PUBLIC HEALTH RESEARCH

Effectiveness of Phone Reminders to Improve Adherence to Anti-Retroviral Therapy: A Meta-Analysis

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ABSTRACT

Introduction	Adherence to anti-retroviral therapy (ART) regimens remains a difficult issue. Thus, it was hoped that the use of phone reminders would improve adherence.
Methods	The Cochrane database was searched using selected keywords for this meta-analysis. We included randomised, controlled trials (RCTs) that utilised interventions with phone reminder and reported adherence outcomes, as the proportion of prescribed pills taken, the scores on an adherence questionnaire, or the follow-up rate. Two independent authors screened titles of article for inclusion, extracted the relevant data, and assessed articles for risk of bias.
Results	Seven RCTs published between 2010 and 2017 were selected for inclusion in this review. The sample size ranged from 76 to 631 participants. Most RCTs used short message service (SMS) and phone call reminders as interventions. The rate of adherence was 1.17-fold greater among those who received phone reminders than those who did not, which was statistically significant ($Z = 2.86$, $p = 0.004$). Those who received phone reminders showed a 17% higher likelihood for adherence compared with those who did not receive any phone reminder interventions.
Conclusions	Phone reminders remain significantly effective means for improving adherence.
Keywords	Anti-Retroviral Agents - Cell Phone- Smartphone - Compliance - Medication Adherence.

INTRODUCTION

Human immunodeficiency virus (HIV), and the associated development of acquired immunodeficiency syndrome (AIDS), has caused 32 million deaths, globally. Regionally, two-thirds of worldwide HIV incidence occurred in the African region, where, as of 2017, nearly 26 million HIV-affected individuals reside.[1] Although since year 2012, the World Health Organization (WHO)[2] introduced the theme "Getting to Zero: Zero new Human Immunodeficiency Virus (HIV) infections, Zero deaths from AIDS-related illness and Zero discrimination" during World AIDS Day, the disease remains a serious public health problem.

The first anti-retroviral therapy (ART) tested in clinical trials was azidothymidine (AZT), which was later called zidovudine (ZDV). Starting in 1987, ZDV was approved for use in patients, but only those with advanced-stage HIV. Today, many types of ARTs are available, ranging from the traditional classes [nucleoside reverse transcriptase inhibitors (NRTIs), non-NRTIs, and protease inhibitors] and newer classes (entry/attachment inhibitors and integrase inhibitors).[3]

Adherence to ART regimens remains a problem, due to high costs and long periods of follow-up. The WHO[4] defines adherence as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider". A great deal of evidence is available on the benefits of adherence to recommended ART regimens among those affected by HIV. For example, a randomised, controlled trial (RCT) found that the early initiation of ART reduced the risk of HIV-transmission among serodiscordant couples by 96%.[5] Furthermore, adherence may be closely related to the infectivity of HIV because increased viral shedding inside the genital compartment can occur due to poor adherence, increasing infectivity.[6,7]

The WHO found that phone reminders were among the most popular types of ART adherence interventions being studied for effectiveness, in addition to cognitive-behavioural interventions, education, treatment supporter, and directly observed therapies. More than 16% of the studies included in this review studied the effectiveness of intervention methods, although these studies yielded conflicting results.[8] In the present meta-analysis, we limited our review to clinical trials that studied phone reminders as interventions, and those that reported the outcome, in terms of ART adherence. The most recent meta-analysis focusing on this topic was done in 2012, more than five years ago. Interestingly, a study found that weekly mobile phone text-messaging was an effective method for improving adherence to ART when compared with standard care alone.[9] The technological landscape has changed tremendously during the past five years and hence, this review provides an updated synthesis of the body of knowledge regarding whether phone reminders remain an effective intervention for improving adherence to ART regimens among patients with HIV.

METHODS

We conducted this review in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.[10] Although many databases exist, we focused on the Cochrane Library because our study objective was to specifically review RCTs examining the effectiveness of phone reminders for improving adherence to ART regimens. The guidelines presented by the Cochrane Collaboration are often regarded as the gold standard for performing meta-analytic reviews. Interestingly, when compared with matched Cochrane reviews, a study found that non-Cochrane reviews showed significantly higher effect sizes and lower precision, based on a matched-pair analysis.[11] Furthermore, an adequate review has been shown to be attainable by searching a single database.[12-14] Data was searched using the patient, intervention, comparison, and outcome (PICO) search strategy.[15] The identified keywords, based on medical subheading (MeSH)[16] terms, were the following:

(anti*retroviral* OR "post*exposure prophylaxis" OR "post*exposure prevention*") AND ("mobile phone*" OR smartphone* OR "cell phone*" OR telephone* OR "mobile telephone*" OR phone* OR "cell* phone*" OR "cell* telephone*") AND (adhere* OR compliance).

A broad search symbol, such as the asterisk (*), was used to ensure the inclusion of all relevant studies. The inclusion criteria for the study selection were as follows: (a) clinical trial; (b) phone as intervention; and (c) outcome reported regarding ART adherence. The exclusion criteria for this review were as follows: (a) review; (b) no intervention; (c) abstract or conference proceedings; (d) not related to ART; (e) no full article; (f) not in English; (g) study protocol or ongoing trials; (h) included other equipment or mobile applications for pill counting; and (i) interventions were combined with other non-phone related or behaviour-related interventions. Irrelevant studies were eliminated.
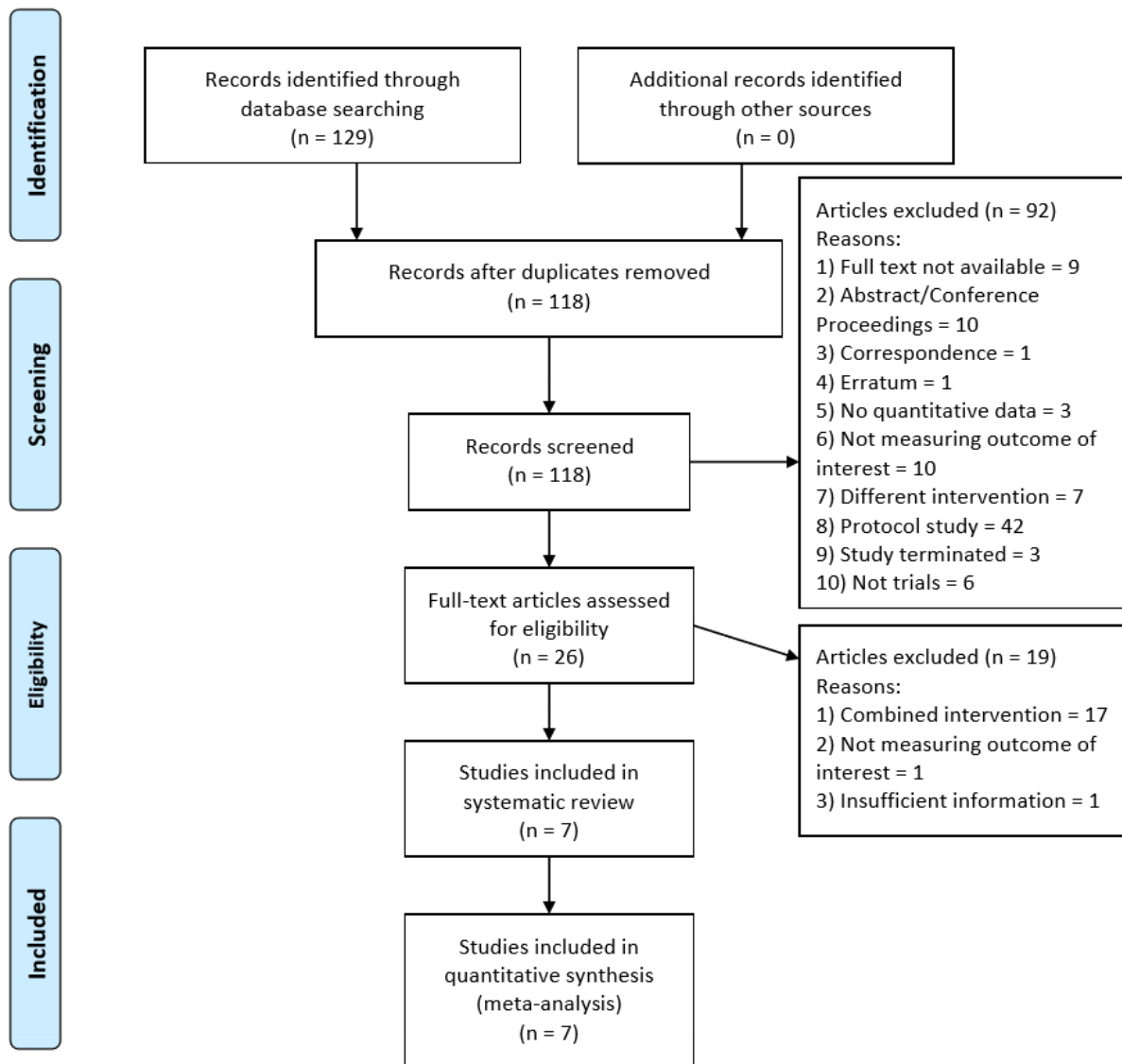
Selection of Studies
During the initial stage, search results were imported into a bibliographic citation management software (EndNote X8). Duplicate references were removed before the authors selected potential papers for inclusion. This process was divided into three phases, during which the articles were screened, first by title, then by abstract, and finally, the whole text was reviewed for relevance. Article selection was

performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram;[17] as outlined in Figure 1. First, the titles of the articles were screened for relevance and duplication. Next, the abstracts and whole texts for each selected article were critically reviewed and appraised. Articles that have combine interventions (non-phone related or behaviour-related interventions) were excluded as they may influence the outcome of adherence being studied. Blinded article selection was performed by two reviewers, a student of Doctor of Public Health (AAAW) and his lecturer (HI), at Universiti Kebangsaan Malaysia (UKM).

PRISMA 2009 Flow Diagram

Figure 1 Process of Study Selection.

Operational Variable Definition
In this study, we included RCTs that assessed adherence in terms of taking medications and attending follow-up visits. Adherence outcomes were measured either via follow-up rate, the proportion of prescribed medications taken by patients, or the total score on an adherence questionnaire.

Data Extraction
Data extraction pertaining to adherence (follow-up rate, the proportion of prescribed medications taken by patients, or the total score on adherence questionnaire) was performed by two authors (AAAW, HI), independently, using a predetermined data collection form. The data was then crossed checked by both authors to minimise errors. In case of dispute between two authors, reconciliation meeting was being exercised.

Risk of Bias Assessment
The risk of bias assessment was performed using the latest Cochrane methods for assessing the risk of bias, which were described in the Cochrane Handbook, version 5.1.0.[10] According to the guidelines described by the handbook, Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach was applied to assess the quality of evidence and to prepare summary of findings tables, using the GRADEpro Guideline Development Tool application.[18]

Data synthesis
Data synthesis was performed using Review Manager 5.2,[19] and, where appropriate, we combined studies using a fixed-effects model. Results were calculated using a risk ratio (RR), with a 95% confidence interval (CI), and a p-value <0.05 was considered to be significant. Funnel plots were used to assess publication bias by plotting the effect sizes and trial sizes.

Statistical heterogeneity was assessed by inspecting forest plots for overlapping confidence intervals, applying the χ^2 test (p-value <0.10 was considered to be statistically significant) and the I^2 statistic (I^2 value of 50% was used to denote moderate levels of heterogeneity). If heterogeneity was detected and if we still considered combining studies to be clinically meaningful, we used a random-effects model. Sensitivity analysis was performed to determine which factors contributed to high heterogenicity.

Our meta-analysis of the data on adherence, based on the proportion of prescribed pills taken, showed great heterogeneity. Therefore, we decided to perform subgroup analyses based on the number of phone interventions that were delivered to subjects (single/combined). Three articles were examined for the sub-group analysis of studies that examined the effects of single intervention. Two articles were included in the sub-group analysis performed for articles that utilised combined interventions, both of them provided two phone interventions to the subjects. Other meta-analyses were performed on adherence data that were based on questionnaire scores and follow-up attendance.

RESULTS
Descriptive Analysis
Seven RCTs were included in this review, published between the years 2010 and 2017.[20-26] The sample size ranged from 76 participants to 631 participants. Five of the RCTs used either short messages service (SMS) and phone call reminders as interventions.[20-24] Two studies[25,26] used combined interventions, both through the phones, with one study using automated voice reminders and pictorial messages, whereas the other study used SMS and phone call reminders. All included RCTs were performed in lower-middle-, upper-middle- and high-income Countries.[27] A summary of all studies included is shown in Table 1.

Table 1 Summary of the Included Studies

Author (year)[citation]	Duration (weeks)	Subjects	Intervention (Single / Combined)	Outcome	Country
Lester (2010)[20]	24	538	Single; SMS	Proportion of prescribed pills taken	Kenya
Uzma (2011)[21]	10	76	Single; Phone call	Proportion of prescribed pills taken	Pakistan
Mbuagbaw (2012)[22]	24	200	Single; SMS	Proportion of prescribed pills taken[a]	Cameroon
Robbins (2013)[23]	160	333	Single; Phone call	Questionnaire Score	USA
Huang (2013)[24]	12	93	Single; Phone call	1) Questionnaire Score 2) Follow-Up Attendance	Myanmar
Shet (2014)[25]	96	631	Combined; 1) Phone call 2) Pictorial message	Proportion of prescribed dose taken	India
Abdul-rahman (2017)[26]	24	242	Combined; 1) SMS 2) Phone call	1) Proportion of prescribed pills taken 2) Questionnaire Score 3) Follow-Up Attendance	Malaysia

[a]Visual Analogue Scale

Abbreviation:
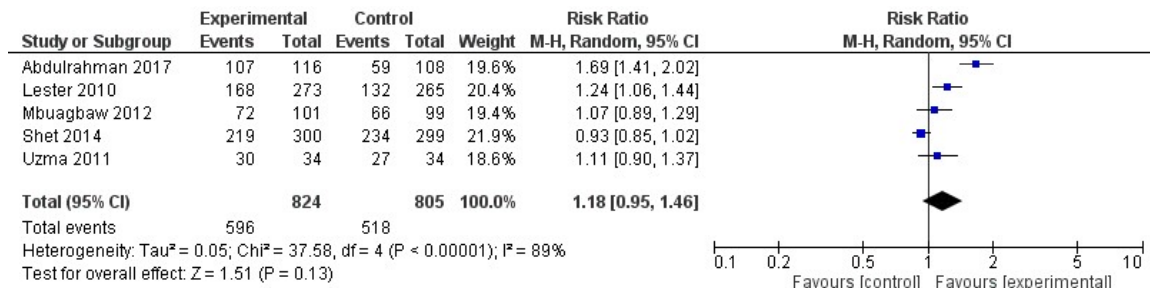USA – United States of America

Meta-Analysis
Adherence Based on the Proportion of Prescribed Pills Taken

       Five RCTs reported adherence outcomes based on the proportion of prescribed pills taken.[20-22,25,26] Our analysis found that those who received any form of phone reminders had no difference in the likelihood of adherence than those who only received standard care (RR=1.18; 95%CI, 0.95, 1.46, Z=1.51, p=0.13, Figure 2a). The certainty of the evidence provided in these studies was graded Low via GRADEpro[18] (Table II). All the five studies were heterogenous for measurements of adherence, based on the results of heterogeneity tests (χ^2=37.58, df=4, p<0.001; I^2=89%, Figure 2a).

Sub-Group Analysis: Adherence Based on the Proportion of Prescribed Pills Taken (Single Intervention)

       Our analysis found that those who received single phone reminders had a 17% higher likelihood for adherence compared with those who did not receive any phone reminders intervention (RR=1.17, 95%CI: 1.05, 1.31), which was statistically significant (Z=2.86, p=0.004). All three studies[20–22] were homogenous for measuring similar outcomes, based on heterogeneity tests (χ^2=1.63, df=2, p=0.44; I^2=0%, Figure 2b). The certainty of the evidence reported by these studies was graded High via GRADEpro[18] (Table 2).
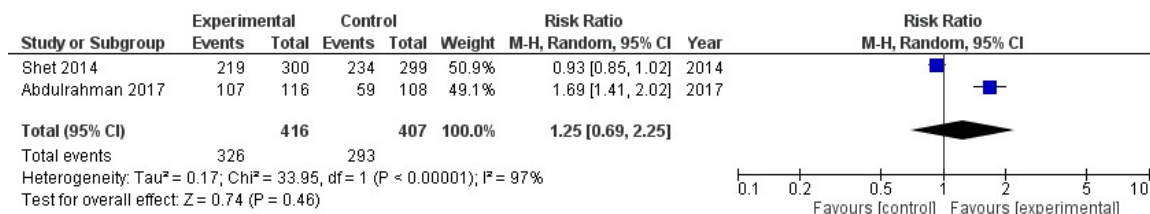
a. Adherence Based on the Proportion of Prescribed Pills Taken (single and combined intervention)

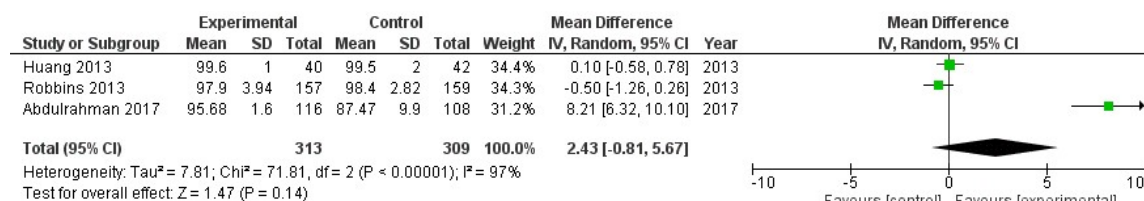b. Adherence Based on the Proportion of Prescribed Pills Taken (Single Intervention)

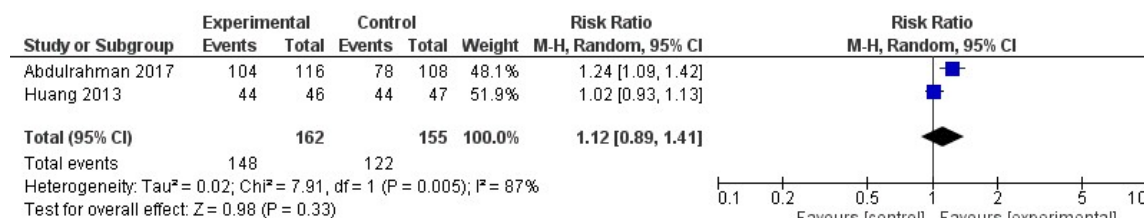c. Adherence Based on Proportion of Prescribed Pills Taken (Combined Intervention)

d. Adherence Based on Questionnaire Score

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Huang 2013	99.6	1	40	99.5	2	42	34.4%	0.10 [-0.58, 0.78]	2013
Robbins 2013	97.9	3.94	157	98.4	2.82	159	34.3%	-0.50 [-1.26, 0.26]	2013
Abdulrahman 2017	95.68	1.6	116	87.47	9.9	108	31.2%	8.21 [6.32, 10.10]	2017
Total (95% CI)			**313**			**309**	**100.0%**	**2.43 [-0.81, 5.67]**	

Heterogeneity: Tau² = 7.81; Chi² = 71.81, df = 2 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.47 (P = 0.14)

Mean Difference IV, Random, 95% CI. Favours [control] Favours [experimental]

e. Adherence Based on Follow-Up Attendance

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abdulrahman 2017	104	116	78	108	48.1%	1.24 [1.09, 1.42]
Huang 2013	44	46	44	47	51.9%	1.02 [0.93, 1.13]
Total (95% CI)		**162**		**155**	**100.0%**	**1.12 [0.89, 1.41]**
Total events	148		122			

Heterogeneity: Tau² = 0.02; Chi² = 7.91, df = 1 (P = 0.005); I² = 87%
Test for overall effect: Z = 0.98 (P = 0.33)

Risk Ratio M-H, Random, 95% CI. Favours [control] Favours [experimental]

Figure 2 Meta-analysis results with forest plot and heterogeneity test comparing adherence based on prescribed pills taken (single and combined intervention, and single and combined intervention), questionnaire score and follow-up attendance

Sub-Group Analysis: Adherence Based on the Proportion of Prescribed Pills Taken (Combined Intervention)

Our analysis found that those who received combined forms of phone reminders had no difference in the likelihood for adherence than those who only received standard care (RR=1.25, 95%CI: 0.69, 2.25, Z=0.74, p=0.46). Neither studies[25,26] was homogenous in measuring adherence, based on heterogeneity tests (χ^2=33.95, df=1, p<0.001; I²=97%, Figure 2c). The certainty of evidence reported by these studies was graded Very Low via GRADEpro[18] (Table 2).

Adherence Based on Questionnaire Scores

Three RCTs reported adherence outcomes based on questionnaire scores.[23,24,26] Our analysis found that those who received phone reminders had no difference in the likelihood of higher adherence scores compared with those who only received standard care [mean difference (MD)=2.43, 95%CI: -0.81, 5.67, Z=1.47, p=0.14]. These three studies were not homogenous in measuring similar outcomes, based on heterogeneity tests (χ^2=71.81, df=2, p<0.001; I²=97%, Figure 2d). The certainty of the evidence reported by these studies was graded High via GRADEpro[18] (Table 2).

Adherence Based on Follow-Up Attendance

Two RCTs reported adherence outcomes based on follow-up attendance.[24,26] Our analysis found that those who received phone reminders had no difference in the likelihood of adherence compared with those who only received standard care (RR=1.12, 95%CI: 0.89, 1.41, Z=0.98, p=0.33). These studies were not homogenous in measuring similar outcomes, based on heterogeneity tests (χ^2=7.91, df=1, p=0.005; I²=87%, Figure 2e).

Table 2 GRADEpro Summary of Findings (Phone reminder intervention compared with no phone reminder intervention for improving adherence to anti-retroviral therapy regimens)

Outcomes	No. of partici-pant (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with no phone reminder intervention	Risk difference with phone reminder
Adherence Based on the Proportion of Prescribed Pills Taken	1629 (5 RCTs)	⊕⊕◯◯ LOW[a,b]	RR 1.18 (0.95 to 1.46)	643 per 1,000	116 more per 1,000 (32 fewer to 296 more)
Sub-Group Analysis: Adherence Based on the Proportion of Prescribed Pills Taken (Single Intervention)	806 (3 RCTs)	⊕⊕⊕⊕ HIGH	RR 1.17 (1.05 to 1.31)	565 per 1,000	96 more per 1,000 (28 more to 175 more)

Sub-Group Analysis: Adherence Based on the Proportion of Prescribed Pills Taken (Combined Intervention)	823 (2 RCTs)	⊕○○○ VERY LOW[c,d,e]	RR 1.25 (0.69 to 2.25)	720 per 1,000	180 more per 1,000 (223 fewer to 900 more)
Adherence Based on Questionnaire Score	622 (3 RCTs)	⊕⊕⊕⊕ HIGH	MD 2.43 (-0.81 to 5.67)	The mean adherence Based on Question-naire Scores was 0	MD 2.43 higher (0.81 lower to 5.67 higher)
Follow-up Attendance	317 (2 RCTs)	⊕⊕⊕○ MODERATE[f]	RR 1.12 (0.89 to 1.41)	787 per 1,000	94 more per 1,000 (87 fewer to 323 more)

Abbreviations: CI: Confidence interval; RR: Risk ratio; MD: Mean difference
The certainty of the evidence reported by these studies was graded Moderate via GRADEpro[18] (Table 2).

[a]Different outcome measurements for adherence across studies
[a]Indirect intervention
[a]Evidence of publication bias, as determined by plots that fell outside of the effective zone
[a]Different intervention being applied, with a different adherence measurement tool being used
[a]Indirect outcome measured
[a] Total number of events was less than 300 (rule of thumb)

DISCUSSION

Several types of adherence outcomes were measured in the studies included in our meta-analysis. Most of the studies measured adherence in terms of the proportion of prescribed medications taken. Only the study by Mbuagbaw et al.,[22] measured adherence using the Visual Analogue Scale, which was represented as adherence in terms of the proportion of prescribed medications taken for this study.

Majority of the articles had low risks of publication bias, as shown by funnel plots generated during the meta-analysis, except when examining two studies that used combined interventions,[25,26] during sub-group analyses. Many adherence outcomes measured in this study were shown to be heterogenous, which is likely due to different operational definitions used for the adherence outcome measured and differences in the interventions given to the experimental groups being studied.

An analysis of five articles[20-22,25,26] that gauged adherence based on the proportion of prescribed pills taken yielded high heterogeneity, primarily due to the interventions being delivered differently between studies. Three of these articles[20-22] delivered only one type of intervention, whereas the other two articles[25,26] delivered combined interventions.

During sub-group analyses, only adherence based on the proportion of prescribed pills taken after a single intervention yielded significant results.[20-22] The certainty of the evidence reported by these studies was graded High via GRADEpro.[18] Thus, we were able to conclude from this meta-analysis study that those who received a phone reminder had a 17% higher likelihood for adherence compared with those who did not receive a phone reminder intervention. This finding was consistent with the previous meta-analysis performed by Horvath et al.,[9] which found that weekly mobile phone text-messaging was effective for improving adherence to ART compared with standard care.

In this meta-analysis, our results suggested that phone reminders were a good method for improving adherence. This contemporary finding bears a close resemblance to the conventional information-motivation-behavioural (IMB) skills model described by Fisher et al.[27] Phone reminders may serve as both the information and motivation arms that influence adherence behavioural skills and behaviour. For example, the reminder may contain information regarding the medication dose, side-effects, and follow-up. Alternatively, social motivation may be gained from perceived social support for adherence, through phone calls, SMS, and pictorial messages.

Although SMS was thought to be the most common mode of communication, other technological advancements, such as WhatsApp and Snapchat, have also gained increasing popularity.[28] Moreover, a separate study indicated that that the most popular form of social media for receiving messages was WhatsApp.[29] Much evidence has supported the use of social media as stepping stones to improve adherence for medication and follow-up attendance among patients. For example, social media interventions using social applications and Facebook have resulted in significant improvements in adherence to HIV follow-up attendance.[30] Similarly, other researchers found that social media

forums improved adherence to medication regimens among patients with Systemic Lupus Erythematosus.[31]

Although not significant, we reviewed the sub-group analysis examining adherence based on the proportion of prescribed pills taken with combined interventions further explore the contradictory findings reported by these RCTs compared with those studies that only used phone reminder interventions. On the one hand, those subjects who received automated voice reminders and pictorial messages had a 7% reduced likelihood for adherence compared with those who received standard care.[25] On the other hand, those who received individualised SMS, combined with telephone call reminders, had a 69% increased likely hood for adherence compared with those who received standard care.[26] Comparatively, we can assume that a human touch was still valued to motivate adherence behaviour; therefore, receiving person-to-person communications as reminders, such as individualised SMS or phone calls, was shown to produce relatively better outcomes compared with automated reminders, which were assumed to have lost the invaluable human touch necessary to promote adherence.

Furthermore, although the meta-analyses consisted of High and Moderate certainty of evidence, respectively, further meta-analyses performed on adherence data based on questionnaire scores and follow-up attendance yielded no significant findings. We noticed that the validity of certain articles measuring adherence through self-reported questionnaire were questionable. Therefore, could be one of the reasons for non-significant finding in our meta-analysis. However, we continued to observe that the results were generally favourable, suggesting that phone reminders were an effective means for improving adherence. Such empirical evidence could obviously be seen in one local study by contemporary researcher that yield relatively large effect sized despite small number of participants, albeit rather ordinary intervention being delivered[26].

When examined further, nearly all of the RCTs were performed on patients who were receiving first-line ART regimens.[20-23,25,26] Although, significant improvements in ART adherence were observed in RCTs with study durations up to 12 months,[23,26] increasing the study length to 160 weeks did not yield significant improvements in ART adherence.[23] Moreover, weekly reminders yielded significant improvements for ART adherence,[20,21,26] whereas RCTs using longer intervals between reminders, as long as every 8 weeks, did not yield significant improvements in ART adherence.[23]

Although nearly all of the RCTs were performed successfully, privacy issues remain a stumbling block, and one of the RCTs reported that one participant who was receiving motivational SMS messages withdrew from this study, citing loss of privacy. Previous privacy concerns have been discussed, as phone reminders may involve direct patient-provider communication. However, efforts can be made to reduce potential privacy concerns, such as coded messages.[32]

Likewise, the effectiveness of phone reminders may also be influenced by differences in HIV stigmatisation among the regions being studied. For example, Shet et al.,[25] raised the issue of stigmatisation risk among participants who received phone reminder interventions in India. However, another study performed in India found that stigma was not an issue among HIV patients.[33]

Of the seven RCTs included in this meta-analysis, two RCTs relied on SMS, three relied on phone calls, and two relied on both. However, the acceptance of these methods was only briefly mentioned. Differences in the method through which reminder interventions are delivered likely deserve further attention, as the desirability of person-to-person phone calls may vary generationally, and the generation referred to as "Millennials" are often described as disliking phone calls compared with older generations.[34-36]

In summary, phone reminders as interventions for improving adherence to ART regimens were shown to be beneficial. However, the reminder should be individualised, without neglecting the importance of human touch for the promotion of adherence. Advancements in technology can help improve adherence, without losing the human touch associated with soft-skills and communications during patient management among healthcare workers. The attitude of patients is also important for adherence behaviour with regards to medications and follow-up schedules.

In the future, careful consideration and proper evaluation of emerging technological advancements should be examined to determine whether social media be a promising approach for promoting patient adherence to ART regimens. We hope that the WHO's goal of "Getting to Zero: Zero new Human Immunodeficiency Virus (HIV) infections. Zero deaths from AIDS-related illness" maybe realised.[2]

LIMITATIONS

The limitation of this meta-analysis was that the adherence measured was based on different operational definition across study. In addition, the intervention also differed from study to study, as some RCTs was testing difference forms or methods of phone reminders. However, as these studies were considered clinically meaningful to be combined, random-effects model was used while in case if high heterogeneity detected, sub-group analysis was performed.

CONCLUSIONS

The conclusions of this review should be interpreted with caution. On the one hand, the meta-analysis examining RCTs that delivered single interventions showed that interventions were effective when adherence was measured based on the proportion of prescribed pills taken. On the other hand, other meta-analyses referred here showed trends towards improved adherence that were not significant. These findings may add to the growing body of literature regarding adherence to ART regimens. We strongly believe that phone reminders remain an effective means of improving adherence to ART regimens. We hope that our findings may offer useful information to policymakers, who could consider phone reminders, as a means of intervention to improve adherence in the healthcare services.

Declaration of Conflicting Interests
The Authors declare that there is no conflict of interest.

Ethics approval
Ethics approval was obtained from the Ministry of Health Malaysia Medical Research & Ethics Committee [NIH.800-4/4/1 Jld. 75(10)].

Consent
Not Applicable.

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