Directly observed antiretroviral therapy: a systematic review and meta-analysis of randomised clinical trials

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Summary

Background **Directly observed therapy has been recommended to improve adherence for patients with HIV infection who are on highly active antiretroviral therapy, but the benefit and cost-effectiveness of this approach has not been established conclusively. We did a systematic review and meta-analysis of randomised trials of directly observed versus self-administered antiretroviral treatment.**

Methods **We did duplicate searches of databases (from inception to July 27, 2009), searchable websites of major HIV conferences (up to July, 2009), and lay publications and websites (March–July, 2009) to identify randomised trials assessing directly observed therapy to promote adherence to antiretroviral therapy in adults. Our primary outcome was virological suppression at study completion. We calculated relative risks (95% CIs), and pooled estimates using a random-effects method.**

Findings **12 studies met our inclusion criteria; four of these were done in groups that were judged to be at high risk of poor adherence (drug users and homeless people). Ten studies reported on the primary outcome (n=1862 participants); we calculated a pooled relative risk of 1·04 (95% CI 0·91–1·20, p=0·55), and noted moderate heterogeneity between the studies (I^2= 53·8%, 95% CI 0–75·7, p=0·0247) for directly observed versus self-administered treatment.**

Interpretation **Directly observed antiretroviral therapy seems to offer no benefit over self-administered treatment, which calls into question the use of such an approach to support adherence in the general patient population.**

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Introduction

Highly active antiretroviral therapy (HAART) has greatly affected the course of disease for patients with HIV infection, resulting in an important reduction in AIDS-related morbidity and mortality in both developed and developing countries.[1] Strategies to improve adherence remain crucial for successful outcomes on any HAART regimen. HAART requires lifelong and high adherence to ensure maximum virological outcomes,[2] prevent antiretroviral drug resistance,[3] prevent disease progression, and improve survival.[4] Many behavioural interventions have been developed to support adherence such as adherence case management, counselling, pharmacist-based education, telephone support, reminder devices, home visits by nurses, and directly observed therapy.[5] Of these interventions, directly observed therapy is perhaps the most contentious.[6,7]

In directly observed therapy, a health-care worker or other designated individual witnesses the patient swallowing their drugs. The intervention was developed to support adherence to tuberculosis programmes in the 1960s,[8] and has been promoted by WHO since 1994 as part of its global tuberculosis control strategy. However, concerns have been raised with respect to the poor evidence of effectiveness and the high cost of this approach. Results of a systematic review of randomised trials on treatment for tuberculosis showed no benefit to cure or completion of treatment of directly observed versus self-administered treatment,[9] and critics have raised concerns that the intervention is coercive to patient autonomy.[10]

Tuberculosis and HIV treatment differ in several ways. The most important difference for patients is that tuberculosis treatment (directly observed therapy short-course [DOTS]) is of a finite duration (6–8 months for non-resistant strains) whereas HAART is a lifelong treatment. Therefore, concerns about the feasibility and cost-effectiveness of directly observed therapy for tuberculosis are even more relevant for HAART. Nevertheless, the intervention has been promoted as a potential adherence support strategy for HAART, largely on the basis of small observational studies.[11]

Adherence support is an essential component of HAART. Direct observation has been proposed as a strategy to promote adherence and avoid drug resistance. However, patients and health services could both be affected by the potential burden of implementation of such a strategy. Therefore, clear evidence of benefit is needed. We did a systematic review and meta-analysis of randomised trials of directly observed versus self-administered antiretroviral treatment.

Methods

Inclusion criteria

We included all randomised trials assessing directly observed therapy as an intervention to promote adherence to antiretroviral therapy as a primary or secondary outcome within any population in any setting. We

regarded the supervised swallowing of HAART pills as direct observation; this strategy contrasts with the DOTS framework for tuberculosis, which provides a range of approaches to patient support in addition to observation.[12] We included trials of any duration or exposure to directly observed therapy, irrespective of regularity, and examined differences in a sensitivity analysis. We included studies of adults receiving any HAART combination in any dosing format. Non-randomised studies were excluded.

Search strategy

We searched Medline via PubMed, EmBase, Cochrane Central Register of Controlled Trials, CINAHL, PsycInfo, LILACS, Current Controlled Trials, and ClinicalTrials.gov for articles and reviews (from inception of every database to July 27, 2009) using a highly sensitive search strategy that combined key terms associated with adherence (eg, "adherence", "compliance", "directly observed", "DOT"), medical subject headings ("HIV" or "acquired immunodeficiency syndrome"), and search terms for randomised trials. A full list of search terms is given in the study protocol. We used the same strategy on the searchable websites of all conferences of the International AIDS Society (April, 1985–July, 2009), and every Conference on Retroviruses and Opportunitistic Infections (January, 1997–February, 2009). NF and EJM searched independently, in duplicate, the full list of databases between March and July, 2009.

For more on **medical subject headings** see http://www.nlm.nih.gov/mesh

For the **study protocol** see http://tinyurl.com/ylyb6zu

We hand searched abstracts of the International Conference on HIV Treatment Adherence (International Association of Physicians in AIDS Care; March, 2006–April, 2009). We also searched several lay publications and websites between March and July, 2009: The Body, the Canadian AIDS Treatment Information Exchange publications, AIDS Treatment News, Google Scholar, and the Networked Digital Library of Theses and Dissertations. Last, we complemented the search by reviewing bibliographies of relevant papers and contacting individual clinical researchers and AIDS trials groups by email and phone (National Institute of Mental Health, International AIDS Society, and International Association of Physicians in AIDS Care). No language or date restrictions were placed on searches. Our search identified all studies matching our inclusion criteria that were suggested by these groups. We contacted all potentially relevant study authors by email and telephone for details on their trials. JBN was primary investigator on a trial in South Africa.[13]

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Study selection

NF and EJM used a predefined protocol to independently, in duplicate, scan all abstracts for the suggestion that directly observed therapy was used, and obtain the full text of relevant articles. From the full text of candidate studies (either in full peer-reviewed publications, as conference abstracts, or as articles that had not been peer-reviewed), NF and EJM independently assessed eligibility. Reviewers were not masked to study authors, conclusions, and outcomes because masking has been shown to have little effect on systematic reviews.[14] To obtain full information for conference abstracts and registered trials, we attempted contact with all study authors for full information by email and telephone communication. Once all potentially relevant full-text articles and abstracts were identified, we consulted as a team (NF, JBN, EJM) to achieve consensus regarding eligibility, and consulted an arbitrator (MEE) for adjudication.

Data extraction

Data extraction was done independently and in duplicate with a standardised, previously tested form. NF and EJM gathered information about the study setting, study populations, sample size, and methods of adherence measurement. Since there is no gold standard for assessment of adherence to medication,[15] we included different measures of adherence, as reported in the studies. Our primary endpoint was viral suppression at study endpoint. Secondary outcomes were self-reported adherence, immunological progression (as measured by CD4 T cells per mm^3), loss to follow-up, all-cause mortality, development of resistance mutations, and new or recurrent AIDS-defining illnesses. We entered the data into an electronic database (MS Access) such that duplicate entries existed for each study and when the two entries did not match we reached consensus through discussion. We judged study quality according to a predefined assessment instrument that assessed randomisation method, adjustment of experimental confounders, allocation concealment, masking of analysts, objectivity of outcome measures, use of intention-to-treat analysis, and less than 20% of participants lost to follow-up.

Statistical analysis

To assess inter-rater reliability on inclusion of articles, we calculated the φ statistic, which provides a measure of inter-observer agreement independent of chance.[16] NF and EJM did all statistical analyses. We calculated the relative risk (RR, 95% CI) of the primary and secondary outcomes according to the number of events reported in the original studies or sub-studies as intention-to-treat analyses. If studies did not report intention to treat, we analysed outcomes as all-patients randomised.[17] In the unlikely event of zero outcome events in one group in a trial, we prepared to apply the Haldane method and add 0·5 to each group.[18]

Study outcomes were pooled with the DerSimonian-Laird random-effects method,[18] which recognises and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability.[18] We calculated the I^2 statistic (95% CI) for each analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity.[18] We ran a sensitivity analysis on our

primary outcome using a Bayesian random-effects model with Monte Carlo Markov chain simulations of variability.[19] In view of the expected small number of included trials we did univariate sensitivity analysis with the χ^2 test to assess the effect of methodological variables on outcome: groups at high risk of non-adherence versus the general population, intervention type (full *vs* partial directly observed therapy), allocation concealment, location of study, previous treatment experience, and the effect of short-term (≤6 months) versus long-term (>6 months) study duration. We assessed change in CD4 T-cell count by applying a weighted mean difference meta-analysis and transformed data to mean (SD) when reported as median (range).[20] A forest plot is shown for the analysis of directly observed versus self-administered treatment for every study reporting the primary outcome, with individual study proportions (95% CIs), and the overall DerSimonian-Laird pooled estimate.

All p values are two-sided; we judged the threshold of significance to be α=0·05. Analyses were done with StatsDirect (version 2.5.2), Stata (version 11.0), and OpenBUGS (version 2.1).

Role of the funding source

There was no funding source for this study. NF and EJM had full access to the data and take responsibility for submission for publication.

Results

Figure 1 shows the flow diagram of study selection for the analysis. 83 studies passed the first screening of articles from titles and abstracts; there was near perfect agreement between reviewers on inclusion of abstracts for further analysis (φ=0·91). A further seven studies were included from article bibliographies and conference abstracts, and 78 were excluded because they did not meet our inclusion criteria (one because the author did not respond so we failed to secure sufficient data[21]). Overall, 12 studies were included for analysis (table 1): six from the USA,[22,23,27,30–32] five from Africa (Mozambique,[24] Kenya,[25] Nigeria,[26] and South Africa[13,29]), and one multicentre study from the USA and South Africa.[28] All full-text papers and abstracts were published in English. Authors provided additional data for six abstracts.[13,26,29–32]

When we examined study reporting of methodological features in full-text studies and where authors provided information (n=7), we found moderate reporting of important methodological issues. Six studies reported sequence generation,[13,22–25,28] three reported allocation concealment,[13,24,25] none reported masking of study analysts, and four reported results as a full intention-to-treat analysis.[13,22,27,28] Five studies reported less than 20% of participants lost to follow-up.[13,23,24,27,28] The method of implementation of directly observed therapy varied across studies. Two studies used full directly observed therapy (observation of every single dose),[23,31] and the remainder had a partial regimen whereby only a proportion of doses was observed. Six studies[25,28–32] used health workers as observers, and all others used community or peer supporters. All studies used self-administered treatment as the control intervention.

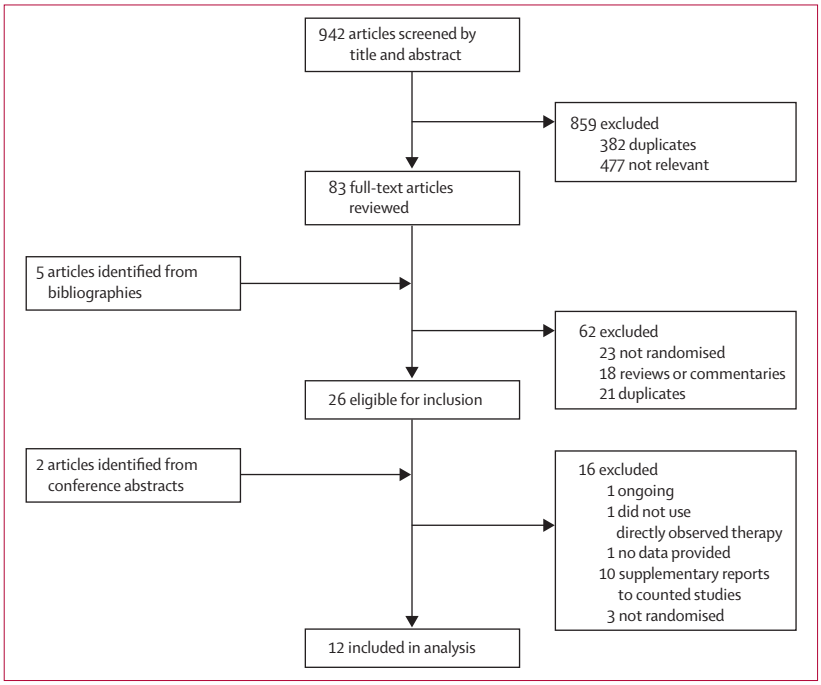

Figure 1: **Flow diagram for selection of studies**

We pooled all studies that reported our primary outcome of viral suppression at study completion (n=1862 participants) to assess the effectiveness of directly observed versus self-administered treatment. The combined relative risk from these studies indicated that the difference was not significant (p=0·55; figure 2). The Bayesian sensitivity analysis reinforced this finding: RR 1·05, 95% credible interval 0·96–1·14. Moderate heterogeneity was recorded for the studies included in the meta-analyses (I^2= 53·8%, 95% CI 0–75·7, p=0·0247). We recorded similar mean event rates for virological suppression across the pooled trials: 0·53 (95% CI 0·46–0·61) for directly observed therapy versus 0·50 (0·39–0·59) for self-administered treatment.

We further analysed these data to look at the difference between directly observed and self-administered treatment in several subgroups for studies reporting the primary outcome of viral suppression (webappendix). From the four studies that enrolled populations at high risk of non-adherence (drug users[23,27,32] and homeless[30]), we calculated a RR of 1·31 (95% CI 1·00–1·71, p=0·0464; I^2=27·6%, 95% CI 0–75·9, p=0·24). For general populations in the remaining six studies,[13,22,25,26,28,29] the RR was 0·96 (0·82–1·13, p=0·63; I^2=58·3%, 0–81·1, p=0·0348). No significant differences in outcome were recorded for: studies using full[23] versus partial directly observed therapy[13,22,25–30,32] (p=0·40); studies reporting allocation concealment[13,25] versus those that did not report

See Online for webappendix

	Location of study population	Mean age (years)	Number of patients	Men	Intervention			Duration of follow-up	Primary outcome
					Type	Observer and location	Duration		
Wohl et al (2006)[22]	Clinic, USA	82% more than 30 years	166	125 (75%)	Partial DOT (once daily)	Community worker, clinic	6 months	6 months	Viral load <400 copies per mL
Macalino et al (2007)[23]	Drug users, USA	42	87	61 (70%)	Full DOT (once daily)	Outreach worker, community	3 months	3 months	Viral load <50 copies per mL
Pearson et al (2007)[24]	Clinic, Mozambique	36	350	162 (46%)	Partial DOT (once daily)	Peer supporters, clinic	6 weeks	12 months	Adherence (30-day recall)
Sarna et al (2008)[25]	Clinic, Kenya	37	234	85 (36%)	Partial DOT (once daily, twice weekly)	Nurse, clinic	6 months	18 months	Viral load <400 copies per mL
Taiwo et al (2008)[26]	Clinic, Nigeria	33	500	220 (44%)	Partial DOT (once daily)	Peer supporters, community	6 months	6 months	Viral load <200 copies per mL
Maru et al (2009)[27]*	Drug users, USA	44	141	97 (69%)	Partial DOT (once daily)	Outreach worker, mobile clinic	6 months	12 months	Viral load <400 copies per mL
Nachega et al (2009)[13]	Clinic, South Africa	36	274	116 (43%)	Partial DOT (once daily)	Peer supporter, community	24 months	24 months	Viral load <50 copies per mL
Gross et al (2009)[28]	Clinics, USA and South Africa	39	243	192 (79%)	Partial DOT (weekdays only)	Medical practitioner, clinic and community	6 months	12 months	Viral load <200 copies per mL
Naidoo et al (2009)[29]	Clinic, South Africa	..	58	..	Partial DOT (weekdays only)	Nurse, clinic	10 months	..	Viral load <200 copies per mL
Bangsberg et al (2009)[30]	Homeless, USA	42	82	65 (79%)	Partial DOT (weekdays only)	Health worker, community	3 months	12 months	Viral load <400 copies per mL
Grodensky et al (2009)[31]	Prisoners, USA	38	43	34 (79%)	Full DOT (twice daily)	Health worker, prison	12 months	12 months	Adherence (% of doses taken)
Arnsten et al (2009)[32]	Drug users, USA	47	77	41 (53%)	Partial DOT (weekdays only)	Clinic staff, clinics	6 months	6 months	Viral load <400 copies per mL

Data are number (%) unless otherwise indicated. Control group was self-administered treatment for all studies. DOT=directly observed therapy. ..=data unavailable. *Implementation of this trial was reported in an earlier paper.[33]

Table 1: **Baseline characteristics of participants and study design of clinical trials**

allocation concealment[22,23,26–30,32] (p=0·27); or studies done in Africa[13,25,26,29] versus those done in the USA[22,23,27,30,32] (p=0·60). Three studies reported on previous treatment experience,[22,27,33] but information was insufficient to undertake a sensitivity analysis. Difference in duration of study (≤6 months[22,23,26,32] *vs* >6 months[13,25,27,28,30]) did not significantly affect outcome (p=0·82), but trials of 6 months' duration or less seemed to be associated with improved outcome under directly observed therapy (RR 1·24, 95% CI 1·03–1·50, p=0·212; I^2=32·5%, 95% CI 0–77·2, p=0·21). In a post-hoc analysis, we compared studies published in peer review journals with conference abstracts and recorded no significant differences in outcomes (p=0·56).

Table 2 shows data for the main secondary outcomes, and we were also able to extract data for resistance mutations, and new or recurrent AIDS-defining illnesses. Self-reported adherence—defined as any pills missed during a limited (<1 week) recall period—was available for six studies (n=1308; table 2). For directly observed versus self-administered treatment, RR was 1·02 (95% CI 0·98–1·06, p=0·29). Two of the trials reported adherence data on only a subset of patients.[22,25] Adherence in both groups was high: the overall mean adherence at study completion was 89% (SD 12·7) for directly observed and 88% (11·6) for self-administered treatment.

Eight studies were included in our assessment of immunological changes between groups at study conclusion (n=1577; table 2). We were unable to show a significant weighted mean difference for CD4 T-cell count between the treatment groups (0·35, 95% CI –2·49 to 3·20, p=0·80); data were weighted by the inverse variance method.[34] For assessment of loss to follow-up, pooled data from nine trials (n=1635) gave an RR of 1·00 (0·75 to 1·32, p=0·97). One study reported a high number of refusals to participate in the intervention group after randomisation,[27] but this did not contribute to identifiable heterogeneity between studies (I^2=0%, 95% CI 0–54·4, p=0·45). From data on all-cause mortality from seven trials (n=1490), we recorded a pooled RR of 0·67 (95% CI 0·41 to 1·07, p=0·09), indicating that method of therapy did not affect all-cause mortality (table 2).

The development of resistance mutations was only reported for two trials,[28,35] with no difference between directly observed and self-administered treatment (RR 1·66, 95% CI 0·47–5·90, p=0·42). Three trials reported on AIDS-defining events,[13,22,28] and the difference between the treatment groups was not significant (0·92, 0·44–1·95, p=0·83).

Discussion

Our study shows no benefit to virological suppression of directly observed versus self-administered antiretroviral

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treatment in people with HIV infection. Despite expectations that directly observed therapy could be an effective intervention to promote adherence both for the general population[11] and for groups at high risk of poor adherence,[36] we did not find any evidence to support such use.

Our study is not the first to question the effectiveness of directly observed therapy for chronic disease care: a similar absence of effect was reported for tuberculosis treatment by Volmink and Garner's[9] meta-analysis (RR 1·02, 95% CI 0·86–1·21). Such lack of success in both meta-analyses could be caused by attrition due to intensive clinic visitation requirements for daily observation that not all patients can meet,[37] resistance by patients to losing their autonomy[38] and a desire to take responsibility for their own treatment,[39] absence of actual delivery of the intervention, or patients maintaining excellent adherence irrespective of the intervention, indicating that self-administered treatment is successful for long-term care.[6] Additionally, treatment effects were small across all trials, such that a much larger sample size would be needed to measure an effect; small trials in general populations are underpowered to show important effects.

In our sensitivity analyses, we recorded marginal benefit of directly observed therapy in groups that were judged to be at high risk of non-adherence and in trials of short duration (<6 months). Although not definitive, these findings provide direction for future research with directly observed therapy to investigate the potential for targeted interventions of finite duration and for specific groups. Some researchers have suggested that directly observed therapy might offer benefit during the period of intervention, but that this benefit could wane afterwards.[7] We did not consider this possibility in our a priori sensitivity analysis, but note that of the trials that included a follow-up period after the study period, none of their findings indicated any benefit.[25,27,28,30] Therefore, although directly observed therapy has been promoted to reinforce adherence, any benefit will probably wane after the study period for the intervention, as has been reported for other punctual adherence interventions.[40]

Strengths of this systematic review are explicit eligibility criteria, and the comprehensive search that identified several eligible articles that were not published or available via electronic databases. We contacted all authors to complete missing information, and in most cases this was provided. Independent reviewers assessed eligibility and agreement was high.

Although our a priori analysis of heterogeneity did not find differing effects across study populations, duration, or quality, the difference in population groups and intervention used (full or partial directly observed therapy) warrants attention to possibly differing effects across specific populations or delivery of the intervention. We used a random-effects model to pool results since the model assumes that individual studies have estimated different treatment effects, but we cannot discount some degree of heterogeneity. We also undertook sensitivity analyses to assess differences in trial location, study duration, different populations, and type of intervention (full or partial directly observed therapy) and these were consistent with the overall pooled estimate of effect. Nevertheless, important differences in population groups could still lead to substantial differences in outcomes; the fact that individual trials found opposing results with respect to benefit of directly observed therapy underscores the importance of considering contextual factors in assessment of adherence interventions.

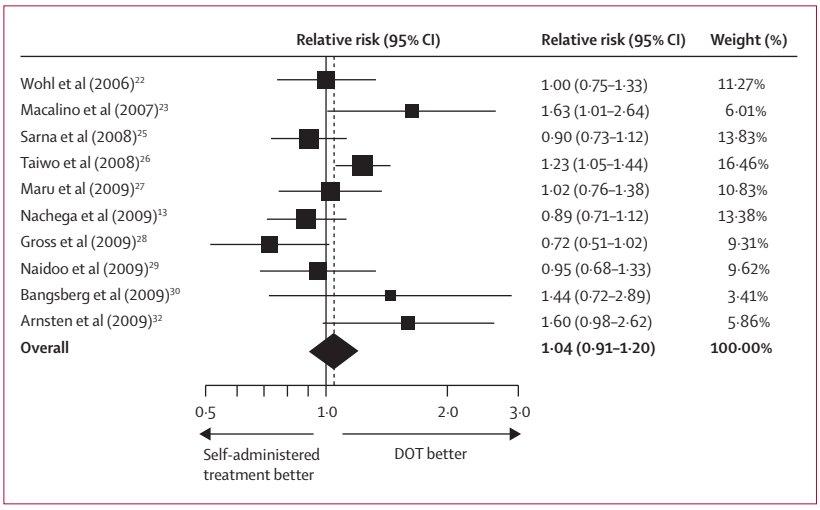

Figure 2: **Relative risk for viral suppression at study completion with directly observed versus self-administered antiretroviral treatment**

Data for viral suppression were not reported in two studies.[24,31] Weights were calculated from random-effects analysis. DOT=directly observed therapy.

Any assessment of adherence is limited by the absence of a gold standard for such assessment.[15] We used a pharmacodynamic outcome (viral load) as our major outcome because we did not expect pharmacodynamics to be affected by a placebo effect. We note that viraemia can be affected by both adherence and drug resistance; drug resistance was not consistently assessed across studies, but no difference was recorded for studies in which data were available. We included studies that used both full and partial directly observed therapy for a range of study periods. Our sensitivity analysis did not find evidence that either type or duration of intervention affected study outcomes, although we recognise that short interventions might have residual effects through education of patients experiencing problems with adherence. The fact that all secondary outcomes (self-reported adherence, immunological change, loss to follow-up, all-cause mortality, resistance mutations, and AIDS-defining events) were not significant supports the inference that the intervention had no major effects on virological suppression.

Another limitation, general to any systematic review, is the possibility that we did not capture all trial data. We

	Self-reported adherence	CD4 T-cell count (mean difference, 95% CI)	Loss to follow-up*	All-cause mortality
Wohl et al (2006)[22]	1·03 (0·91 to 1·21)†	7 (–51·12 to 65·12)	0·82 (0·46 to 1·45)	0·51 (0·07 to 3·84)
Macalino et al (2007)[23]	..	44 (–36·28 to 124·28)	0·81 (0·28 to 2·35)	..
Pearson et al (2007)[24]	1·06 (0·96 to 1·16)	0·4 (–2·47 to 3·28)	1·00 (0·18 to 5·62)	0·50 (0·16 to 1·53)
Sarna et al (2008)[25]	1·02 (0·95 to 1·10)†	–14 (–62·95 to 34·95)	1·14 (0·63 to 2·06)	1·40 (0·60 to 3·27)
Taiwo et al (2008)[26]	..	..	..	..
Maru et al (2009)[27]	..	–48·3 (–113·38 to 16·79)	11·44 (2·08 to 66·53)	1·20 (0·16 to 9·10)
Nachega et al (2009)[13]	0·97 (0·81 to 1·15)	18 (–26·5 to 62·5)	1·00 (0·42 to 2·38)	0·45 (0·22 to 0·93)
Gross et al (2009)[28]	1·01 (0·91 to 1·09)	4 (–5·3 to 13·3)	0·88 (0·48 to 1·57)	0·49 (0·07 to 3·19)
Naidoo et al (2009)[29]	..	..	1·13 (0·51 to 2·49)	..
Bangsberg et al (2009)[30]	..	–9 (–96 to 78)	0·30 (0·02 to 4·02)	0·30 (0·02 to 4·02)
Grodensky et al (2009)[31]	0·99 (0·79 to 1·21)	..	..	..
Arnsten et al (2009)[32]	..	..	..	..

Data are relative risk (95% CI) unless otherwise indicated. ..=data unavailable. *Includes refusals. †Only a subset of patients were followed up for self-reported adherence.

Table 2: **Main secondary outcomes**

failed to gain sufficient information for one completed trial.[21] However, the results of this trial have been reported in a conference abstract that concluded that there was no difference between directly observed and self-administered treatment.[41] Data from six studies included in the meta-analysis were derived from abstracts that have yet to be published as full studies. Although inclusion of these abstracts provides reassurance that all available data were captured, it could result in publication bias; however, results from our sensitivity analysis indicate no significant difference between abstracts and studies published in journals (webappendix).

Randomised trials to assess the benefit of directly observed therapy are challenging because part of the inclusion criteria needs to be that patients are poorly adherent to potentially measure an effect. Since patients on HAART are generally adequately adherent[42] and the degree of adherence can vary while still suppressing viraemia,[43] researchers face a major challenge to enrol a large enough population size to detect a difference, as indicated by the similar event rates of virological suppression across the pooled trials.[44,45] Possible explanations for viraemia beyond adherence include polypharmacy, drug resistance, treatment failure, and unknown effects of the disease or drugs.[46,47] Thus use of viral suppression as a primary outcome is important from a clinical perspective, but challenging from a methodological perspective. Additionally, although not significant, we recorded decreased mortality in the intervention group, suggesting that mortality should be routinely reported as an outcome in future trials.

Our analysis should be interpreted according to the size of treatment effects reported, and not only the statistical significance of these effects. The confidence intervals around our primary outcome show that even if the treatment effect were at the upper interval of effectiveness, widespread use of directly observed therapy would not be justified. Supporters of directly observed therapy have argued that the effect of such an intervention goes beyond observation of drug doses for tuberculosis[48] and HIV,[49] by promoting patient education and interaction with health systems and peer supporters. However, the absence of a measurable benefit together with the burden of directly observed therapy on patients and health services calls into question the effectiveness of this intervention (as distinct from auxiliary forms of support) for promotion of adherence for the general patient population. The feasibility and cost of daily observation of lifelong treatment should also be taken into account, especially in resource-limited settings where patients might have to travel long distances to access under-resourced health services. Moreover, concerns about the intervention being a violation of patient autonomy and human rights give further cause for caution in use of this approach in the absence of clear benefit.

Efforts to sustain adherence remain important to achieve optimum outcomes with HIV treatment for the individual and globally. Continuing efforts are needed to assess interventions to support adherence, especially for groups at high risk of poor adherence. Considerations of cost and feasibility of interventions, together with acceptability for patients, should be a central part of this future research agenda.

Contributors

NF coordinated the study. NF wrote the protocol and MEE supervised the protocol design. NF and EJM ran all searches and selected studies, and NF, EJM, and JBN consulted as a team to select eligible studies; MEE arbitrated the study inclusion. NF did the data extraction, NF and MEE assessed the methodological quality, and MEE clarified ambiguities in the data extraction. JBN provided guidance on study design and technical issues of adherence measurement. EJM provided technical guidance on methodological support and adherence measurement issues, and acted as a duplicate for study selection, data extraction, and assessment of methodological quality. NF undertook all communications with investigators of published and unpublished studies. NF and EJM did all statistical analyses. JBN undertook additional searches, provided unpublished data for one of the included studies, and contributed to data interpretation. NF wrote the first draft of the paper, with participation from JBN, MEE, and EJM.

Conflicts of interest

We declare that we have no conflicts of interest.

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