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Interventions to improve the performance of HIV health systems for treatment-as-prevention in sub-Saharan Africa: the experimental evidence

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Abstract

Purpose of review—To reduce HIV incidence, treatment-as-prevention (TasP) requires high rates of HIV testing, and antiretroviral treatment (ART) uptake, retention, and adherence, which are currently not achieved in general populations in sub-Saharan Africa. We review the experimental evidence on interventions to increase these rates.

Recent findings—In four rapid reviews, we found nine randomized controlled trials (RCTs) on HIV-testing uptake, two on ART uptake, one on ART retention, and 15 on ART adherence in sub-Saharan Africa. Only two RCTs on HIV testing investigated an intervention in general populations; the other examined interventions in selected groups (employees, or individuals attending public-sector facilities for services). One RCT demonstrated that nurse-managed ART led to the same retention rates as physician-managed ART, but failed to show how to increase retention to the rates required for successful TasP. Although the evidence on ART adherence is strongest – several RCTs demonstrate the effectiveness of cognitive and behavioural interventions – contradictory results in different settings suggest that the precise intervention content, or the context, are crucial for effectiveness.

Summary—Future studies need to test the effectiveness of interventions to increase testing and treatment uptake, retention, and adherence under TasP, that is, ART for all HIV-infected individuals, independent of disease stage.

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Conflicts of interest

There are no conflicts of interest.

Keywords

adherence; antiretroviral treatment; HIV testing; HIV treatment-as-prevention; randomized controlled trials; retention

INTRODUCTION

Results from the HIV Prevention Trials Network (HTPN) 052 trial released in August 2011 showed that early HIV antiretroviral treatment (ART) prevents onward transmission of the virus to the uninfected partner in heterosexual HIV-discordant couples [1]. However, the HPTN 052 trial took place under highly controlled conditions, in stable partnerships, and with high levels of ART adherence and only 5% virologic failures in the intervention group over the 42 months study period. Thus, although the trial results support the use of treatment-as-prevention (TasP) in discordant couples as part of a public-health strategy to reduce the spread of HIV, it remains unknown whether the effect observed in the trial can be replicated in general populations when ART is delivered through routine public-sector health systems.

In particular, the effectiveness of TasP in real life will depend crucially on the uptake of HIV testing with identification of HIV-infected individuals soon after infection, and the willingness and ability of HIV-infected individuals to enroll and remain enrolled in ART programmes, and to adhere well to the prescribed drug regimens. In a mathematical modelling study [2], which suggested that TasP could substantially reduce HIV incidence in the generalized epidemic of South Africa, the authors assumed that ‘all HIV-infected people started ART as soon as they were diagnosed HIV positive’, and that ‘8% of people drop out immediately or soon after starting treatment’ and 1.5% drop out in each subsequent year. The model further assumed an ART failure rate of 3% per year, which implies very high levels of treatment adherence. Both in resource-rich settings [3–6] and in the resource-poor settings of sub-Saharan Africa [5,7■,8,9■,10-13], the rates of HIV testing, ART uptake, retention, and adherence are substantially lower than those assumed in the mathematical modelling study. It is therefore likely that TasP needs to be accompanied by interventions to increase the performance of HIV health systems in identifying HIV-infected individuals and initiating and successfully maintaining them on ART.

In this study, we review the evidence from RCTs on interventions to increase the rates of HIV testing, ART linkage and uptake, retention and adherence in sub-Saharan Africa. Currently, a number of trials that investigate the effectiveness of TasP in general populations in sub-Saharan Africa, either as the main trial intervention or as part of a complex HIV combination prevention, are in different stages of planning and funding [14■]. For these community-based trials, and for the real-life implementations of TasP, it is urgent to consider what measures to take in order to ensure high levels of HIV-testing uptake, ART uptake, and ART retention and adherence. Given the limited resources of small research teams, systematic reviews typically take many months to conduct [15]. As several of the planned trial teams are currently finalizing their protocols, we decided to review the

experimental evidence on interventions using an alternative to systematic reviews, rapid reviews, which can generate results within a shorter time frame [16].

METHODS

Rapid reviews are distinct from systematic reviews in that they typically apply stricter inclusion criteria and search fewer databases and sources than systematic reviews [16], although the rapid review methodology varies widely in application [15]. To identify experimental studies reporting on interventions to increase HIV-testing uptake, ART linkage and uptake, ART retention, and ART adherence in sub-Saharan Africa, we conducted four searches in the *PubMed* database. We limited our search to studies conducted in sub-Saharan Africa and to articles published since 1 January 2002, when rapid ART scale up on the subcontinent started [17]. We searched only for studies that used one of three designs (RCT, review, and meta-analysis), with the aim to identify the existing experimental evidence on the four topics. Table 1 shows the algorithms we used for the four searches. In addition, we asked colleagues during a recent international meeting on TasP (Bill & Melinda Gates Foundation Modelling Consortium meeting, Stellenbosch University, Stellenbosch, South Africa; 3 –5 November 2011) to point out to us any RCTs, reviews, or meta-analysis relevant to our four topics. We screened the reference sections of the systematic reviews and meta-analyses identified in this rapid review for experimental studies on the four topics. One author (T.B.) extracted the data from the articles into an excel spreadsheet.

RESULTS

Our initial *PubMed* searches identified 507 (for HIV-testing uptake), 21 (ART linkage and uptake), 77 (ART retention), and 75 (ART adherence) records. After title and abstract screening, 31 (HIV-testing uptake), five (ART linkage and uptake), six (ART retention), and 32 (ART adherence) records remained for full-text review. In addition to these records, colleagues pointed us to two relevant systematic reviews, one on HIV-testing uptake and one on ART adherence. The review on HIV testing included only one relevant RCT [18], which was also included in our *PubMed* search. The review on ART adherence included 15 relevant RCTs [19■]. All 11 of the 15 RCTs published as journal articles were also included in our *PubMed* search; however, the review also included four RCTs that were only published as conference abstracts. We added the latter to the final set of studies included in this review.

The final sets of articles for this review were nine (for HIV-testing uptake), two (for ART linkage and uptake), one (for ART retention), and 15 (for ART adherence). Table 2 shows the extracted data, including the country where the study took place, intervention, unit of randomization, length of follow-up, and trial results. All of the 27 identified studies were published recently; the earliest study in 2004 and two-thirds of all studies in either 2010 or 2011. The studies were conducted in South Africa (six), Kenya (four), Tanzania (four), Nigeria (three), Uganda (three), Malawi (two), Democratic Republic of Congo (one), Swaziland (one), Zambia (one), and Zimbabwe (two). The majority (20) of the studies took place in large cities. Nineteen studies found significant intervention effects in the desired direction. Sample sizes ranged from 222 to 22 850 with a median size of 500.

DISCUSSION

For TasP strategies to succeed, very high proportions of HIV-infected people in sub-Saharan Africa need to know their HIV status. According to past estimates, however, only one in 10 adults in sub-Saharan Africa currently know their status [12]. Although recent HIV counselling and testing initiatives may have increased this proportion [46], it is likely that even after these campaigns HIV status knowledge on the subcontinent remains far below the levels required to successfully reduce HIV incidence through TasP. It is thus important to identify effective interventions to increase HIV-testing uptake. Passive systems, such as public sector voluntary counselling and testing (VCT) clinics, are likely insufficient for this purpose. Even in countries such as South Africa, where the density of VCT clinics has been high and HIV testing has been available free of charge, about half of all individuals have never tested for HIV [47].

Our rapid review identified only nine RCTs on interventions to increase HIV-testing uptake in sub-Saharan Africa. Moreover, only two of these RCTs investigated an intervention in a general population [24,27], the other seven studies examined interventions in employees or individuals attending public-sector facilities for services [antenatal care (ANC), ART, hospital in-patient care or education]. People who are employed or attend service facilities, however, are likely to be the selection of the more active and resourceful individuals in a population and thus not the part of the population that interventions need to reach most to ensure success of TasP strategies.

The comparison of two RCTs investigating interventions to increase HIV-testing uptake illustrates some of the problems that can arise when specialized testing interventions are used. Mohlala *et al.* [26] used a written invitation to ANC attendees' male partners as mechanism to increase the uptake of couple HIV counselling and testing, documenting effectiveness of the intervention (a 36% increase) in comparison to another approach to reach the male partners (a verbal invitation during a standard pregnancy information session). In contrast, Becker *et al.* [20] compared the rate of HIV counselling and testing uptake in ANC attendees when they were offered either couple counselling and testing (with a written invitation for the male partners) or standard individual counselling and testing. Interestingly, this study showed that the women attending ANC who were offered couple counselling and testing were significantly less likely to receive an HIV test than women offered individual counselling and testing, suggesting that approaches to encourage couples to test may have harmful consequences for women, even when some such approaches perform better than others in motivating male partners to test for HIV.

Two RCTs in general populations in sub-Saharan Africa suggest that offering HIV testing in people's home or in the community can increase testing uptake in comparison to settings where HIV tests are only available in health clinics [24,27]. However, although the effect sizes were large, testing uptake was below 60% even in the presence of the interventions. Further experimental evidence on interventions to increase HIV-testing uptake in general populations in sub-Saharan Africa (such as intensified education, financial incentives, or gifts) is urgently needed, if population-based TasP is to succeed. In particular, as TasP requires repeat testing to detect newly HIV-infected individuals, it would be important to

gain an understanding of intervention effectiveness if interventions are delivered repeatedly in the same population.

The experimental evidence on linkage and uptake of ART and on ART retention is even scarcer than the evidence on HIV-testing uptake, with only three studies in these two categories. Sanne *et al.* [30■■] show that nurse-managed ART will lead to the same retention rates as physician-managed ART, a result that supports the case for task shifting of ART in sub-Saharan Africa [48]. However, this result does not tell us how to achieve the high long-term retention rates that are required to ensure TasP success. Wanyenze *et al.* [28] found that ART uptake is better if HIV counselling, testing, and referral is offered to in-patients during their hospital stay, rather than to invite them to come back for those same services after discharge. Zwarenstein *et al.* [29] did not detect any significant effect of an educational outreach programme in health clinics in increasing ART uptake in HIV-infected individuals. For TasP strategies, evidence is needed on the effectiveness of approaches to link people who are not attending a health facility to programmes that provide HIV treatment and care.

The evidence on ART adherence is broadest, with 15 well conducted RCTs on a range of interventions. These studies demonstrate that behavioural interventions (i.e., interventions that affect adherence directly through behaviour modification), cognitive interventions (i.e., interventions that affect ART adherence indirectly through teaching, clarification, or instruction), and mixed interventions affecting adherence through cognitive, behavioural, and emotional support can be effective in sub-Saharan African settings. Cognitive interventions found to be effective in some of the RCTs included in our review consisted of education through group teaching programmes or through individual counselling; behavioural interventions found to be effective in some RCTs included mobile-phone messages and directly observed therapy (DOT); a mixed intervention found to be effective was treatment supporters.

However, the synthesis of results across all studies on adherence-enhancing interventions shows a number of issues in drawing conclusions for future interventions in sub-Saharan Africa. First, for three adherence-enhancing intervention types – education, treatment supporters, and DOT – our review suggests that our understanding of intervention effectiveness needs to improve further. For all three intervention types, some studies demonstrated effectiveness, whereas others failed to do so, suggesting that either the context (e.g., the particular country in sub-Saharan Africa or the type of health facility) or specific features of intervention content (e.g., the content of education, choice of treatment supporter, or frequency of DOT) are important for intervention success [19■]. Second, for one other intervention type – mobile-phone messages – the only two existing RCTs demonstrate effectiveness. However, it would be premature to conclude that mobile-phone messages are universally effective in increasing ART adherence in sub-Saharan Africa based on only two trials. Moreover, the two mobile phone messaging interventions differed substantially in content: one was passive, consisting of messages sent to patients to remind them to take their ART pills [42■■], the other one was interactive, consisting of a general question about patient's well being and a follow-up call if the patient replied that she had a problem [35■■]. Such differences in intervention content increase the import of additional information on

feasibility and costs for decision-making on intervention implementation in trials or routine treatment delivery.

The fact that two systematic reviews on relevant topics did not identify any studies that were not included in the results of our *PubMed* searches suggests that our search algorithms were sensitive in detecting relevant evidence. However, our study also has several limitations. First, because we conducted a rapid review, rather than a full systematic review, we constrained our search for evidence to one electronic database, references lists, and interviews with colleagues at one international meeting. Several other electronic databases, such as Excerpta Medica Database or the Cumulative Index to Nursing and Allied Health Literature, may include relevant publications. In addition, in future full systematic reviews on the same topics, researchers should contact a broader set of colleagues, who might have conducted or know of relevant studies, and include searches of conference databases and the general internet, in order to identify study results that have not yet been published in academic articles. Second, we constrained our search to experimental evidence. Future systematic reviews should consider observational evidence, which can provide important insights into intervention effectiveness, including quasi-experimental studies and qualitative studies elucidating the mechanisms of intervention effect.

In general, results of investigations of interventions conducted in settings in which people in the early stages of HIV disease are not eligible for ART – such as all of the studies included in this review – may not be generalizable to the TasP setting in which ART are offered independent of disease stage. First, testing uptake and, in particular, treatment uptake, retention, and adherence depend on personal motivation, which in turn is likely to be affected by whether treatment is perceived to be primarily for one's own health or to protect sex partners from infection. Second, experience of advanced HIV disease and recovery on ART may affect ART retention and adherence. The earlier the ART is initiated, the rarer such experience will be. It seems possible that TasP could decrease ART retention or adherence because, unlike ART patients in sub-Saharan Africa today, most TasP patients will lack first-hand experience of ART effectiveness. Lastly, reductions in HIV incidence and HIV-related mortality due to TasP will, in the long run, change the composition of the HIV-infected population (e.g., the age structure), which in turn may affect HIV testing and ART uptake, retention, and adherence behaviours.

More empirical evidence on the key health systems ingredients for successful TasP is clearly necessary. In choosing interventions, researchers conducting future studies should consider that population-based TasP strategies in sub-Saharan Africa must be feasible and sustainable in resource-poor routine public-sector settings. Future studies should thus incorporate investigations of feasibility in routine settings and measurement of intervention costs to allow economic evaluation of the trade-offs between different interventions that can support TasP strategies.

CONCLUSION

The experimental evidence on interventions to increase HIV-testing uptake, and ART uptake, retention, and adherence in sub-Saharan Africa remains scarce. Moreover, the

existing evidence is of limited applicability to TasP delivered through routine public-sector health systems. Future studies in sub-Saharan Africa need to test the effectiveness of interventions to increase the behaviours essential for enrolling and maintaining high proportions of HIV-infected people in TasP.

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KEY POINTS

- To reduce HIV incidence, treatment-as-prevention (TasP) requires high rates of HIV testing, and antiretroviral treatment (ART) uptake, retention, and adherence, which are currently not achieved in general populations in sub-Saharan Africa.
- In four rapid reviews, we identified nine randomized controlled trials (RCTs) on HIV-testing uptake, two on ART uptake, one on ART retention, and 15 on ART adherence in sub-Saharan Africa.
- Only two RCTs on HIV testing investigated an intervention in general populations; the other examined interventions in selected groups (employees or individuals attending public-sector facilities) for services.
- Although the evidence on ART adherence is strongest, with RCTs showing effectiveness of several cognitive and behavioural interventions, contradictory results in different settings suggest that the precise intervention content, or context, are crucial for effectiveness.
- Overall, experimental evidence on interventions to increase HIV-testing uptake, ART uptake, retention, and adherence in sub-Saharan Africa is scarce, and – as all of the existing trials took place when ART eligibility was limited to the sickest patients – unlikely to be generalizable to settings in which TasP is implemented.

Table 1

The four search algorithms

Search topic	Search algorithm
HIV testing uptake	((HIV OR HIV[MeSH] OR 'antiretroviral therapy, highly active' [MeSH] OR 'anti-HIV agents' [MeSH] OR antiretroviral) AND (testing OR test OR uptake OR 'voluntary HIV counseling and testing' OR 'voluntary HIV counselling and testing' OR VCT OR 'HIV counseling and testing' OR 'HIV counselling and testing' OR HCT) AND Africa[MeSH]) AND '2002/01/01' [Date - Publication] : '2011/10/01' [Date - Publication]) AND '0' [Date - Publication] : '3000' [Date - Publication] limits: meta-analysis, randomized controlled trial, review
ART uptake	(('antiretroviral therapy, highly active' [MeSH] OR 'anti-HIV agents' [MeSH] OR antiretroviral) AND (uptake OR linkage OR integration) AND Africa[MeSH]) AND '2002/01/01' [Date - Publication] : '2011/10/01' [Date - Publication]) AND '0' [Date - Publication] : '3000' [Date - Publication]; limits: meta-analysis, randomized controlled trial, review
ART retention	(('antiretroviral therapy, highly active' [MeSH] OR 'anti-HIV agents' [MeSH] OR antiretroviral) AND ('lost to follow-up' [MeSH] OR 'loss to follow up' OR retention OR 'appointment adherence' OR 'adherence to visit schedule') AND Africa[MeSH]) AND '2002/01/01' [Date - Publication] : '2011/10/01' [Date - Publication]) AND '0' [Date - Publication] : '3000' [Date - Publication]; limits: meta-analysis, randomized controlled trial, review
ART adherence	(('antiretroviral therapy, highly active' [MeSH] OR 'anti-HIV agents' [MeSH] OR antiretroviral) AND ('patient compliance' [MeSH] OR adherence) AND Africa[MeSH]) AND '2002/01 /01' [Date - Publication] : '2011/10/01' [Date - Publication]) AND '0' [Date - Publication] : '3000' [Date - Publication]; limits: meta-analysis, randomized controlled trial, review

ART, antiretroviral therapy; HCT, HIV counselling and testing; MeSH, Medical Subject Headings; VCT, voluntary counselling and testing.

Table 2

The experimental evidence on interventions to increase HIV-testing uptake, antiretroviral therapy linkage and uptake, retention, and adherence in sub-Saharan Africa

Authors	Country (city or region)	Intervention	Unit of randomization	Sample size	Length of follow-up (months)	Effective	Results
HIV-testing uptake							
Becker *et al.* [20]	Tanzania (Dar es Salaam)	Written and verbal invitation to ANC attendees to bring their male partner to the clinic for VCT for couples.	ANC attendee	1521	NR	Yes (negatively)	Women who received an invitation to bring their male partner to the clinic for couple VCT were significantly less likely to receive an HIV test than women who received standard individual VCT (39 vs. 71%, $P<0.001$).
Burnett *et al.* [21]	Swaziland (Manzini)	School-based HIV education programme 'It's our future tool' (13 weekly half-day sessions).	Individual student	312	NR	Yes	In the intervention group, the proportion of students who reported that they 'ever had HIV test' increased from 11 to 42% ($P<0.001$), whereas in the control group it increased from 5 to 9% ($P=0.13$).
Corbett *et al.* [22]	Zimbabwe (Harare)	On-site rapid testing at an occupational health clinic.	Business occupational health clinic	7482	2 years	Yes	HIV-testing uptake was significantly higher in the intervention group compared with the control group, which were offered vouchers for off-site HIV testing (RR=2.7; 95%, CI=1.8–3.9).
Ditekemena *et al.* [23]	Democratic Republic of Congo (Kinshasa)	Offer of VCT to ANC attendees' male partners at neighbourhood health centre vs. bar vs. church.	ANC attendee	2706	5 months	Yes	Male HIV-testing uptake higher in bars (26%, $P<0.001$) and churches (21%, $P=0.163$) compared with neighbourhood

Authors	Country (city or region)	Intervention	Unit of randomization	Sample size	Length of follow-up (months)	Effective	Results
							health centres (18%).
Fylkesnes and Siziya [24]	Zambia	VCT offered at an optional location (including home).	Participants in a population-based HIV survey	1445	NR	Yes	HIV-testing uptake was 4.7 times higher in the intervention group, which was offered VCT in an optional location (including homes if desired) compared with the control group, which was offered VCT in the local health clinic (56 vs. 12%).
Lugada *et al.* [25■]	Uganda (Jinja, Kamuli, Iganga, Mayuge, Mukono)	Home-based VCT for household members of ART patients.	ART patient	7184	NR	Yes	Household members in the intervention group were significantly more likely to receive VCT than household members in the control group who were offered clinic-based VCT (56 vs. 11%, $P<0.001$).
Mohlala *et al.* [26]	South Africa (Cape Town)	Written and verbal invitation to the male partner of ANC attendees to attend a VCT session.	ANC attendee	500	1 week	Yes	Women who received a written invitation to bring their male partner to the clinic for VCT were significantly more likely to do so than women who received standard pregnancy information without a written partner invitation (RR=1.36, $P=0.002$).
Sweat *et al.* [27]	Tanzania, Zimbabwe, Thailand	Community-based VCT.	Community	12 983 (in Tanzania) and 22 850 (in Zimbabwe)	3 years (in Tanzania) and 3.5 years (in Zimbabwe)	Yes	In the communities receiving community-based VCT, VCT clients were

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							substantially more likely to receive their first HIV test than VCT clients in the control communities, which offered only standard clinic-based VCT (37 vs. 9% in Tanzania, and 51 vs. 5% in Zimbabwe).
Wanyenze *et al.* [28]	Uganda (Kampala)	In-patient HCT.	Hospital inpatient	500	6 months	Yes	Patients who were offered in-patient HCT were substantially more likely to receive HCT than patients in the control group, who were offered to return to the hospital for HCT 1 week after discharge (99 vs. 69%).
ART linkage and uptake							
Wanyenze *et al.* [28]	Uganda (Kampala)	In-patient HCT.	Hospital in-patient	500	6 months	Yes	Patients who were offered in-patient HCT and found to be HIV-infected were significantly more likely to attend a HIV clinic than the patients in the control group who were offered to return for out-patient HCT after discharge and subsequently found to be HIV-infected (74 vs. 56%, P=0.032).
Zwarenstein *et al.* [29]	South Africa	On-site educational outreach programme in health clinics.	Health clinic	10136	23 weeks (intervention group) and 28 weeks (control group)	No	Enrolment in ART programme through new HIV testing was not significantly different in the intervention compared with the control

Authors	Country (city or region)	Intervention	Unit of randomization	Sample size	Length of follow-up (months)	Effective	Results
							group (53 vs. 50%, *P*=0.695).
ART retention							
Sanne *et al.* [30■]	South Africa (Cape Town and Johannesburg)	Nurse vs. doctor-managed ART (a noninferiority trial).	ART patient	812	120 weeks	Yes	Patients who received nurse-managed ART were not significantly different in their ART retention than patients who received doctor-managed ART (HR=1.13, 95%CI=0.81–1.59).
ART adherence							
Busari *et al.* [31]	Nigeria (Abuja)	Structured adherence education programme.	ART patient	420	8	Yes	99% mean adherence rate in intervention group vs. 88% in control group (*P*<0.001); 0.51 OI per patient per month in intervention group vs. 1.31 OI in control group (*P*=0.002); mortality significantly lower in intervention vs. control group (*P*=0.008); rate of hospital admission significantly lower in intervention vs. control group.
Busari *et al.* [32]	Nigeria (Abuja)	Structured adherence education programme.	ART patient	620	8	Yes	Patients in the intervention group had significantly higher mean adherence than patients in the control group (99 vs. 88%, *P*<0.001). They also had significantly higher CD4 cell count (238 vs. 141 cells/μl, *P*<0.001) and a significantly

Authors	Country (city or region)	Intervention	Unit of randomization	Sample size	Length of follow-up (months)	Effective	Results
							lower rate of hospital admissions.
Chang *et al.* [33■]	Uganda (Rakai)	Treatment supporter.	ART patient	1336	27	Yes	Patients in the intervention group had significantly lower risk of virologic failure than patients in the control group at 96 weeks (RR 0.50, 95% CI 0.31–0.81), 120 weeks (RR 0.59, 95% CI 0.22–1.60), 144 weeks (RR 0.39, 95% CI 0.16–0.95), 168 weeks (RR 0.30, 95% CI 0.097–0.92), and 192 weeks (RR 0.067, 95% CI 0.0065–0.71). There were no significant effects on risk of virologic failure in earlier periods, pill count, self-reported adherence, or median CD4 cell count.
Chung *et al.* [34]	Kenya (Nairobi)	Educational adherence counselling vs. alarm device.	ART patient	400	18	Yes	Patients who received counselling were 29% less likely to have monthly adherence (assessed by pill count) <80% (hazard ratio (HR)=0.71, *P*=0.055) and 59% less likely to experience viral failure (HR=0.41, *P*=0.01) compared with those who received no counselling. The alarm device did not have a significant effect on poor adherence (HR=0.93, *P*=0.7) or viral

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							failure (HR=0.99, P=1.0).
Lester *et al.* [35■]	Kenya (Nairobi)	Mobile-phone text messages (weekly text message asking 'How are you?', with follow-up calls in patients who said that they had a problem or who failed to respond within 48 h).	ART patient	538	12	Yes	Patients in the intervention group were significantly less likely to report nonadherence than patients in the control group (RR=0.81, *P*=0.006) and were significantly less likely to experience virologic failure (RR=0.85, *P*=0.04).
Mugusi *et al.* [36]	Tanzania (Dar es Salaam)	Treatment supporter (first intervention group), calendar, adherence education (second intervention group).	ART patient	621	12	No	There were no significant differences between the three groups in any of three assessed adherence outcomes.
Nachega *et al.* [37]	South Africa (Cape Town)	DOT.	ART patient	222	24	No	Patients in the intervention group had l arger median CD4 cell count increases than patients in the control group at 6 months (148 cells/μl vs. 111 cells/μl, *P*=0.02), but the increases were not significantly different at any other observation time-points. There were no significant effects of the intervention on viral suppression or adherence assessed by pill count.
Nachega *et al.* [38■]	South Africa (Cape Town)	DOT and educational adherence counselling.	ART patient	274	24	No	There were no significant differences in self-reported adherence, CD4 cell count, or viral load.

Authors	Country (city or region)	Intervention	Unit of randomization	Sample size	Length of follow-up (months)	Effective	Results
Ndekha *et al.* [39]	Malawi (Blantyre)	Lipid paste vs. flour supplement.	ART patient	336	9	(No)	There were no significant differences in self-reported adherence, CD4 cell count, or viral load.
Ndekha *et al.* [40]	Malawi (Blantyre)	Lipid paste vs. flour supplement.	ART patient	491	3	No	There were no significant differences in self-reported adherence, CD4 cell count, or viral load.
Pearson *et al.* [41]	South Africa (Western Cape)	Treatment supporter, DOT, and adherence education.	ART patient	350	12	Yes	Patients in the intervention group had significantly higher mean medication adherence than patients in the control group at 6 months (93 vs. 85%) and at 12 months (94 vs. 88%). There was no significant difference in mean CD4 change.
Pop-Eleches *et al.* [42■]	Kenya	Mobile-phone text messages in four intervention groups (short reminders every day, short reminders every week, long reminders every day, or long reminders every week).	ART patient	431	12	Yes	Patients in the groups receiving weekly reminders were significantly more likely to adhere than patients in the control group at 48 weeks (53 vs. 40%, P=0.03) at 48 weeks. Treatment interruptions were significantly less likely in the groups receiving weekly reminders at 48 weeks (81 vs. 90%, *P*=0.03).
Sarna *et al.* [43■]	Kenya (Mombasa)	DOT.	ART patient	234	18	Yes	According to pill count, patients in the DOT group were five times more likely to

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							adhere to ART than patients in the control group (P<0.001) during the interventions, after adjustment for depression and HIV-related admission to hospital (P<0.001). There were no significant differences in adherence after the intervention, nor were there significant differences in CD4 cell count or viral load suppression. BMI increase was significantly greater in the DOT vs. the control group during the intervention (P=0.014).
Taiwo *et al.* [44]	Nigeria (Jos)	Treatment supporter and DOT.	ART patient	499	12	Yes	Patients in the intervention group had significantly higher odds of adherence than patients in the control group at 24 weeks (OR 3.06, P<0.01) and 48 weeks (OR 1.95, P<0.01). They were also significantly more likely to have undetectable viral load at week 24 (62 vs. 50%, P<0.05). There were no significant differences in either viral load suppression at week 48 or CD4 cell count increases at weeks 24 and 48.

Authors	Country (city or region)	Intervention	Unit of randomization	Sample size	Length of follow-up (months)	Effective	Results
van Loggernberg *et al.* [45]	South Africa (Durban)	Individual vs. group educational adherence counselling.	ART patient	297	9	No	There was no significant difference in viral load suppression between the intervention and the control group (demonstrating noninferiority of the group educational counselling in comparison to the individual educational counselling).

ART, antiretroviral therapy; CI, confidence interval; DOT, directly observed therapy; HCT, HIV counselling and testing; OI, opportunistic infections; RR, relative risk; VCT, voluntary counselling and testing.