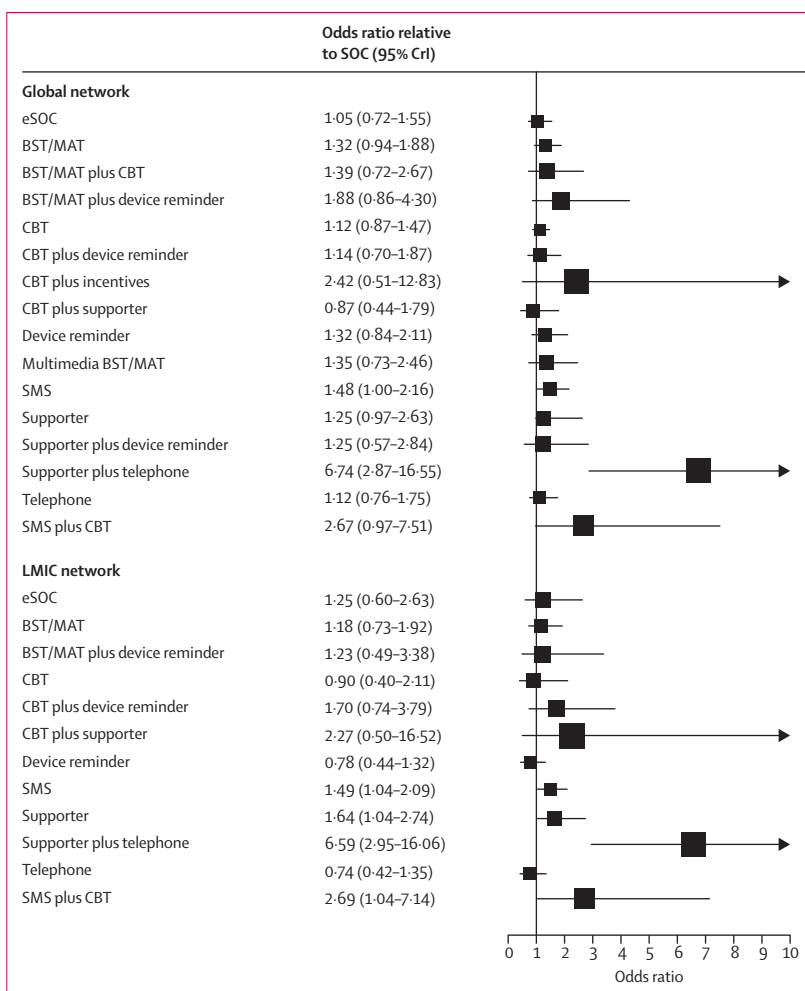


Figure 3: Forest plots for the effect of interventions on adherence in the global and LMIC networks. SOC=standard of care. 95% CrI=95% credible interval. eSOC=enhanced standard of care. BST/MAT=behavioural skills training or medication adherence training. CBT=cognitive behavioural therapy. SMS=short message services (text messaging). LMIC=low-income and middle-income countries.

improving adherence compared with SMS plus cognitive behaviour therapy, supporter interventions alone, and supporter plus telephone interventions. Effects on viral suppression did not differ between interventions in the LMIC network (appendix p 78); however, the network was sparse (appendix p 77) and thus likely to have little power to detect statistically significant differences.

The results from the sensitivity analysis of studies reporting adherence and viral suppression at 12 weeks, 24 weeks, and 48 weeks (appendix pp 79–81, 83–85) and from per-protocol results (appendix pp 82, 86) were relatively consistent with those from the global network, except in a few instances where the comparison was made with a restricted evidence base from a single trial.

Discussion

Supportive strategies, including peer support, two-way text messaging, and counselling, and behavioural strategies,

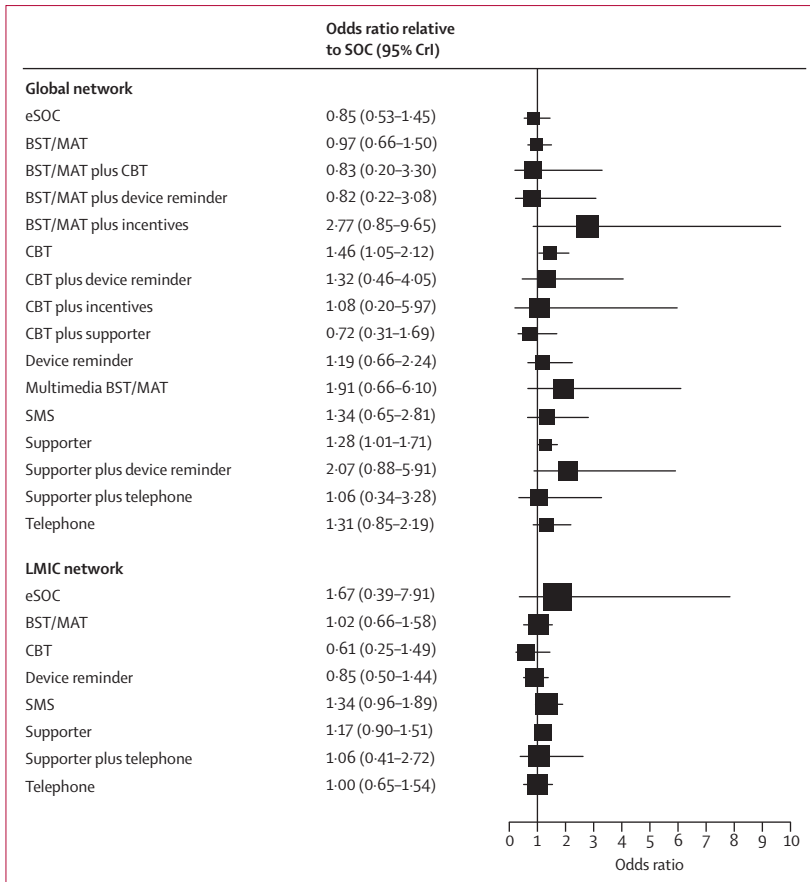


Figure 4: Forest plots for the effect of interventions on viral suppression in the global and LMIC networks
 A random-effects model was used for the global network and a fixed-effects model was used for the LMIC network. SOC=standard of care. 95% CrI=95% credible interval. eSOC=enhanced standard of care. BST/MAT=behavioural skills training or medication adherence training. CBT=cognitive behavioural therapy. SMS=short message services (text messaging). LMIC=lower-income and middle-income countries.

such as training, improve adherence compared with standard adherence support. In general, the effects of even the most effective interventions were slight, and might wane after the intervention is withdrawn, although adherence seemed to increase when effective interventions were combined. In many settings, particularly in LMICs, programmes already include treatment supporters via adherence clubs, family disclosure, and peer supporters, suggesting that, rather than introducing new interventions, a focus on rendering the delivery of existing services to be more holistic might be a practical way to improve outcomes.

Some interventions are more directly applicable to geographical settings. Cognitive behaviour therapy and other counselling interventions that require trained professionals might be more feasible in high-income countries where appropriately trained professionals are generally already part of the health service and the number of patients in need is low. Despite some limitations (eg, lack of full population coverage, shared phones, and unstable phone numbers), SMS interventions might be particularly suitable for LMICs given the ability to reach large numbers

of patients at comparatively lower cost. By analysing the data in multiple ways, we were able to draw stronger inference on the generalisability of findings across settings. For example, the LMIC network analysis showed that telephone-based interventions were less efficacious in this setting than in the global setting. Outside of supporter plus telephone interventions, no interventions were trialled only in very-high-risk populations, making it plausible that the results are generalisable.

We also found that the effects of any interventions seem to wane over time after they are withdrawn. Because adherence to antiretroviral therapy is a lifelong requirement, the paucity of information about how to promote adherence within populations who have been receiving therapy for long periods of time is important. Barriers to adherence are complex and change over time.¹⁰³ Long-term interventions are clearly needed to differentiate individuals at higher risk of poor adherence and treatment failure.¹⁰⁴

The main strength of our work is the assessment of a large network of evidence and the use of network meta-analysis, which allowed for a broad assessment of the effectiveness of different interventions. However, the existing evidence base limited our analysis. Very few trials were available for the viral suppression outcome. Another limitation related to our categorisation of interventions; we combined interventions into broad categories to assist with interpretation and acknowledge that a different approach to categorisation might have altered the results. Moreover, there was notable variation in the assessment method of adherence (eg, use of medication event monitoring system, self-reporting, and pill counts; appendix p 65). These inconsistent measurements might have introduced heterogeneity in our meta-analyses. We excluded studies that used real-time monitoring of patients for adherence assessment because this changes adherence behaviours.¹⁰⁵

Our findings identified several directions for future research. First, screening interventions are needed to better identify individuals who are at risk of poor adherence. Second, high-quality research is needed to support certain patient populations, notably adolescents and children. Third, understanding the waning effect of interventions is needed and strategies should be tailored accordingly. Finally, outcome measures for adherence intervention research should be standardised to improve comparability of studies and consequently the formulation of policy recommendations.

Previous WHO guidance focused narrowly on promoting the use of text messaging to improve adherence on the basis of efficacy data from simple and robust trials.¹⁰⁶ WHO has recently expanded its recommendations for adherence support due to the findings of this Article and they recommend a series of options that include peer counsellors, text messages, reminder devices, cognitive behavioural therapy, behavioural skills training, and medication adherence

	Intervention		Adherence outcome results, OR (95% CrI)					Viral suppression outcome results, OR (95% CrI)									
SOC	0.85 (0.53-1.45)	0.97 (0.66-1.50)	0.83 (0.20-3.30)	0.82 (0.22-3.08)	2.77 (0.85-9.65)	1.46 (1.05-2.12)	1.32 (0.46-4.05)	1.08 (0.20-5.97)	0.72 (0.31-1.69)	1.19 (0.66-2.24)	1.91 (0.66-6.10)	1.34 (0.65-2.81)	1.28 (1.01-1.71)	2.07 (0.88-5.91)	1.06 (0.34-3.28)	1.31 (0.85-2.19)	..
1.05 (0.72-1.55)	eSOC	1.15 (0.64-2.01)	0.98 (0.26-3.44)	0.98 (0.25-3.74)	3.25 (1.13-9.88)	1.72 (1.08-2.70)	1.55 (0.48-5.06)	1.27 (0.22-6.97)	0.85 (0.32-2.15)	1.39 (0.64-3.04)	2.23 (0.71-7.59)	1.59 (0.63-3.70)	1.51 (0.87-2.58)	2.42 (0.88-7.87)	1.25 (0.35-4.24)	1.53 (0.78-3.07)	..
1.32 (0.94-1.88)	1.25 (0.79-2.02)	BST/MAT	0.85 (0.20-3.48)	0.84 (0.24-2.92)	2.84 (0.86-10.00)	1.50 (0.91-2.50)	1.35 (0.44-4.41)	1.11 (0.19-6.32)	0.74 (0.28-1.87)	1.22 (0.59-2.55)	1.96 (0.64-6.55)	1.39 (0.59-3.15)	1.31 (0.83-2.15)	2.11 (0.81-6.61)	1.09 (0.32-3.60)	1.34 (0.74-2.57)	..
1.39 (0.72-2.67)	1.32 (0.65-2.62)	1.05 (0.51-2.11)	BST/MAT plus CBT	0.98 (0.16-6.52)	0.33 (0.63-18.90)	1.76 (0.46-7.16)	1.58 (0.29-9.38)	1.32 (0.15-11.09)	0.87 (0.17-4.41)	1.45 (0.32-6.70)	2.29 (0.42-13.72)	1.63 (0.34-7.79)	1.53 (0.39-6.51)	2.49 (0.50-12.95)	1.29 (0.22-7.88)	1.59 (0.38-7.09)	..
1.88 (0.86-4.30)	1.79 (0.77-4.32)	1.43 (0.66-3.22)	1.36 (0.50-3.86)	BST/MAT plus device reminder	3.34 (0.61-19.59)	1.79 (0.47-6.74)	1.60 (0.30-8.90)	1.30 (0.15-11.18)	0.88 (0.18-4.04)	1.44 (0.35-6.09)	2.34 (0.45-12.49)	1.64 (0.36-7.20)	1.56 (0.41-5.92)	2.52 (0.51-12.14)	1.30 (0.23-7.16)	1.59 (0.40-6.44)	..
..	BST/MAT plus incentives	0.53 (0.16-1.67)	0.48 (0.09-2.39)	0.38 (0.05-2.88)	0.26 (0.06-1.08)	0.43 (0.11-1.95)	0.71 (0.14-3.43)	0.49 (0.11-1.88)	0.47 (0.13-1.52)	0.74 (0.17-4.18)	0.38 (0.07-1.93)	0.47 (0.13-1.71)	..
1.12 (0.87-1.47)	1.07 (0.72-1.58)	0.85 (0.56-1.29)	0.81 (0.41-1.64)	0.60 (0.26-1.35)	..	CBT	0.90 (0.31-2.74)	0.74 (0.14-3.88)	0.49 (0.20-1.14)	0.81 (0.40-1.62)	1.30 (0.45-4.14)	0.93 (0.40-2.03)	0.88 (0.59-1.32)	1.42 (0.55-4.18)	0.73 (0.22-2.36)	0.90 (0.51-1.63)	..
1.14 (0.70-1.87)	1.09 (0.61-1.92)	0.86 (0.48-1.57)	0.82 (0.36-1.86)	0.62 (0.23-1.51)	..	1.02 (0.60-1.71)	CBT plus device reminder	0.81 (0.10-5.93)	0.54 (0.13-2.03)	0.89 (0.26-3.06)	1.42 (0.32-6.84)	1.02 (0.27-3.67)	0.98 (0.31-2.92)	1.55 (0.38-6.76)	0.80 (0.16-3.81)	0.99 (0.30-3.25)	..
2.42 (0.51-12.83)	2.30 (0.46-12.61)	1.84 (0.36-10.02)	1.73 (0.32-10.47)	1.29 (0.22-8.18)	..	2.15 (0.46-11.23)	1.02 (0.60-1.71)	CBT plus incentives	0.68 (0.10-4.33)	1.13 (0.18-6.78)	1.78 (0.24-14.07)	1.25 (0.19-7.92)	1.19 (0.22-6.73)	1.96 (0.28-12.87)	0.97 (0.13-7.79)	1.23 (0.21-7.26)	..
0.87 (0.44-1.79)	0.82 (0.40-1.78)	0.66 (0.31-1.45)	0.63 (0.25-1.65)	0.46 (0.16-1.32)	..	0.77 (0.39-1.60)	2.15 (0.46-11.23)	0.36 (0.06-1.99)	CBT plus supporter	0.68 (0.10-4.33)	1.13 (0.18-6.78)	1.78 (0.24-14.07)	1.25 (0.19-7.92)	1.19 (0.22-6.73)	1.96 (0.28-12.87)	0.97 (0.13-7.79)	..
1.32 (0.84-2.11)	1.26 (0.70-2.28)	1.00 (0.57-1.73)	0.95 (0.43-2.13)	0.70 (0.29-1.64)	..	1.18 (0.70-2.00)	0.77 (0.39-1.60)	0.54 (0.10-2.88)	1.52 (0.65-3.45)	Device reminder	1.61 (0.40-5.96)	1.14 (0.43-2.89)	1.09 (0.57-2.04)	1.75 (0.68-4.32)	0.89 (0.24-3.24)	1.10 (0.52-2.41)	..
1.35 (0.73-2.46)	1.28 (0.62-2.60)	1.02 (0.50-2.03)	0.97 (0.40-2.34)	0.72 (0.25-1.92)	..	1.20 (0.62-2.28)	1.18 (0.70-2.00)	1.56 (0.09-2.99)	1.55 (0.60-3.83)	1.02 (0.47-2.16)	Multi-media BST/MAT	0.70 (0.18-2.51)	0.68 (0.21-2.01)	1.07 (0.26-5.63)	0.55 (0.11-2.60)	0.68 (0.20-2.20)	..
1.48 (1.00-2.16)	1.41 (0.81-2.40)	1.12 (0.66-1.87)	1.06 (0.50-2.29)	1.79 (0.31-1.85)	..	1.32 (0.82-2.07)	1.20 (0.62-2.28)	0.61 (0.11-3.09)	0.70 (0.15-3.67)	1.12 (0.61-2.03)	1.10 (0.63-2.26)	SMS	0.95 (0.45-2.13)	1.54 (0.50-5.01)	0.79 (0.21-3.01)	0.97 (0.43-2.44)	..
1.25 (0.97-1.63)	1.19 (0.78-1.82)	0.94 (0.62-1.44)	0.90 (0.45-1.83)	0.66 (0.28-1.50)	..	1.11 (0.79-1.57)	1.32 (0.82-2.07)	0.51 (0.10-2.51)	1.44 (0.68-2.96)	0.94 (0.57-1.57)	0.92 (0.48-1.83)	0.84 (0.54-1.37)	Supporter	1.60 (0.66-4.52)	0.83 (0.25-2.59)	1.01 (0.60-1.77)	..
1.25 (0.57-2.84)	1.20 (0.49-2.91)	0.95 (0.40-2.27)	0.90 (0.32-2.59)	0.67 (0.21-2.00)	..	1.12 (0.48-2.62)	1.11 (0.79-1.57)	0.52 (0.08-3.04)	1.45 (0.49-4.14)	0.95 (0.41-2.21)	0.93 (0.34-2.58)	0.85 (0.35-2.10)	1.00 (0.44-2.27)	Supporter plus device reminder	0.51 (0.12-2.14)	0.63 (0.22-1.73)	..
6.74 (2.87-16.55)	6.42 (2.55-17.10)	5.13 (1.99-13.27)	4.85 (1.69-14.93)	3.58 (1.09-11.72)	..	5.99 (2.44-15.28)	1.12 (0.48-2.62)	2.80 (0.41-17.46)	7.82 (2.48-23.80)	5.14 (1.90-13.83)	5.00 (1.78-14.76)	4.58 (1.79-12.15)	5.41 (2.19-13.70)	5.41 (1.65-17.67)	Supporter plus telephone	1.24 (0.37-4.33)	..
1.12 (0.76-1.75)	1.07 (0.62-1.91)	0.85 (0.50-1.48)	0.81 (0.38-1.80)	0.60 (0.24-1.45)	..	1.00 (0.62-1.66)	5.99 (2.44-15.28)	0.46 (0.08-2.39)	1.29 (0.57-2.91)	0.85 (0.46-1.60)	0.83 (0.41-1.79)	0.76 (0.44-1.38)	0.90 (0.56-1.48)	0.89 (0.37-2.23)	0.17 (0.06-0.43)	Telephone	..
2.67 (0.97-7.51)	2.54 (0.86-7.59)	2.02 (0.69-5.96)	1.92 (0.57-6.49)	1.42 (0.38-5.13)	..	2.37 (0.84-6.81)	1.00 (0.62-1.66)	1.11 (0.15-7.24)	3.06 (0.90-10.41)	2.02 (0.66-6.20)	1.99 (0.61-6.50)	1.81 (0.61-5.38)	2.14 (0.75-6.15)	2.14 (0.59-7.76)	0.40 (0.10-1.49)	2.38 (0.80-7.12)	SMS plus CBT

Figure 5: Network meta-analyses comparing effects on adherence and viral suppression for the global network
 Data are OR (95% CrI) of the row intervention relative to the column intervention (eg, the effect of eSOC relative to SOC is 1.05 with respect to adherence). Data in bold show comparisons that are statistically significant. ORs above 1 show that the row intervention is superior to the column intervention.
 OR=odds ratio.
 95% CrI=95% credible interval.
 SOC=standard of care.
 eSOC=enhanced standard of care. BST/MAT=behavioural skills training or medication adherence training.
 CBT=cognitive behavioural therapy. SMS=short message services (text messaging).

training.¹⁰⁷ Moreover, WHO now recognises that nutritional and financial support might be of value in addressing specific challenges that affect adherence, although the evidence was not compelling.^{9,33,108}

We identified a number of effective interventions to improve adherence to antiretroviral therapy both generally and in LMICs where most people receiving treatment reside. As the latest WHO guidelines are adopted, HIV programmes should consider adopting or adapting these interventions according to resource availability and programme outcomes. This will provide important opportunity to evaluate the benefit of these interventions in routine practice, in turn generating new evidence that will support an increasingly nuanced evidence-based approach to supporting adherence for the now 37 million people eligible for antiretroviral therapy.

Contributors

SK, MES, NF, KT, and EJM conceptualised and designed the study. SK, JJHP, KC, NF, JIF and KT acquired, analysed, and interpreted data. SK, JJHP, and EJM drafted the manuscript. All authors critically revised the manuscript for important intellectual content. SK, KC, KT, and EJM did the statistical analysis. EJM obtained funding. SK, MES, NF, JBN, and EJM provided administrative, technical, or material support. KT, NF, JBN and EJM supervised the study.

Declaration of interests

We declare no competing interests.

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