Does direct observation of antiretroviral therapy improve outcomes for HIV/AIDS patients compared to non-observed therapy?

A systematic review and meta-analysis of randomized-controlled trials

Nathan Ford
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Supervisor: Mark Engel, Department of Medicine, University of Cape Town

DECLARATION

I, Nathan Ford, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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INDEX

PART A: PROTOCOL

A. 1. INTRODUCTION

Highly active antiretroviral therapy (HAART) has dramatically affected the course of HIV disease, resulting in a significant reduction in AIDS-related morbidity and mortality in both developed[1] and developing[2] countries.

Adherence to antiretroviral therapy is the single most important determinant of clinical outcomes[3] [4] and a dose-response relationship has been demonstrated for virological suppression and adherence. [5] One study of HIV treatment naïve patients found that 95% adherence was associated with maximal therapeutic effects of antiretroviral therapy. The optimal level of adherence may vary according to the drugs being administered, but strategies to improve adherence remain critical to successful outcomes on any HAART regimen.[6]

HAART is life-long and often comprises complicated dosing schedules of medicines that induce numerous side-effects, and for this reason HAART has been described as the most rigorous oral medication regimens ever offered.[7] A range of barriers to adherence have been reported in the literature, including: fear of disclosure, side-effects, concomitant substance abuse, forgetfulness, suspicions of treatment, regimens that are too complicated, decreased quality of life, competing work and family responsibilities, and challenges to consistent access to medication.[8]
Numerous behavioral interventions have been developed to support adherence, including adherence case management, counseling, pharmacist-based education, telephone support, reminder devices, nurse home visits, and directly observed therapy.[9] [10] [11] Among these, direct observation is perhaps the most contentious.[12]

Directly observed therapy (DOT) involves a health care worker or other designee watching the patient swallow their medicines. DOT was developed as an adherence support strategy for tuberculosis programmes in the 1960s,[13] and has been promoted by the World Health Organization from the early 1990s as part of its global TB control strategy.[14] However, concerns have been raised with respect to the poor evidence of effectiveness and the high cost of this approach.[15] A systematic review of 11 randomized and quasi-randomized trials found no benefits of DOTS over self-administration of treatment.[16]

TB and HIV treatment differ in a number of ways. The most important difference is that TB treatment is of limited duration (6-8 months for non-resistant strains) whereas HAART is a life-long treatment. Concerns raised regarding the feasibility and cost-effectiveness of DOT for TB[15] are therefore even more relevant for HAART. Nevertheless, DOT has been promoted as a viable adherence support strategy for HAART in less-developed countries.

A number of observational studies[17 18 19] and randomized trials of DOT HAART[20 21] have been conducted in recent years, with mixed results. One trial conducted in Cape Town, South Africa, was recently terminated due to futility.[22]

Given the conflicting evidence from individual trials, this study proposes a systematic review and meta-analysis of the current evidence. A systematic review is an overview of primary studies that is conducted according to explicit and reproducible methodology. The use of an explicit methodology to identify studies according to a pre-defined criteria aims to limit bias and provide a reliable and accurate synthesis of the current evidence. A meta-analysis is a statistical technique for synthesizing of the results all studies to provide a single (pooled) estimate of effect.[23] No systematic reviews of DOT HAART trials have been published to date.

A.1.1 Objective

The objective of this study is to undertake a systematic review of all randomized and quasi-randomized trails of DOT versus non-DOT HAART among adults to assess whether the former leads to greater adherence and improves clinical outcomes for HIV/AIDS patients compared to the latter.

A.2. METHODS

A.2.1. Inclusion criteria

A.2.1.1 Types of studies

Randomized and quasi-randomized trials.·

· A trial using a quasi-random method of allocating participants (such as alternation)

A.2.1.2 Types of participants

Adults on HAART. HAART is defined as at least three antiretroviral drugs consisting of: at least one protease inhibitor; at least one non-nucleoside reverse transcriptase inhibitor; or three or more nucleoside reverse transcriptase inhibitors, of which one is abacavir. This definition is in keeping with a recent Cochrane review of adherence interventions to HAART.[24]

A.2.1.3 Types of interventions

Intervention: Direct observation of administration of HAART. This may be either full (all pills) or modified (a proportion of pills)
Control: non directly-observed administration of HAART.

A.2.1.4 Types of outcomes

This review will have to consider the following primary and secondary endpoints:

Primary

- viral load, expressed as the number of patients achieving virological suppression.

Secondary

- any measure of adherence to HAART. Where more than 1 adherence measurement is used, data on all measures will be extracted and the most objective method chosen for analysis (e.g. electronic monitoring)[8]
- immunological progression (as measured by CD4 cells/mm^3)
- all cause mortality
- development of new resistance mutations
- new or recurrent AIDS-defining illnesses

A.2.2. Search strategy for identification of studies

The proposed review will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress). Trial registers and databases will be searched for all studies using a highly-sensitive search strategy developed for this study (see Annex A.1).

For databases that do not allow the use of highly-sensitive search strategies, a simple search strategy will be used as follows: (Direct observation OR Directly observed OR DOT OR DAART) AND (ART OR HAART OR Antiretroviral).

A.2.2.1. Databases to be searched

The following electronic databases will be searched using the highly sensitive search strategy:

- MEDLINE
- EMBASE
- Cochrane CENTRAL
- CINAHL
- PsycInfo

Databases to be searched according the simple search strategy include:

Database of publications:

- LILACS (La Literatura Latinoamericana y del Caribe de Informacion en Ciencias de Salud) www.bireme.br

Clinical trials registers:

- US National Institutes of Health: www.clinicaltrials.gov
- Current Controlled Trials: www.controlled-trials.com

Abstract databases of major HIV/AIDS conferences:

- Conference on retroviruses and opportunistic infections (1998-2009): www.retroconference.org
- International AIDS Society Conferences (2001-2009): http://www.iasociety.org/AbstractSearch.aspx?search=Search%20IAS%20Abstract%20Archive
- International Conference on HIV Treatment Adherence (www.iapac.org)

Grey literature sites:

- Google Scholar: www.scholar.google.com
- The networked digital library of theses and dissertations: www.ndltd.org
- AIDS Treatment News: http://www.aidsnews.org/
- The Body http://www.thebody.com/
- Canadian AIDS Treatment Information Exchange publications: http://www.catie.ca/

The bibliography of review articles and primary studies will also be scanned, and experts in the field of HAART adherence will be contacted to identify additional trials (unpublished and ongoing).

A.2.3. Study selection

The results of the search will be screened to select potentially relevant studies. Two or more reviewers will independently apply eligibility criteria based on the study design, types of participants, and intervention detailed above. Differences in opinion will be resolved through discussion with a third party. Where the abstracts are unclear or there is any other reason for uncertainty, the full article will be obtained before making any decision regarding eligibility for inclusion. When abstracts are not available in English the assistance of translators will be sought.

A.2.4. Data extraction

Data extraction will be done according to the data extraction forms presented in Annex A.2. with all data independently cross-checked and disagreements resolved by a third party. The following information will be extracted for each trial:

Trial characteristics

- Method of randomization
- Allocation concealment
- Blinding
- Type, frequency and duration of follow up
- Duration of trial
- Adherence assessment

Participant characteristics

- Number (sample size)
- Gender
- Age

Intervention characteristics

- **Intervention**
  - Drug regimen
  - Type and frequency of DOT
  - Location
  - Observer

- **Control**
  - Drug regimen
  - Administration
  - Location

Outcomes

- Primary outcomes
- Secondary outcomes

A.2.5. Assessment of methodological quality of trials

The quality of included trials will be independently assessed by two investigators using a checklist to rate the following issues (Annex A.3.):

- Methods of randomization
- Concealment of allocation
- Blinding status (of analyst)
- Analysis done as intention-to-treat
- Loss to follow up of greater than 20%

Differences in opinion will be resolved through discussion with a third party.

A.2.6. Data Analysis

Estimates of effect will be pooled using relative risks for binary data. Heterogeneity will be assessed by forest plot and calculation of the I^2 statistic. In the absence of homogeneity of effects, a random effects model will be used. Primary and secondary outcomes will be included in the meta-analysis. Sensitivity analyses will be done using a univariate random-effects logistic regression model to assess the following: high- vs low-risk groups, type of DOT, trial location, trial duration, prior treatment experience and allocation concealment.

A.3. ETHICS

Systematic reviews draw on publicly available data and do not directly involve human subjects, and therefore do not require formal ethical review. Nevertheless some ethical principles for clinical research can be extended to systematic reviews, notably the principles of scientific validity and independent review.[25] These are noted below.

Scientific validity requires, among other things, that the scientific design of the research realizes social value, which implies that a dissemination strategy be planned in advance of the study. The results of this review will be disseminated through submission of an article to a peer-review journal. In addition, copies of the article will be sent to all investigators involved in DOT HAART studies contacted during the course of this study.

Independent review requires that public accountability is met through scientific review according to international standards. This study protocol will be reviewed by experts with knowledge of both methodology (systematic reviews and meta-analyses) and content (HAART adherence) and submitted to the University of Cape Town Departmental Research Committee for approval.

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ANNEX A.1

HIGHLY-SENSITIVE SEARCH STRATEGY·

1 human immunodeficiency virus
2 human immunodeficiency virus infection
3 anti human immunodeficiency virus agent
4 hiv.tw.
5 human immunodeficiency.tw.
6 acquired immunodeficiency syndrome.tw.
7 acquired immune deficiency syndrome.tw.
8 aids.tw.
9 or/1-8
10. patient compliance
11. complian:.tw.
12. comply.tw.
13. complied.tw.
14. noncomplian:.tw.
15. non-complian:.tw.
16. adher:.tw.
17. non-adher:.tw.
18. nonadher:.tw.
19. or/10-18
20. direct observation
21. directly observed
22. direct observ:.tw.
23. directly observ:.tw.
24. DOT
25. DAART
26. supervis:.tw.
27. or/20-26
28. randomization
29. random:.tw.
30. double blind procedure
31. single blind procedure
32. clinical trial
33. meta analysis
34. meta-analy:.tw.
35. or/28-34
36. 9 and 19 and 27 and 35

· Adapted from highly sensitive search strategies used in Cochrane reviews of treatment adherence in TB[16] and HIV[24]

ANNEX A2: DATA EXTRACTION FORM

First author:

Full article title:
Notes:

_____
_____

TRIAL CHARACTERISTICS

Randomization method:
Allocation concealment:
Duration of trial:
Duration of follow up:

Loss to follow up

	Intervention	Control	Total
Total number randomized			
Number available at follow up			
Number Loss to follow up			
Number Died			
Other			

Was analysis done as intention to treat **Yes** ☐ **No** ☐ **Unclear** ☐

Adherence assessment

	Yes	No	Unclear
Viral Load			
Electronic monitoring Indicate type (eg MEMS)			
Patient self-reports Indicate type (medication diaries)			
Provider Reports Indicate type (pill count)			
Clinical progression			
Clinic/pharmacy records			
Other Specify			

PARTICIPANT CHARACTERISTICS

Country and setting:

_____

Number of persons in trial

	Intervention	Control	Total
Number			
% of Total			100%

Gender

	Intervention		Control		Total	
	N	%	N	%	N	%
Male						
Female						
Total						

Age

	Intervention	Control	Total
Mean Age			

INTERVENTION CHARACTERISTICS

Intervention (DOT)

Drug regimen(s)	
Frequency Once a day Twice a day	
Administration Health care provider Family member, peer supporter Other	
Location Health centre Home Other	
Other remarks	

Control (non-DOT)

Drug regimen(s)	
Administration Self-administration Other	
Location Health centre Home Other	
Other remarks	

OUTCOMES

1. Primary outcomes: Viral load

	Intervention N (%)	**Control N (%)**
Number with viral load undetectable		

2. Secondary outcomes

a) Adherence (describe according to measure used):

b) Other events

	Intervention N (%)	**Control N (%)**
Mortality (any cause)		
Immunological progression		
Development of new resistance mutations		
Any HIV-associated events		

ANNEX A3: ASSESSMENT OF METHODOLOGICAL QUALITY[1]

Reviewers Initials:

Validity criteria

1. Formation of groups

Random allocation	☐
Quasi-random allocation	☐
Selected controls	☐
Not stated	☐

2. Experimental confounders

Baseline difference between groups potentially related to outcome

No, or yes but statistically adjusted	☐
Yes, no statistical adjustment	☐
Can't tell	☐

3. Unit of allocation

patient	☐
group	☐
clinic	☐

4. Concealment of allocation

random	☐
quasi-random	☐
not stated	☐

5. Blinding

Assessor blinded	☐
no blinding or not stated	☐

6. Outcome measures

Objective (not open to interpretation) or Subjective (raters blind to allocation)	☐
Subjective with no blinding but with explicit criteria for outcome definition	☐
Subjective with no blinding but with no mention of explicit criteria	☐

7. Intention to treat analysis

Yes	☐
No	☐

8. Follow up

Outcome reported for >90% of participants	☐
Outcome reported for 80-90% of participants	☐
Outcome reported for <80% of participants	☐

[1] Adapted from Haynes B. Conducting Systematic Reviews *In*: Haynes R, Sackett D, Guyatt G, Tugwell P. Clinical Epidemiology: How to do clinical practice research (third edition). Lippincott Williams & Wilkins, Baltimore, 2006.[26]

PART B: ARTICLE

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

Nathan Ford,[1*] Jean B Nachega,[2,3,4§] Mark E Engel,[3§] Edward J Mills[4]

1. Médecins Sans Frontières, 49 Jorissen Street, Orion Building, Braamfontein South Africa.

2. Department of Medicine and Centre for Infectious Diseases, Faculty of Health Sciences, Stellenbosch University, Tygerberg Campus, Cape Town, South Africa.

3. Johns Hopkins University, Bloomberg School of Public Health, Department of International Health, Global Disease Epidemiology and Control Program, Baltimore, Maryland, United States

4. Department of Medicine, University of Cape Town, Cape Town, South Africa.

5. Faculty of Health Sciences, University of Ottawa, Ontario, Canada.

§ Authors contributed equally to the study

*Correspondence: Nathan.ford@joburg.msf.org

B.1. Abstract

Background: Directly observed therapy of highly active antiretroviral therapy (DOT-HAART) has been suggested for both high-risk populations for improving poor adherence and generalized epidemics.

Objectives: We conducted a systematic review and meta-analysis of randomized trials of DOT HAART versus self-administered treatment.

Data sources: Using a highly sensitive search strategy, duplicate searches were conducted for the following databases from inception to March 26, 2009: MEDLINE via PubMed, EMBASE, Cochrane CENTRAL, CINAHL, PsycInfo, LILACS, Current Controlled Trials and US National Institutes of Health. Searchable websites of major HIV conferences (IAS, IAPAC and CROI) and grey literature websites complemented this search. Investigators of all identified unpublished trials were contacted.

Review methods: Abstracts were scanned in duplicate for all randomized and quasi-randomized trials comparing direct observation of HAART administration with non directly-observed administration of HAART among adults. Our primary outcome was virological suppression at study completion. Secondary outcomes included self-reported adherence, immunological changes (CD4 T-cell), loss-to-follow up, all cause mortality, resistance mutations, and major AIDS-defining events. We calculated relative risks (RR) and appropriate 95% Confidence Intervals (CIs) for all primary and secondary outcomes. Pooled estimates were calculated using a random effects method. Sensitivity analyses assessed high and low risk groups, study duration and location, and allocation concealment. We applied a Bayesian sensitivity analysis on our primary outcome and conducted a post-hoc optimal information size to determine whether effect sizes were adequate to conclusively determine an effect.

Results: Twelve studies met our inclusion criteria, of which four were done in groups considered at high risk of poor adherence (drug users and homeless). Of the 10 studies reporting our primary outcome (n=1862) we found a pooled non-significant effect of RR 1.04 (95% CI, 0.91-1.20, P=0.55, I^2= 53.8%, 95% CI, 0-76%, P=0.02) for viral suppression at study completion. Bayesian results were no different (RR 1.05, 95% credible intervals 0.96-1.14). Self-reported adherence (RR 1.02, 95% CI, 0.98-1.06, P=0.26), immunological progression (CD4 T-cell change 0.35, 95% CI, -2.49 – 3.20, P=0.80, 0% 96%CI 0-56%, P=0.71) and all-cause mortality (95% CI, 0.41-1.07, P=0.09) were all non-significant. Our optimal information size indicates a further 17,000 patients with a similar baseline risk need to be randomized to detect conclusively any potential effect of DOT-HAART.

Conclusion: DOT offers no benefit over self-administration of antiretroviral therapy.

B.2. Introduction

Highly active antiretroviral therapy (HAART) has dramatically affected the course of HIV disease, resulting in an important reduction in AIDS-related morbidity and mortality in both developed and developing countries. [1,2]

Strategies to improve adherence remain critical to successful outcomes on any HAART regimen.[3] HAART is life-long and requires high levels of adherence to ensure maximum virologic outcomes,[4,5] prevent antiretroviral drug resistance,[6,7] prevent disease progression,[8] and improve survival.[9] Numerous behavioral interventions have been developed to support adherence including adherence case management, counseling, pharmacist-based education, telephone support, reminder devices, nurse home visits, and directly observed therapy (DOT).[10,11,12] Among these, direct observation is perhaps the most contentious.[13,14]

Directly observed therapy involves a health care worker or other designee witnessing the patient swallow their medicines. DOT was developed as an adherence support strategy for tuberculosis (TB) programmes in the 1960s,[15] and has been promoted by the World Health Organization since 1994 as part of its global tuberculosis (TB) control strategy. However, concerns have been raised with respect to the poor evidence of effectiveness and the high cost of this approach.[16] A systematic review of TB randomized trials found no benefits of DOT over self-administration of treatment.[17] Critics have also raised concern that DOT is coercive to patient autonomy.[18,19]

TB and HIV treatment differ in a number of ways. The most important difference for patients is that TB treatment is of limited duration (6-8 months for non-resistant strains) whereas HAART is a life-long treatment. Concerns raised regarding the feasibility and cost-effectiveness of DOT for TB are therefore even more relevant for HAART. Nevertheless, DOT has been promoted as a potential adherence support strategy for HAART, largely on the basis of small observational studies.[20,21]

Given the potential cost to both patients and health services of implementing DOT programmes for HAART there is a need for clear evidence of its benefit as an adherence support strategy. We conducted a systematic review and meta-analysis of randomized trials of DOT HAART versus self-administered treatment.

B.3. Methods

B.3.1. Eligibility criteria

We included all randomized trials assessing direct observation of antiretroviral therapy as an intervention to promote adherence as a primary or secondary outcome within any adult population in any setting. We considered the supervised swallowing of HAART pills as direct observation. We included randomized clinical trials (RCTs) of any duration or exposure to DOT, regardless of regularity and examined differences in a sensitivity analysis. We included studies among adult populations receiving any antiretroviral combination therapy in any dosing format. Non-randomized studies were excluded.

B.3.2. Search strategy

We developed a highly sensitive search strategy (Search strategy provided in Appendix) combining key terms that may indicate adherence (e.g. adherence, compliance, directly

observed, DOT) with the MeSH headings "HIV" or "Acquired Immunodeficiency Syndrome" and search terms for randomized trials from January to April 2009. Initial searches were developed (NF, JN). Investigators then searched independently (NF, EM), in duplicate the following databases (from inception to March 26, 2009): MEDLINE via PubMed, EMBASE, Cochrane CENTRAL, CINAHL, PsycInfo, LILACS, Current Controlled Trials (www.controlled-trials.com) and US National Institutes of Health (www.clinicaltrials.gov), and the searchable websites of major HIV conferences: all International AIDS Society conferences (up to Mexico, August 2008) and all Conferences on Retroviruses and Opportunitistic Infections (up to Montreal, February 2009). We also hand searched abstracts of the International Conference on HIV Treatment Adherence (International Association of Physicians in AIDS Care, Miami, April 2009) and searched a number of lay publications and websites, including The Body, the Canadian AIDS Treatment Information Exchange publications, AIDS Treatment News, Google Scholar and the networked digital library of theses and dissertations (ww.ndltd.org). Our search was complemented by reviewing bibliographies of relevant papers and contacting individual clinical researchers and AIDS trials groups through email and phone (National Institutes of Mental Health, International AIDS Society, and International Association of Physicians in AIDS Care); from our searches, we had identified all studies matching our inclusion criteria suggested by these groups. We contacted all potentially relevant study authors by email and telephone for details on their trials. One of the authors (JN) was primary investigator on a trial.

B.3.3. Study selection

Using a predefined protocol (available from the corresponding author on request), two investigators (NF, EM) worked independently, in duplicate, scanning all abstracts and obtaining the full text of articles and abstracts that indicated or suggested that direct

observation of pill-taking was conducted. After obtaining full reports of the candidate studies (either in full peer-reviewed publication, conference abstract or non peer-reviewed article) the same reviewers independently assessed eligibility. Reviewers were not blinded to study authors, study conclusions and outcomes as blinding has been shown to have little effect on systematic reviews.[22] To obtain full information regarding conference abstracts and registered trials, we attempted contact with all study authors for full information through email and telephone communication. After all potentially relevant full-text articles and abstracts were identified, we consulted as a team (NF, JN, EM) to achieve consensus regarding eligibility and consulted an arbitrator (ME) for adjudication.

B.3.4. Data extraction

During March 2009, we conducted data extraction independently and in duplicate, using a standardized, pre-piloted form. Data abstractors collected information about the study setting, study populations, sample size, and methods of adherence measurement. Because there is no gold standard for evaluating adherence to medication,[23] we included different measures of adherence as reported in the studies. Our primary endpoint was the number of individuals in the exposure and control groups achieving viral suppression at study endpoint. Secondary outcomes include all-cause mortality; immunological progression (as measured by CD4 T-cells/mm^3); development of resistance mutations; and new or recurrent AIDS-defining illnesses. We entered the data into an electronic database such that duplicate entries existed for each study and when the two entries did not match we reached consensus through discussion. We considered study quality according to reporting of randomization method, adjustment of experimental confounders, allocation concealment, blinding of analysts, objectivity of outcome measures, use of intent-to-treat analysis, and loss to follow-up larger than 20%.

B.3.5. Data analysis

In order to assess inter-rater reliability on inclusion of articles, we calculated the *Phi* statistic, which provides a measure of inter-observer agreement independent of chance.[24] We calculated the Relative Risk (RR) and appropriate 95% Confidence Intervals (CIs) of the primary and secondary outcomes according to the number of events reported in the original studies or sub studies as intent-to-treat analyses. Where studies did not report intent-to-treat, we analyzed outcomes as all-patients randomized.[21] In the unlikely event of zero outcome events in one arm of a trial, we prepared to apply the Haldane method and add 0.5 to each arm.[22] We pooled studies as an analysis of all-DOT combined using the DerSimonian-Laird random effects method,[23] which recognizes and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability.[24] We calculated the I^2 statistic for each analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity,[25] and calculated the appropriate I^2 confidence intervals.[26] We ran a sensitivity analysis on our primary outcome using a Bayesian random effects model with Monte Carlo Markov Chain simulations of variability.[25] Given the expected small number of included trials we conducted univariate sensitivity analysis assessing the impact of study quality as determined by groups at high vs low risk for non-adherence, prior treatment experience, the impact of study duration defined as short (≤6 months) or long term (>6 months) and allocation concealment reporting on outcomes and intervention versus post-intervention outcomes. We assessed CD4 T-cell changes by applying a weighted mean difference meta-analysis and transformed data to mean and standard deviations (SD) when reported as median and ranges.[26] We calculated the optimal information size post-hoc for our meta-analysis on the primary outcome of viral suppression to determine the conservative number of patients required to provide an authoritative answer of therapeutic efficacy.[27] We imputed the experimental and control event rates from our meta-analysis and applied a 95%

power at the 5% significance level. Primary outcomes are reported as intent-to-treat. Forest plots are displayed for each all-DOT analysis, showing individual study proportions with 95% CIs, and the overall DerSimmonian-Laird pooled estimate. All p-values are exact and 2-sided. We considered a p-value <0.05 to be significant. Analyses were conducted using StatsDirect (version 2.5.2, www.statsdirect.com), Stata (version 9, www.stata.com), and OpenBUGS version 2.1. (www.mathstat.helsinki.fi.libaccess.lib.mcmaster.ca/openbugs/).

B.3.6. Role of the Funding Source

We did not receive funding for this study.

B.4. Results

From our initial searches up to March 2009, we identified 942 abstracts of full text articles, among which 83 studies passed first screening. There was near perfect agreement between reviewers on inclusion of abstracts for further analysis (*Phi*=0.91). A flow diagram of studies included in the analysis is detailed in Figure 1.

Table 1 displays the study characteristics. Overall, 12 studies were included for analysis. All full-text papers and abstracts were published in English. Six studies were conducted within USA;[28,29,30,31,32,33] another five were conducted in Africa (in Kenya,[34] Mozambique,[35] Nigeria,[36] and South Africa,[37,38]), and one was a multi-site study conducted in the USA and South Africa.[39] Authors provided additional data for five abstracts[31,32,33,37,39] and partial data for one unpublished, completed study.[38] We failed to secure sufficient data for two identified studies (authors did not respond).[40,41]

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,[29,30,34,35,37,42] three allocation concealment,[34,35,37] none reported blinding of study analysts, and four reported results as a full intention-to-treat analysis, [28,30,37,42] the others as modified intent-to-treat. Five reported an overall proportion lost-to-follow up of less than 20%.[28,29,35,37,42]

The method of implementing DOT varied across studies. Three studies used directly observation of every study dose,[29,32,37] the rest had a modified DOT regimen whereby only a proportion of doses was observed. Two studies[32,34] used health workers as observers; the rest used community or peer supporters. All studies used self-administered pill-taking (SAT) as the control intervention.

B.4.1. Meta-analysis

B.4.1.1. Viral Suppression

When we pooled all studies as an analysis of all-DOT versus SAT that reported our primary outcome of viral suppression (total n=1863), we found a pooled non-significant effect of RR 1.04 (95% CI, 0.91-1.20) on viral suppression at the study completion. (Figure 2.) Bayesian results were no different (RR 1.05, 95% credible intervals 0.96-1.14) When we examined the four studies enrolling populations considered at high risk of non-adherence (drug users[28,29,33] and homeless[31]) we found a relative risk of 1.31 (95% CI, 1.00-1.71, P=0.05); for general populations the relative risk was 0.96 (95% CI, 0.82-1.13, P=0.63, I^2=58.3%, 95% CI, 0-81.1%, P=0.03, test for difference P=0.64). Studies using full observation[29,37] (every dose) were not significantly different than those using modified DOT (P=0.54). Studies reporting allocation concealment[34,35] were not different than those that did not report it (0.27). Three studies

reported on prior treatment experience[28,30,43] but information was insufficient to undertake a sensitivity analysis. Duration of study (≤6 months[29,30,33,36] vs >6 months) did not significantly affect outcome (P=0.82). Studies conducted in Africa[34,36,37,38] were not significantly different from studies conducted in the USA (P=0.60). No significant heterogeneity was found to be present amongst the studies comprising the meta-analyses (P=0.55, I^2= 53.8%, 95% CI, 0-75.5%, P=0.02) (Figure 3.)

We were able to extract data on the following secondary outcomes: self-reported adherence, immunological change, loss-to-follow up, all-cause mortality, resistance mutations, and new or recurrent AIDS-defining illnesses (Table 2).

B.4.1.2. Self-reported adherence

Self-reported adherence was available for six studies (total n=1,308),[30,32,34,35,37,39] defined as any pills missed during a limited (<1 week) recall period. We found a pooled RR of 1.02 (95% CI, 0.98-1.06, P=0.29, I^2=0%, 95% CI, 0-61%, P=0.94). Two of the trials reported adherence data on only a subset of patients.[30,34]

B.4.1.3. Immunological Changes

Eight studies were included in our assessment of CD4 changes between groups at study conclusion (total n=1577). We were unable to display a significant weighted mean difference between the DOT and SAT arms (CD4 T-cell change 0.35, 95% CI, -2.49 – 3.20, P=0.80).

B.4.1.4. Loss-to-follow-up

When we assessed loss to follow-up among trials, we pooled data from nine trials (n=1,635) and found a pooled RR of 1.00 (95% CI, 0.75-1.32, P=0.97). One study reported a high

number of refusals to participate in the intervention arm post-randomization[28] but this did not contribute to identifiable heterogeneity between studies (I^2=0%, 95% CI, 0-54.4%, P=0.45).

B.4.1.5. All-cause mortality

We assessed the impact of DOT on all-cause mortality from six trials (total n=1,490), and found a pooled RR of 0.67 (95% CI, 0.41-1.07, P=0.09, I^2=0%, 95% CI, 0-59%, P=0.59) indicating that mode of therapy made no important difference on all-cause mortality.

B.4.1.6. Resistance mutations

The development of resistance mutations was only reported for two trials,[42,44] with no difference between DOT and SAT arms (RR 1.66, 95% CI, 0.47-5.90, P=0.42).

B.4.1.7. New or recurrent AIDS-defining illnesses

Three trials reported on AIDS-defining events[30,37,39] and had a non-significant difference between DOT and SAT arms (RR 0.92, 95% CI, 0.44-1.95, P=0.83; I^2 = 49.8% 95% CI, 0-84.5%, P=0.14).

B.4.1.8. Optimal information size

We applied a post-hoc sample size calculation, the optimal information size,[27,45] whereby the median event rates across control and intervention arms were used to determine the appropriate sample size required to evaluate a therapeutic role of DOT. Given that this post-hoc analysis is based on actual data from RCTs rather than expected event rates or observations from cohort studies, the optimal information size provides reliable estimates on the number needed to evaluate this intervention.[45] When we applied the median event rates at

80% and a 5% alpha, we found that 19,690 individuals with a similar baseline risk would need to be enrolled.

B.5. Discussion

There have been considerable expectations that DOT could be an effective intervention to promote adherence both for the general population[21] and for groups at high risk of poor adherence.[46] We did not find any evidence to support DOT for general populations, while the effect for high-risk groups in the sensitivity analysis was found to be on the margin of significance. Ours is not the first study to question the effectiveness of a DOT approach to chronic disease care: a similar lack of effect has been reported for DOT-TB treatment (RR 1.02, 95% CI 0.86 to 1.21).[17] Possible explanations of the intervention's lack of success in both meta-analyses include attrition due to the intensive clinic visitation requirement of daily observation that not all patients can meet,[47] resistance by patients to losing their autonomy[48] and a desire to take responsibility for their own treatment,[49] a possible lack of actual delivery of DOT in the intervention arm, and/or that patients maintain excellent ART adherence regardless of the intervention indicating that self-administration is a successful approach to long-term care.[13,50]

Strengths of this systematic review include explicit eligibility criteria, and conduct of a comprehensive search that identified a number of eligible articles 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. Our *a priori* explanations of heterogeneity did not find differing effects across study populations, time, or study quality, reinforcing the validity of our study findings.

A limitation to any adherence assessment is the lack of a 'gold standard' for evaluating adherence.[23] We used a pharmacodynamic outcome (viral load) as our major outcome as we do not expect a placebo effect to influence pharmacodynamics. Objective outcomes such as viremia may be influenced by both adherence and drug resistance, an issue that was not consistently evaluated across studies. We included studies that used both consistent (every dose) and modified DOT (select dosing) for varying study periods. Our sensitivity analysis did not find evidence that either type or duration of intervention affected study outcomes, although we recognize that short interventions may have residual effects by educating patients experiencing problems with adherence. The fact that all secondary outcomes (self-reported adherence, immunological change, all cause mortality, resistance mutations, and AIDS-defining events) were non-significant supports the inference of no major effects of DOT on virological suppression.

Authors did not respond to requests to provide outcomes that are not in the public domain. This displays a publication-bias that we infer as absent from for-profit motivations, but influenced by authors desire to publish findings as a full-text article initially, which is understandable. The largest of these trials (n=650[51]) reported in a conference abstract that no difference was detected between DOT and SAT arms. This, together with the large numbers of patients required to show a measurable effect as determined by the optimal information size gives us confidence that this missing data would not importantly change our findings.

Conducting randomized evaluations of DOT is challenging as inclusion requires that patients be poorly adherent in order to measure an effect. Because patients on HAART generally display excellent adherence[52] and viremia can be suppressed at varying levels of adherence,[53]

enrolling an adequate population size to detect a difference is a major challenge.[54,55] Although we found similar event rates of virological suppression, possible explanations beyond adherence include polypharmacy, drug resistance, treatment failure, and unknown effects of the disease or drugs.[42,56,58] Studies enrolling patients at a high-risk of having events require patients that would experience multiple adherence failures and are capable of demonstrating virological escape. These populations are difficult to identify in programmes due to patient heightened self-report of successful adherence[59] and the previously mentioned alternative explanations for viremia. It is worth noting that the goal of adherence is to prevent viremia (and resistance), rather than using clinical failures to identify poor adherence;[42] thus using viral suppression as a primary outcome is important from a clinical perspective, but challenging from a methodological perspective.

The impact of DOT has been argued to be more than just observed doses for both TB[60] and HIV,[61] because DOT programmes may educate patients and encourage interaction with health systems and peer supporters, which may be broadly beneficial.[62] However, the absence of a measurable benefit together with the burden of direct observation for both patients and health services calls into question the specific role of direct observation in promoting adherence, particularly for the general patient population. Efforts to sustain adherence remain important to optimize individual and global HIV treatment outcomes, and ongoing efforts are required to evaluate to adherence support interventions, particularly for groups at high-risk of poor adherence. Considerations of cost and feasibility of administration, and acceptability by patients, should be a central part of this future research agenda.

B.6. Conflict of interest

None

B.7. References

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B.7.1. Table 1: Trial characteristics

Study	Study population	Age (Mean)	Gender % male	n	Intervention		Control	Duration of follow up	Outcome
					Type	Duration			
Wohl, 2006[30]	Clinic population, USA	82% over 30 years	75%	166	Partial DOT (Once daily)	6 months	SAT	6 months	VL<400
Macalino, 2007[29]	Drug users, USA	42	70%	87	Full DOT (Once daily regimen)	3 months	SAT	3 months	VL<50
Pearson, 2007[35]	Clinic population, Mozambique	36	46.3%	350	Partial DOT (Once daily)	6 weeks	SAT	12 months	Adherence (30 day recall)
Sarna, 2008[34]	Clinic population, Kenya	37	36.3%	234	Partial DOT (Once daily, twice weekly)	6 months	SAT	18 months	VL<400
Taiwo, 2008[36]	Clinic population, Nigeria	33	44%	500	Partial DOT (Once daily)	6 months	SAT	6 months	VL<200
Maru, 2009[28]	Drug users, USA	44	68.8%	141	Partial DOT (Once daily)	6 months	SAT	12 months	VL <400
Nachega, 2009[37]	Clinic population, South Africa	36	42.3%	272	Full DOT	24 months	SAT	24 months	VL<50
Mildvan, 2009[39]	Clinic population Multi-site (US &South Africa	39	79%	243	Partial DOT (weekdays only)	6 months	SAT	12 months	VL<200
Karim, 2009[38]	Clinic population, South Africa	---	---	58	Partial DOT (weekdays only)	---	---	---	---
Bangsberg, 2009[31]	Homeless population, USA	42	80%	82	Partial DOT (weekdays only)	3 months	SAT	12 months	VL<400
Grodensky, 2009[32]	Prisoners, USA	38	79%	43	Full DOT	12 months		12 months	Adherence (% doses taken)
Arnsten, 2009[33]	Drug users, USA	47	53%	77	Partial DOT (weekdays only)	6 months	SAT	6 months	VL<400

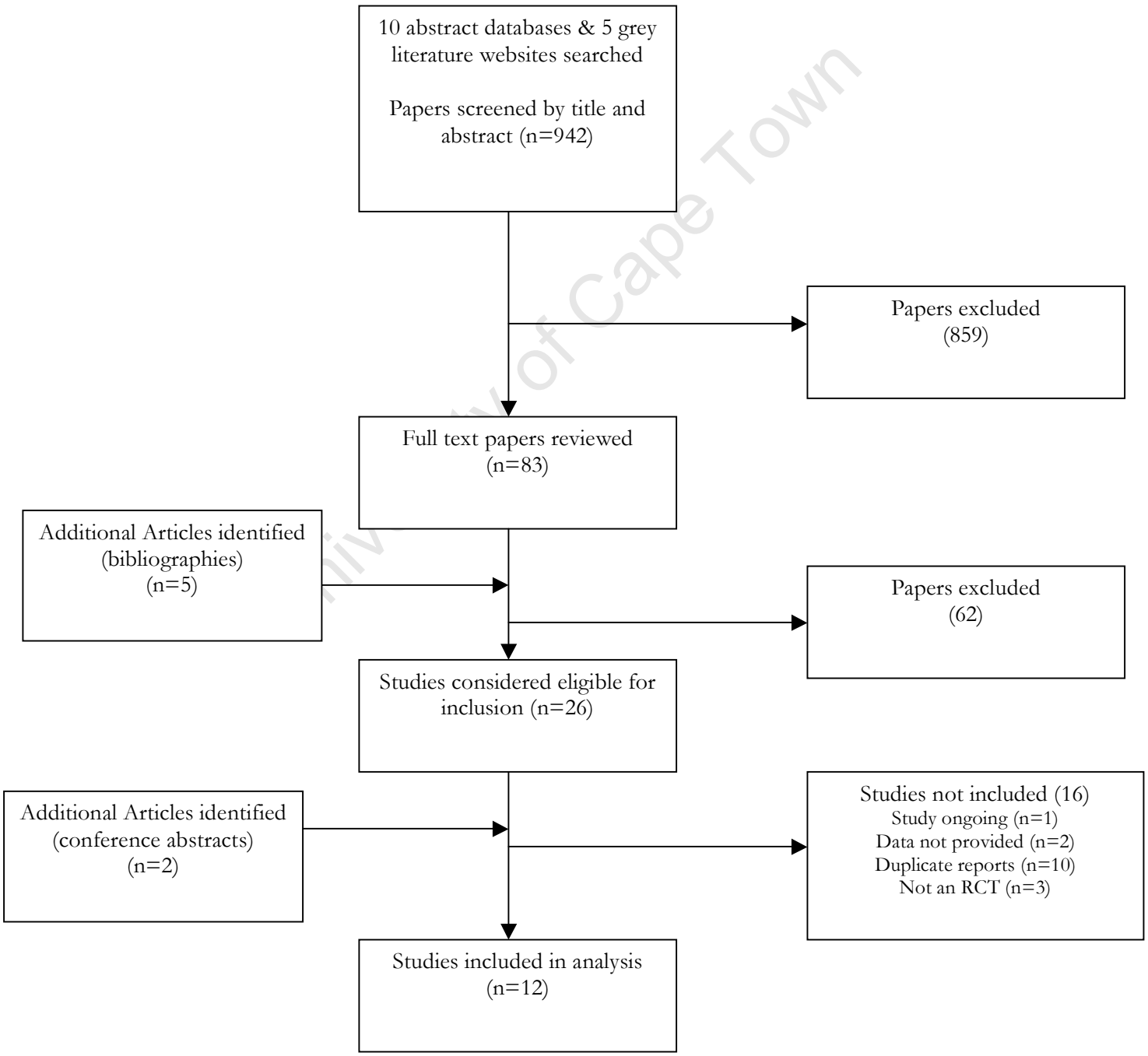
VL, Viral Load; SAT, Self-Administered Therapy; DOT, Directly Observed Therapy.
*Implementation of this trial was reported in an earlier paper.[43]

B.7.2. Table 2. Primary and main secondary outcomes

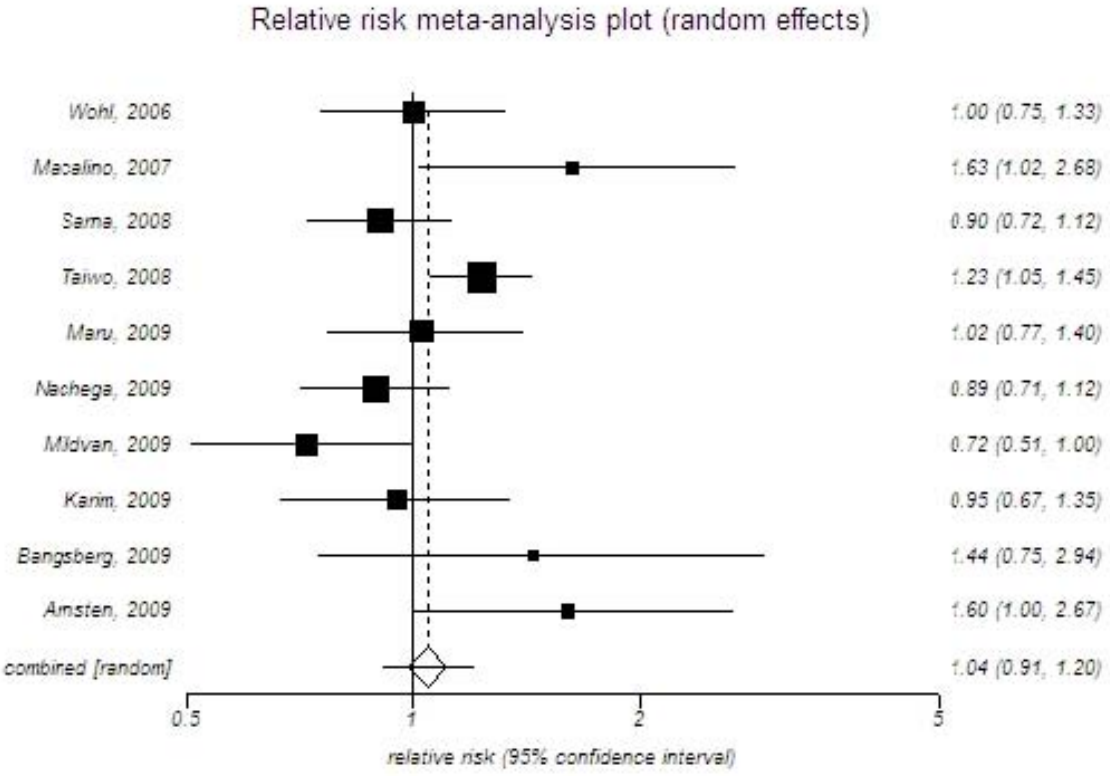
Study	Viral suppression (RR, 95% CI)	Adherence (RR, 95% CI)	CD4 (SMD, 95% CI)	LTFU**§ (RR, 95%CI)	Mortality (RR, 95%CI)
Wohl, 2006[30]	1.00 (0.75-1.33)	1.03* (0.91-1.21)	7 (-51.12-65.12)	0.82 (0.46-1.45)	0.51 (0.07-3.84)
Macalino, 2007[29]	1.63 (1.02-2.68)	---	44 (-36.28-124.28)	0.81 (0.28-2.35)	---
Pearson, 2007[35]	---	1.06 (0.96-1.16)	0.4 (-2.47-3.28)	1.00 (0.18-5.62)	0.50 (0.16-1.53)
Sarna, 2008[34]	0.90 (0.72-1.12)	1.02* (0.95-1.10)	-14 (-62.95-34.95)	1.14 (0.63-2.06)	1.40 (0.60-3.27)
Taiwo, 2008[36]	1.23 (1.05-1.45)	---	---	---	---
Maru, 2009[28]	1.02 (0.77-1.40)	---	-48.3 (-113.38-16.79)	11.44 (2.08-66.53)	1.20 (0.16-9.10)
Nachega, 2009[37]	0.89 (0.71-1.12)	0.97 (0.81-1.15)	18 (-26.5-62.5)	1.00 (0.42-2.38)	0.45 (0.22-0.93)
Mildvan, 2009[39]	0.72 (0.51-1.00)	1.01 (0.91-1.09)	-15 (-7.0 – 4.0)	0.88 (0.48-1.57)	0.49 (0.07-3.19)
Karim, 2009[38]	0.95 (0.67-1.35)	---	---	1.13 (0.51-2.49)	---
Bangsberg, 2009[31]	1.02 (0.88-1.17)	---	-9 (-96-78)	0.30 (0.02-4.02)	0.30 (0.02-4.02)
Grodensky, 2009[32]	---	0.99 (0.79-1.21)	---	---	---
Arnsten, 2009[33]	1.60 (0.91-1.20)	---	---	---	---

* Only a subset of patients were followed up for self-reported adherence
** Includes refusals
§ Loss to follow-up reported for period of intervention only
SMD, standardized mean difference

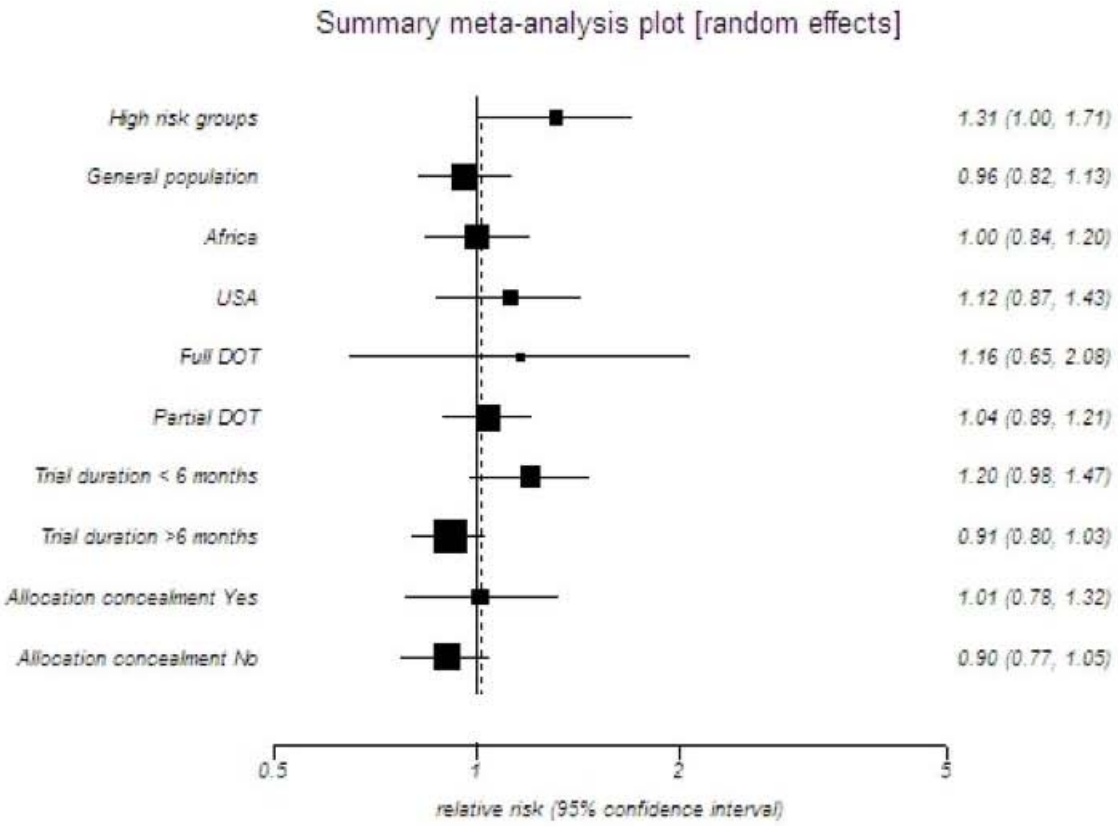
B.7.3. Figure 1. Identification process for elligible studies



B.7.4. Figure 2: Effect of Direct observation of HAART on virological suppression compared to self-administration



B.7.5. Figure 3: Subgroup analysis for the effect of DOT viral suppression



PART C: ANNEXES

Annex C.1. Investigator contributions

Nathan Ford: was overall responsible for co-ordination of this study, from conception to submission. He conceived the study question; wrote the protocol; ran all searches; selected all studies; did the data extraction; assessed methodological quality; undertook all communications with investigators of published and unpublished studies; calculated all summary statistics; ran all meta-analyses; and wrote the first draft of the paper

Jean Nachega: provided guidance on technical issues of adherence measurement; undertook additional searches, provided unpublished data for one of the included studies; and contributed to the writing of the paper.

Mark Engel: provided supervision for the protocol design; arbitration for study inclusion and assessment of methodological quality; clarification of ambiguities in data extraction; contributed to the writing of the article; and managed the overall dissertation submission process.

Ed Mills: Provided technical guidance on methodological support and adherence measurement issues; acted as a duplicate for study selection, data extraction, and assessment of methodological quality; supervised the data analysis; and contributed to the writing of the paper.

ANNEX C2: META-ANALYSES

C.2.1: Sensitivity Analyses of primary outcomes

C.2.1.1. High risk groups vs general population

Summary meta-analysis

Stratum	Relative Risk		SE	Approximate 95% CI		% Weight (fixed, random)	
1	1.31	0.136863	1	1.71	26.322135	43.770134	High risk groups
2	0.96	0.081805	0.82	1.13	73.677865	56.229866	General population

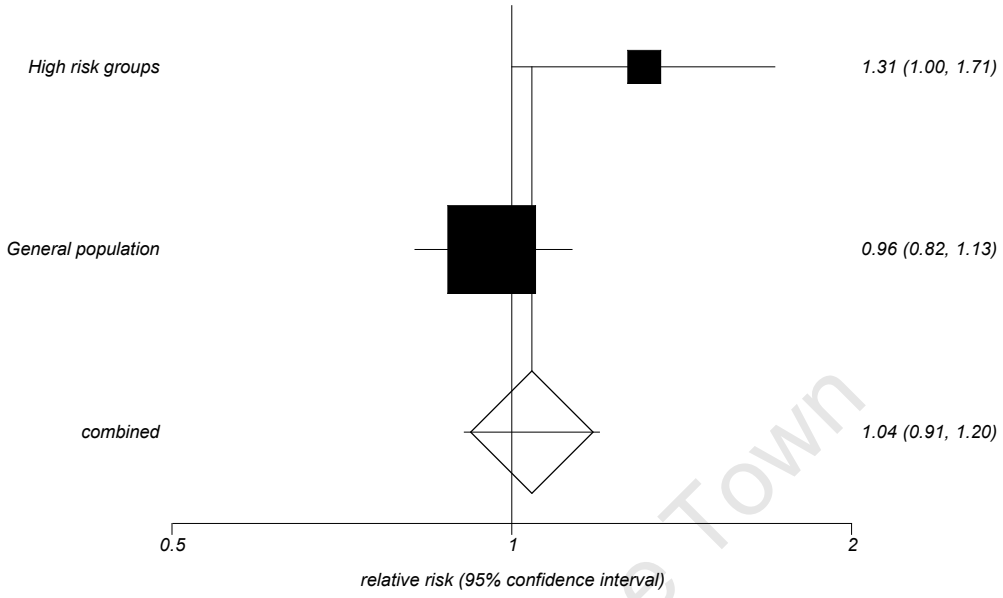
Fixed effects (inverse variance)
Pooled relative risk = 1.041852 (95% CI = 0.907897 to 1.195572)
Z (test test relative risk differs from 1) = 0.5839 P = 0.5593

Non-combinability of studies
Cochran Q = 3.800702 (df = 1) P = 0.0512
Moment-based estimate of between studies variance = 0.035602
I^2 (inconsistency) = *% (95% CI = *% to *%)

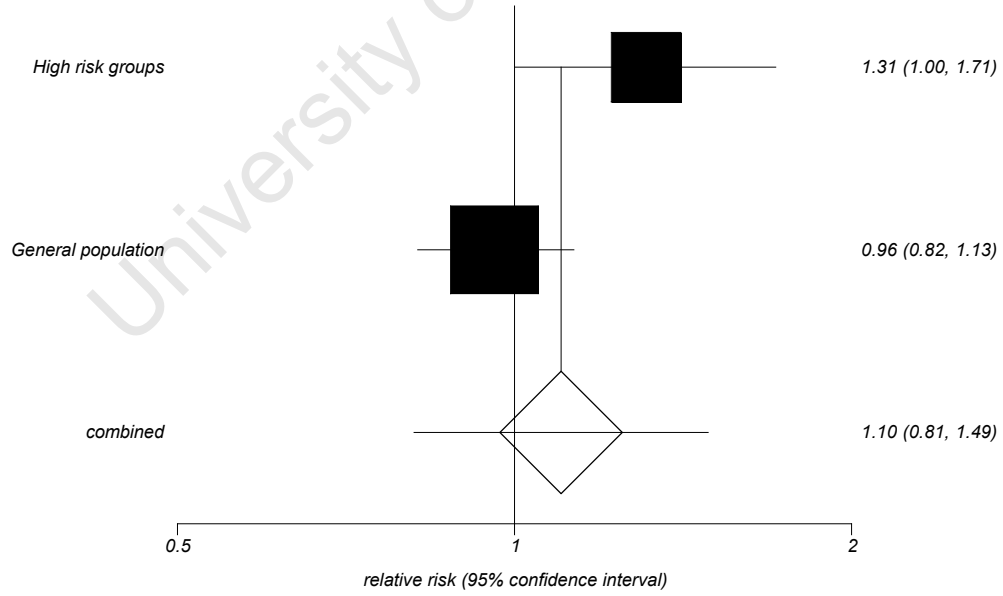
Random effects (DerSimonian-Laird)
Pooled relative risk = 1.09992 (95% CI = 0.813007 to 1.488085)
Z (test test relative risk differs from 1) = 0.617567 P = 0.5369

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *

Summary meta-analysis plot [fixed effects]



Summary meta-analysis plot [random effects]



C.2.1.2. Full vs partial DOT

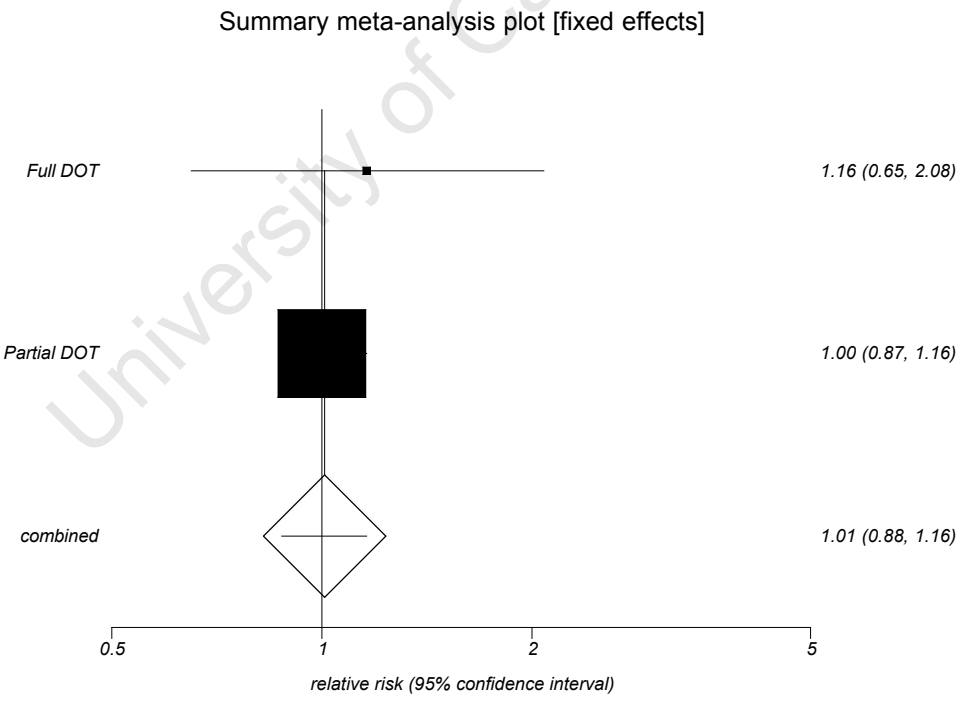
Stratum	Relative Risk	SE	Approximate 95% CI		% Weight (fixed, random)		
1	1.16	0.296728	0.65	2.08	5.764581	5.764581	Full DOT
2	1	0.07339	0.87	1.16	94.235419	94.235419	Partial DOT

Fixed effects (inverse variance)
Pooled relative risk = 1.008592 (95% CI = 0.87715 to 1.159733)
Z (test test relative risk differs from 1) = 0.120093 P = 0.9044

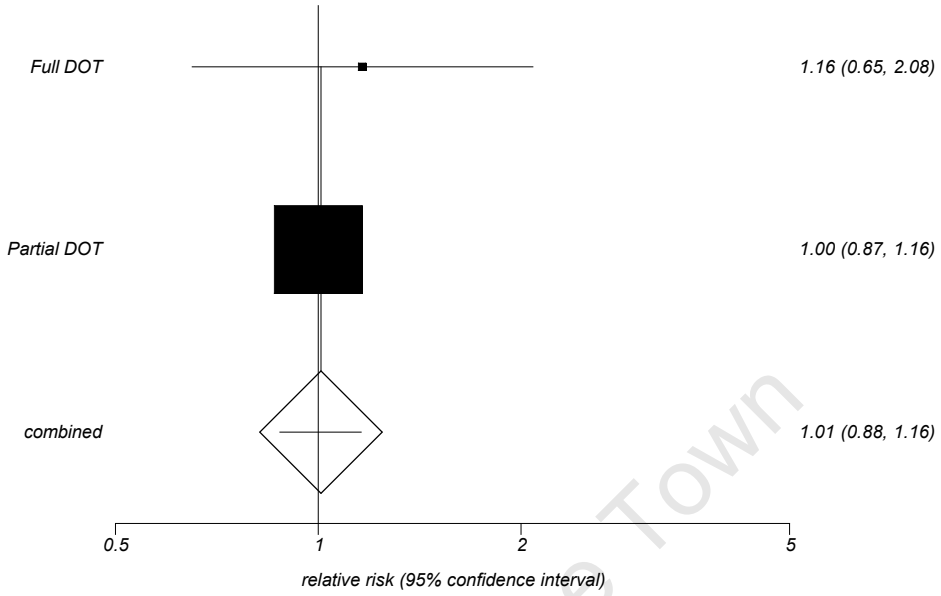
Non-combinability of studies
Cochran Q = 0.235767 (df = 1) P = 0.6273
Moment-based estimate of between studies variance = 0
I^2 (inconsistency) = *% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled relative risk = 1.008592 (95% CI = 0.87715 to 1.159733)
Z (test test relative risk differs from 1) = 0.120093 P = 0.9044

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *



Summary meta-analysis plot [random effects]



C.2.1.3. Africa vs USA

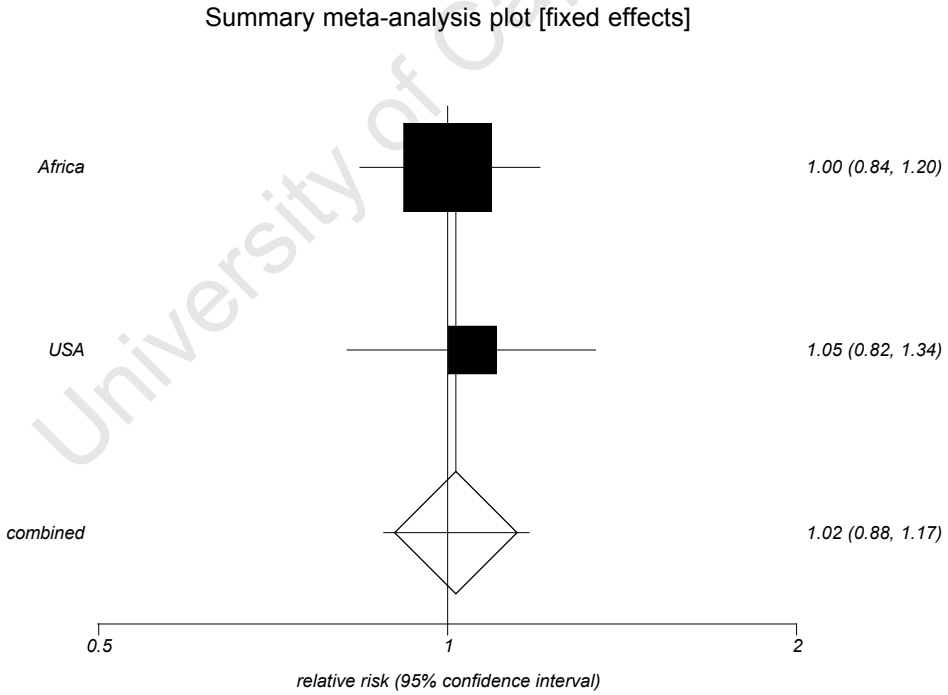
Stratum	Relative Risk	SE	Approximate 95% CI		% Weight (fixed, random)		
1	1	0.09099	0.84	1.2	65.469232	65.469232	Africa
2	1.05	0.125288	0.82	1.34	34.530768	34.530768	USA

Fixed effects (inverse variance)
Pooled relative risk = 1.01699 (95% CI = 0.880337 to 1.174856)
Z (test test relative risk differs from 1) = 0.228837 P = 0.819

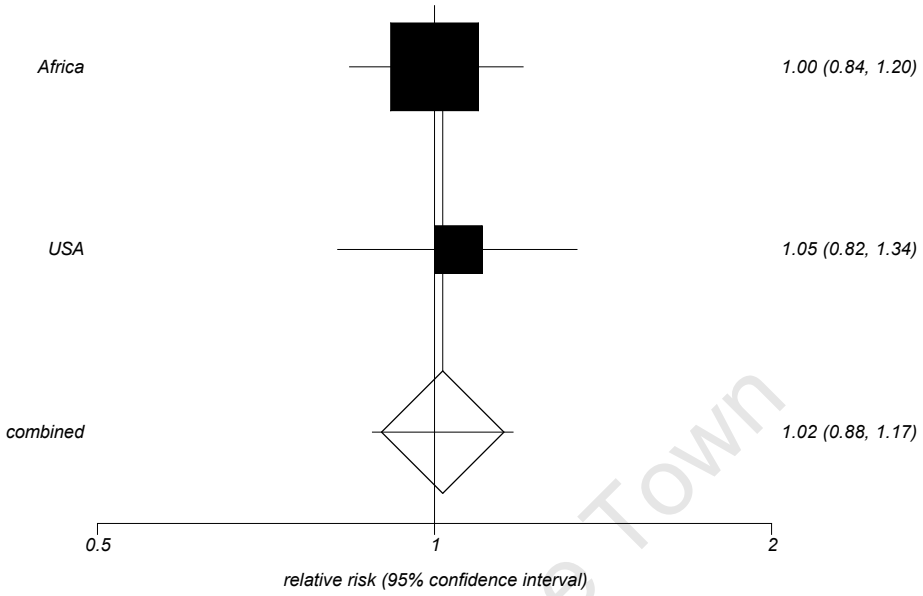
Non-combinability of studies
Cochran Q = 0.099285 (df = 1) P = 0.7527
Moment-based estimate of between studies variance = 0
I^2 (inconsistency) = *% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled relative risk = 1.01699 (95% CI = 0.880337 to 1.174856)
Z (test test relative risk differs from 1) = 0.228837 P = 0.819

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *



Summary meta-analysis plot [random effects]



C.2.1.4. Trial duration

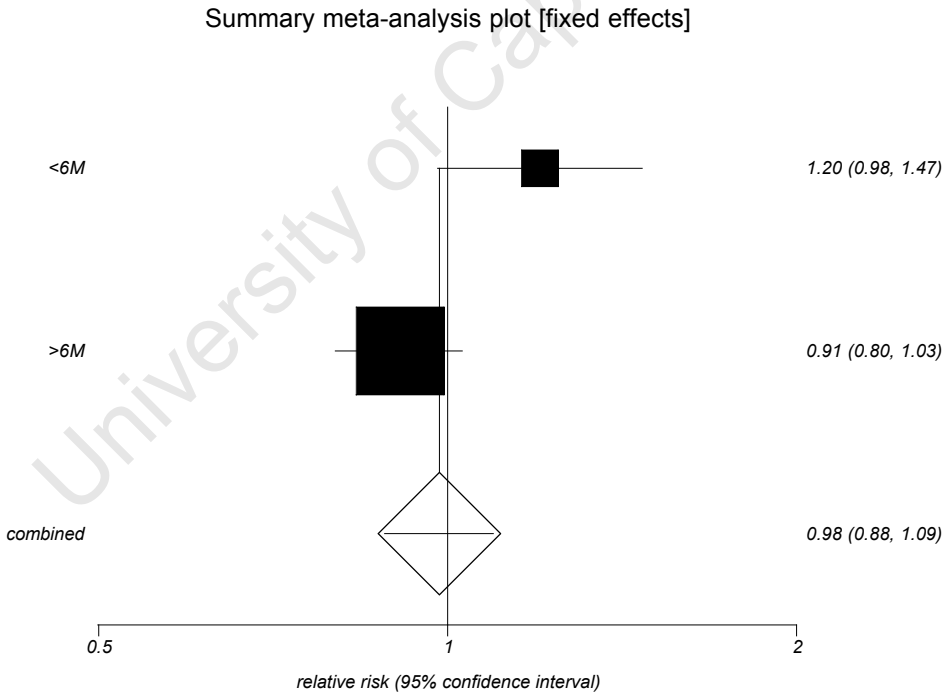
Stratum	Relative Risk	SE	Approximate 95% CI		% Weight (fixed, random)		
1	1.2	0.103437	0.98	1.47	27.976149	45.724744	<6M
2	0.91	0.064466	0.8	1.03	72.023851	54.275256	>6M

Fixed effects (inverse variance)
Pooled relative risk = 0.983223 (95% CI = 0.883247 to 1.094514)
Z (test test relative risk differs from 1) = -0.309258 P = 0.7571

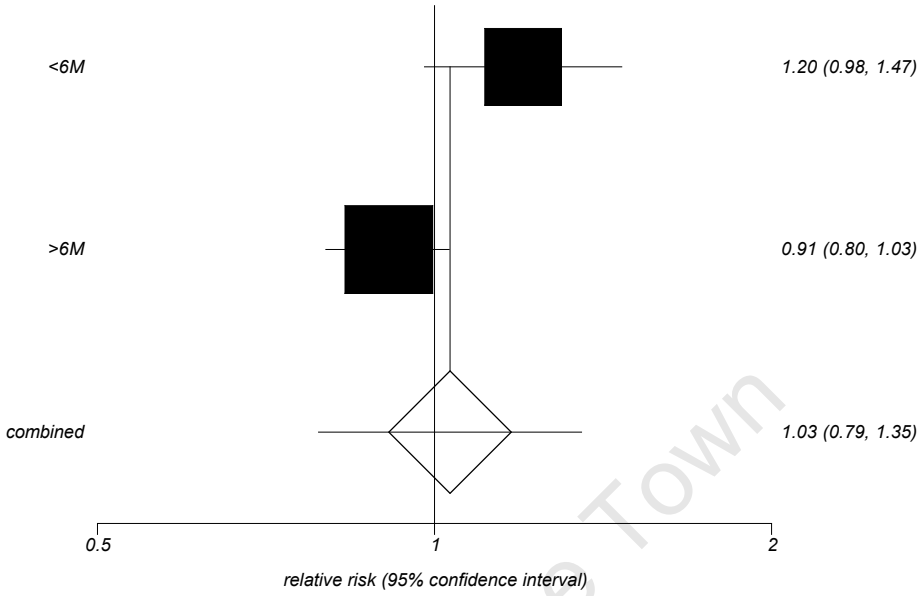
Non-combinability of studies
Cochran Q = 5.151469 (df = 1) P = 0.0232
Moment-based estimate of between studies variance = 0.030835
I^2 (inconsistency) = *% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled relative risk = 1.032702 (95% CI = 0.788263 to 1.352941)
Z (test test relative risk differs from 1) = 0.233501 P = 0.8154

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *



Summary meta-analysis plot [random effects]



C.2.1.5. Allocation concealment

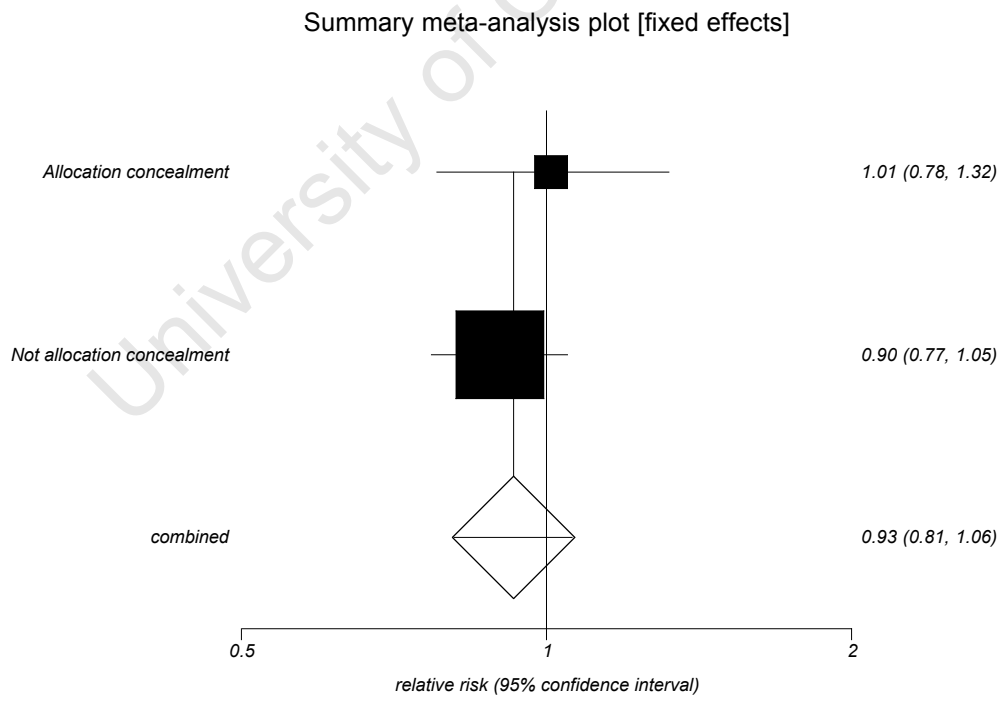
Stratum	Relative Risk	SE	Approximate 95% CI		% Weight (fixed, random)		
1	1.01	0.13421	0.78	1.32	25.791906	25.791906	Allocation concealment
2	0.9	0.079123	0.77	1.05	74.208094	74.208094	Not allocation concealment

Fixed effects (inverse variance)
Pooled relative risk = 0.927169 (95% CI = 0.811225 to 1.059684)
Z (test test relative risk differs from 1) = -1.109452 P = 0.2672

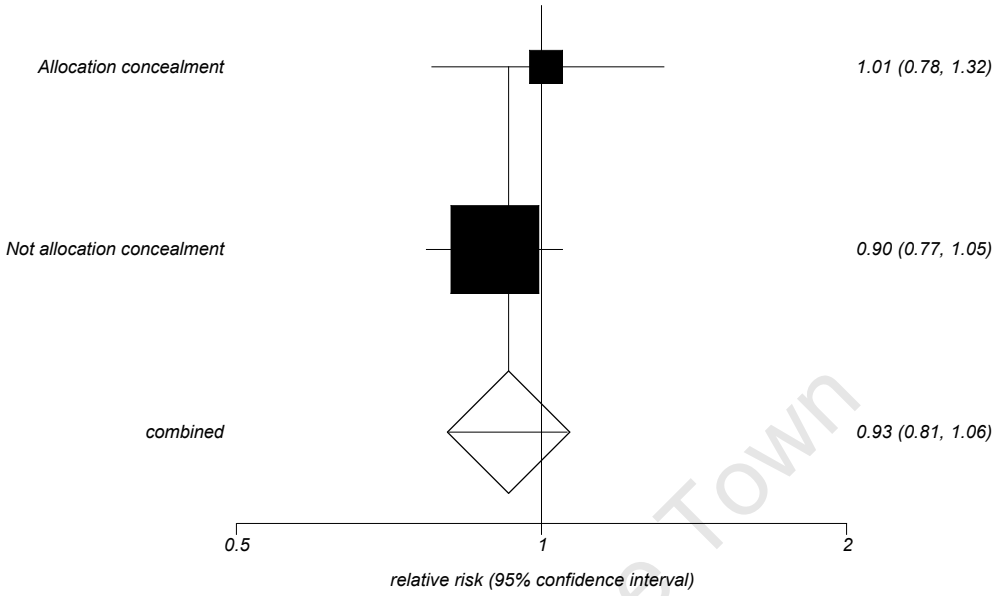
Non-combinability of studies
Cochran Q = 0.547801 (df = 1) P = 0.4592
Moment-based estimate of between studies variance = 0
I^2 (inconsistency) = *% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled relative risk = 0.927169 (95% CI = 0.811225 to 1.059684)
Z (test test relative risk differs from 1) = -1.109452 P = 0.2672

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *



Summary meta-analysis plot [random effects]



C.2.2. Secondary outcomes

C.2.2.1. Adherence

Stratum	Table (xt, xc, nt, nc)				
1	35	32	1	2	Wohl, 2006
2	151	143	24	32	Pearson, 2007
3	75	85	2	4	Sarna, 2008
4	88	91	49	46	Nachega, 2009
5	74	137	6	12	Mildvan, 2009

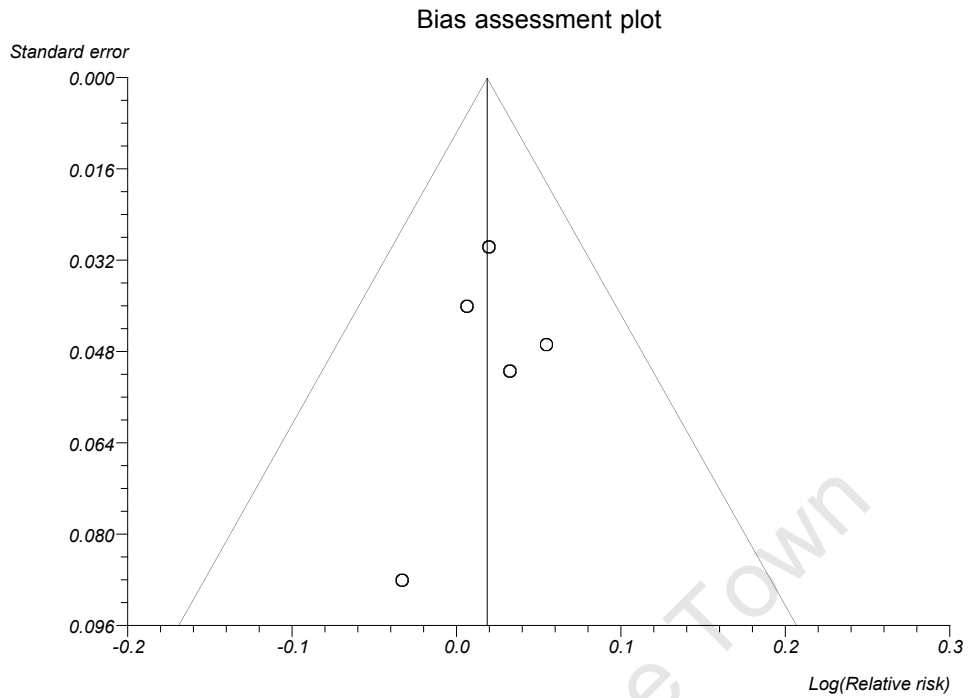
Stratum	Relative risk	95% CI (Koopman)		% Weights (fixed, random)		
1	1.032986	0.905066	1.206077	7.455269	13.900453	Wohl, 2006
2	1.055944	0.962755	1.162107	32.390298	16.728491	Pearson, 2007
3	1.019862	0.948111	1.098316	17.861193	41.807353	Sarna, 2008
4	0.967033	0.811639	1.150729	20.612008	4.718069	Nachega, 2009
5	1.006022	0.913485	1.085584	21.681233	22.845634	Mildvan, 2009

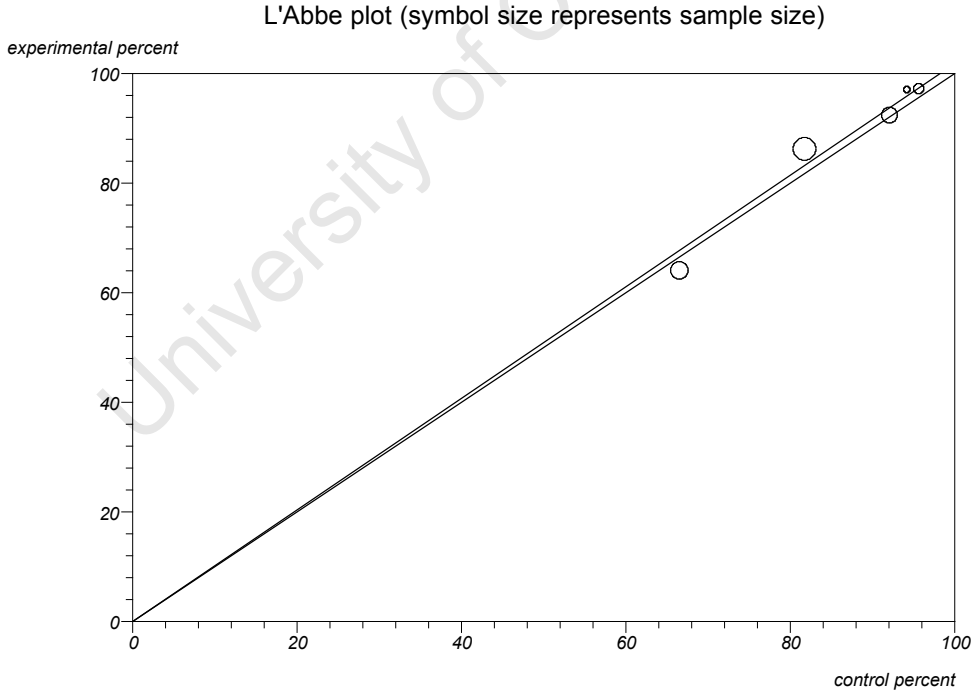
Fixed effects (Mantel-Haenszel, Rothman-Boice)
Pooled relative risk = 1.018638 (95% CI = 0.968332 to 1.071556)
Chi² (test relative risk differs from 1) = 0.510696 (df = 1) P = 0.4748

Non-combinability of studies
Cochran Q = 1.113129 (df = 4) P = 0.8922
Moment-based estimate of between studies variance = 0
I² (inconsistency) = 0% (95% CI = 0% to 64.1%)

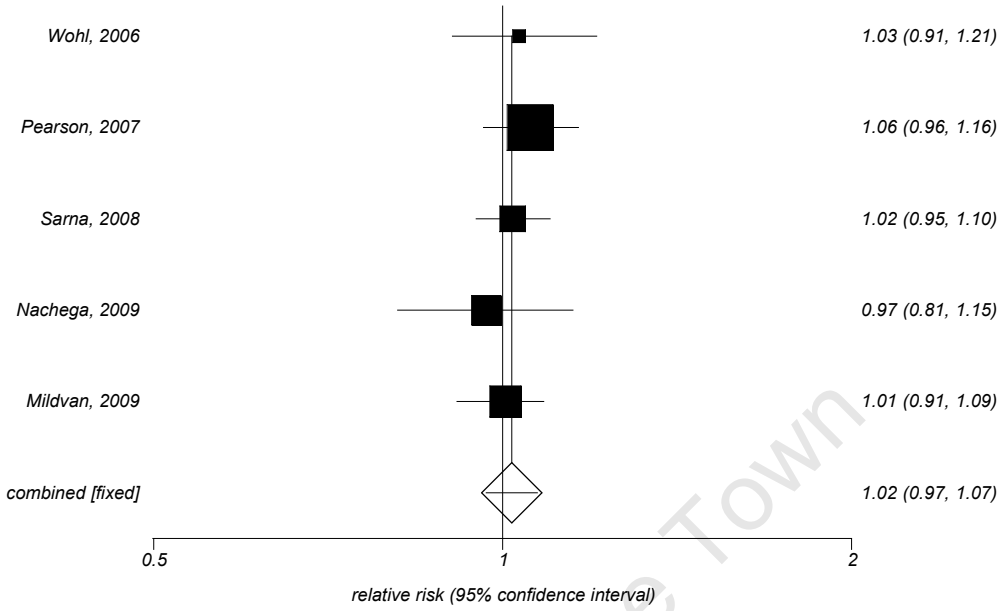
Random effects (DerSimonian-Laird)
Pooled relative risk = 1.021866 (95% CI = 0.984267 to 1.060901)
Chi² (test relative risk differs from 1) = 1.278841 (df = 1) P = 0.2581

Bias indicators
Begg-Mazumdar: Kendall's tau = -0.2 P = 0.4833 (low power)
Egger: bias = -0.348093 (95% CI = -3.006497 to 2.310311) P = 0.7049
Horbold-Egger: bias = -0.387811 (92.5% CI = -2.671766 to 1.896143) P = 0.6799

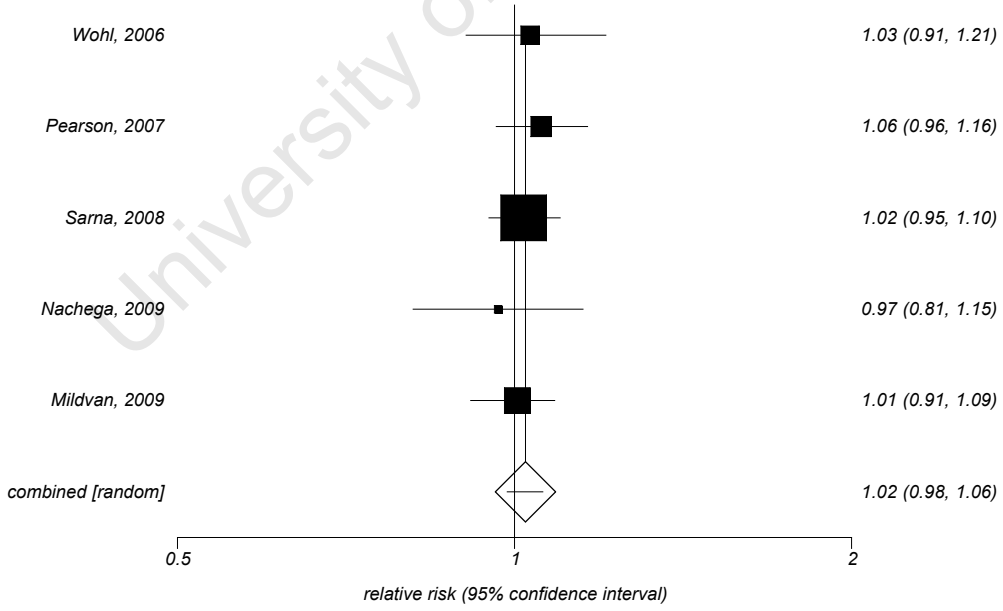




Relative risk meta-analysis plot (fixed effects)



Relative risk meta-analysis plot (random effects)



C.2.2.2. Loss to follow-up

Stratum	Table (xt, xc, nt, nc)				
1	16	20	66	64	Wohl, 2006
2	5	6	39	37	Macalino, 2007
3	2	2	173	173	Pearson, 2007
4	19	17	97	101	Sarna, 2008
5	19	1	69	52	Maru, 2009
6	9	9	128	128	Nachega, 2009
7	13	29	69	132	Mildvan, 2009
8	9	8	20	21	Karim, 2009
9	0.5	1	50.5	30	Bangsberg, 2009

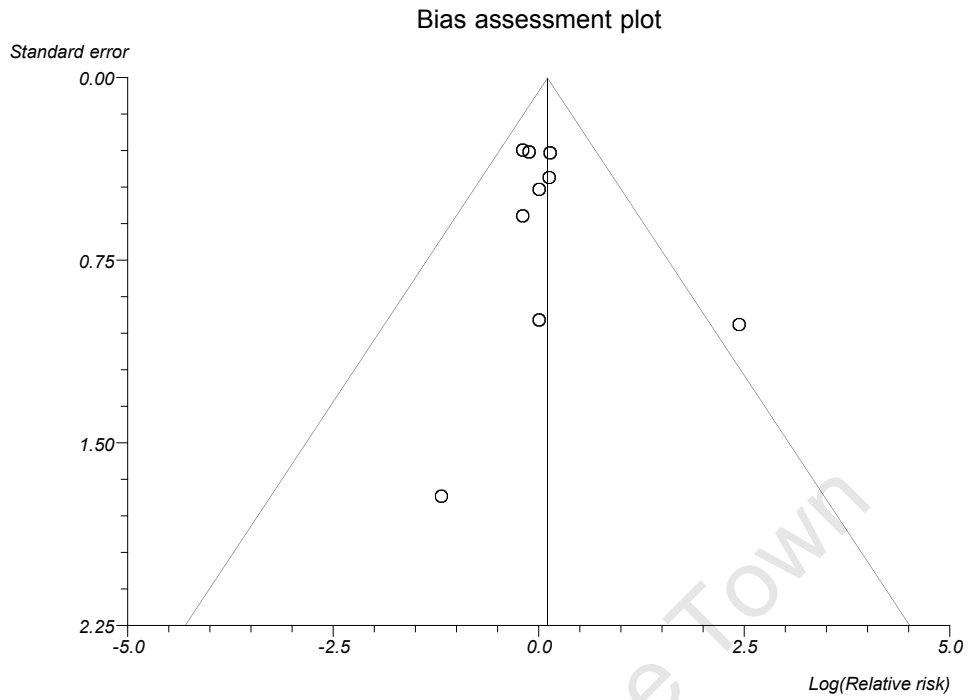
Stratum	Relative risk	95% CI (Koopman)		% Weights (fixed, random)		
1	0.819512	0.459195	1.453775	23.593767	23.129046	Wohl, 2006
2	0.814394	0.280876	2.347887	7.246799	6.375787	Macalino, 2007
3	1	0.17794	5.619861	2.38815	2.068247	Pearson, 2007
4	1.136917	0.628193	2.061067	20.125773	21.668225	Sarna, 2008
5	11.443182	2.082753	66.526288	1.490476	1.999814	Maru, 2009
6	1	0.420587	2.377632	10.746673	9.847674	Nachega, 2009
7	0.880151	0.482961	1.567845	23.370451	21.985168	Mildvan, 2009
8	1.125	0.513138	2.486054	9.552598	12.232511	Karim, 2009
9	0.303922	0.022913	4.02099	1.485313	0.693527	Bangsberg, 2009

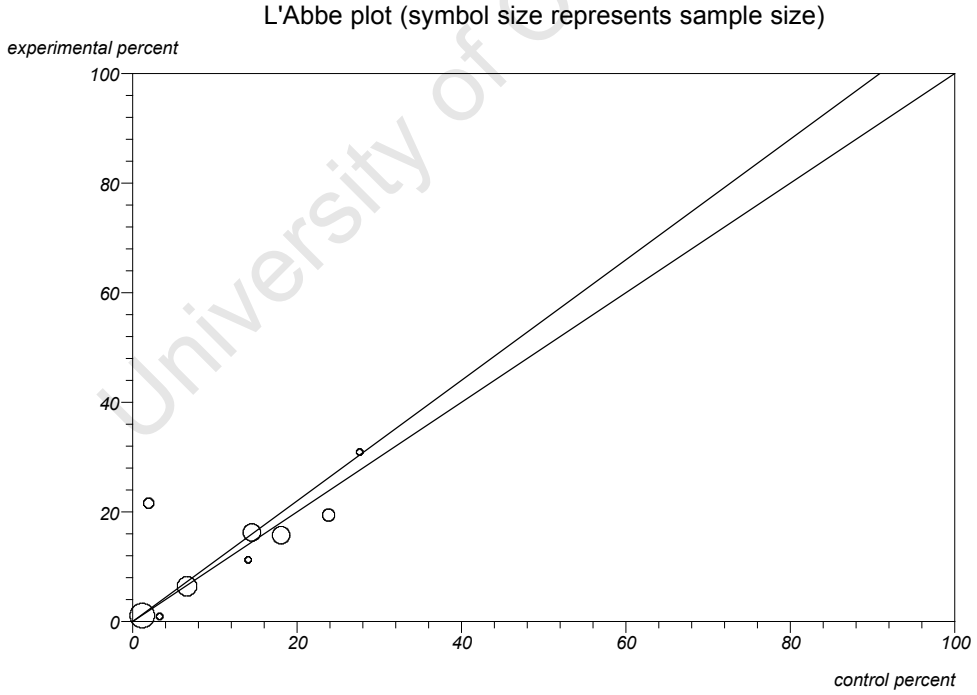
Fixed effects (Mantel-Haenszel, Rothman-Boice)
Pooled relative risk = 1.100767 (95% CI = 0.835983 to 1.449417)
Chi² (test relative risk differs from 1) = 0.467683 (df = 1) P = 0.4941

Non-combinability of studies
Cochran Q = 7.797291 (df = 8) P = 0.4535
Moment-based estimate of between studies variance = 0
I² (inconsistency) = 0% (95% CI = 0% to 54.4%)

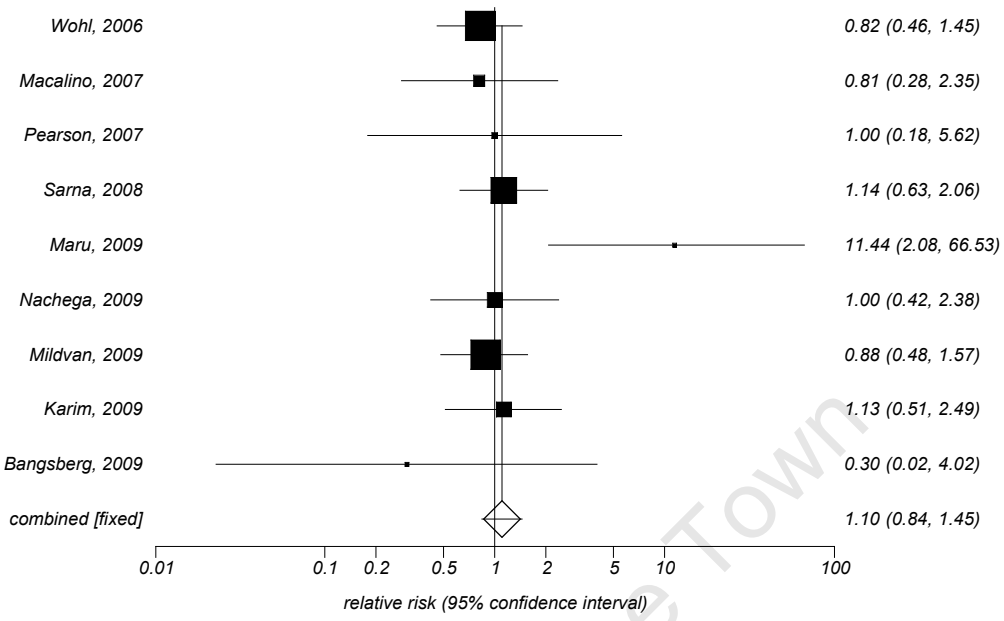
Random effects (DerSimonian-Laird)
Pooled relative risk = 0.995512 (95% CI = 0.7522 to 1.317527)
Chi² (test relative risk differs from 1) = 0.00099 (df = 1) P = 0.9749

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.111111 P = 0.7614 (low power)
Egger: bias = 0.617897 (95% CI = -1.144248 to 2.380042) P = 0.4344
Horbold-Egger: bias = -0.052844 (92.5% CI = -2.377742 to 2.272053) P = 0.9634

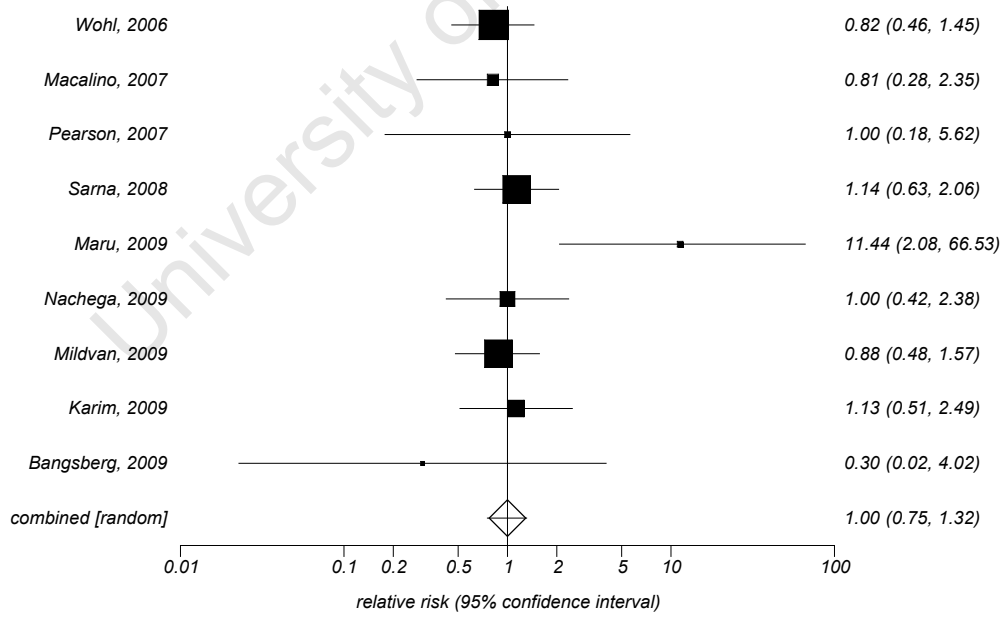




Relative risk meta-analysis plot (fixed effects)



Relative risk meta-analysis plot (random effects)



C.2.2.3. Mortality

Stratum	Table (xt, xc, nt, nc)				
1	1	2	81	82	Wohl, 2006
2	4	8	171	167	Pearson, 2007
3	11	8	105	110	Sarna, 2008
4	2	1	86	52	Maru, 2009
5	9	20	128	117	Nachega, 2009
6	1	4	81	157	Mildvan, 2009
7	0.5	1	50.5	30	Bangsberg, 2009

Stratum	Relative risk	95% CI (Koopman)		% Weights (fixed, random)		
1	0.512195	0.067774	3.843903	4.584543	3.958879	Wohl, 2006
2	0.5	0.162414	1.530627	18.56181	16.070871	Pearson, 2007
3	1.398707	0.599988	3.274891	18.403162	29.388849	Sarna, 2008
4	1.204545	0.161776	9.100943	2.896169	3.975395	Maru, 2009
5	0.45	0.215055	0.932137	46.404525	39.87992	Nachega, 2009
6	0.490854	0.07422	3.187219	6.263656	4.744186	Mildvan, 2009
7	0.303922	0.022913	4.02099	2.886135	1.981901	Bangsberg, 2009

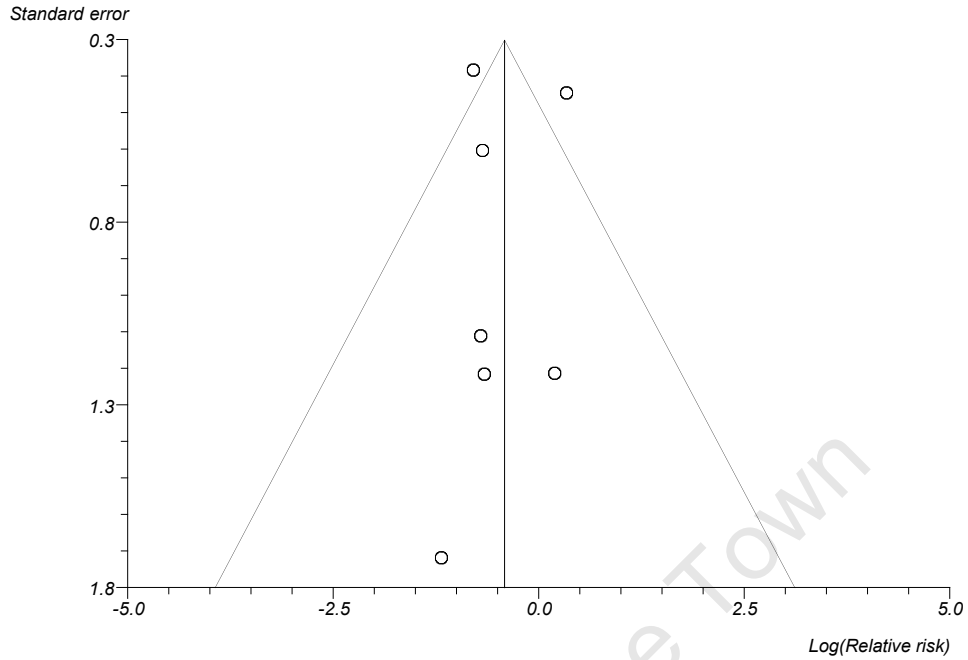
Fixed effects (Mantel-Haenszel, Rothman-Boice)
Pooled relative risk = 0.65692 (95% CI = 0.415006 to 1.039851)
Chi² (test relative risk differs from 1) = 3.215559 (df = 1) P = 0.0729

Non-combinability of studies
Cochran Q = 4.617085 (df = 6) P = 0.5938
Moment-based estimate of between studies variance = 0
I² (inconsistency) = 0% (95% CI = 0% to 58.5%)

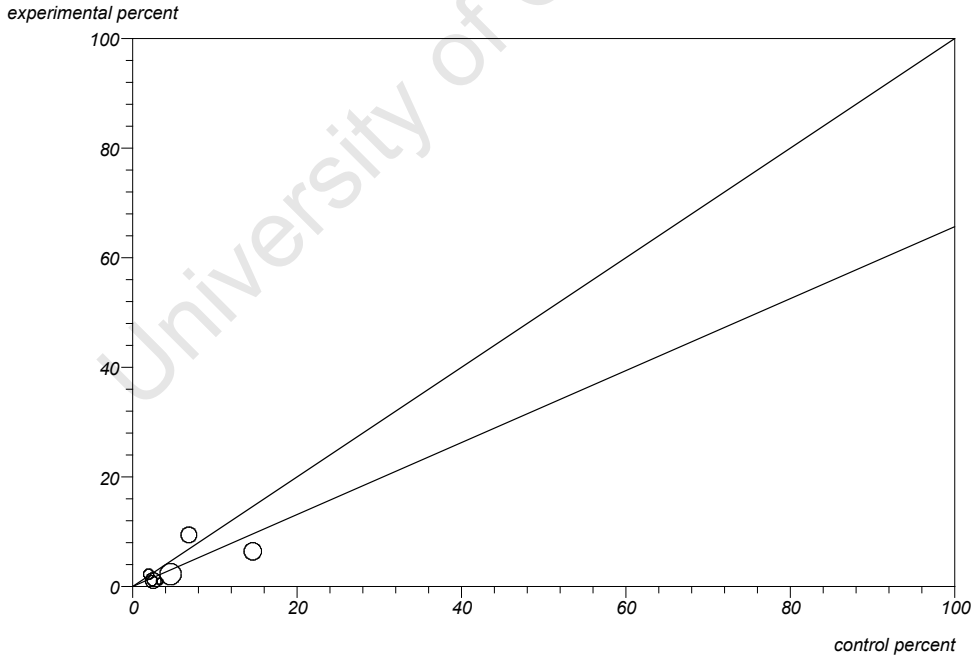
Random effects (DerSimonian-Laird)
Pooled relative risk = 0.665193 (95% CI = 0.414185 to 1.068319)
Chi² (test relative risk differs from 1) = 2.844497 (df = 1) P = 0.0917

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.142857 P = 0.7726 (low power)
Egger: bias = -0.180956 (95% CI = -2.144382 to 1.782469) P = 0.8221
Horbold-Egger: bias = -0.085707 (92.5% CI = -1.815148 to 1.643733) P = 0.9158

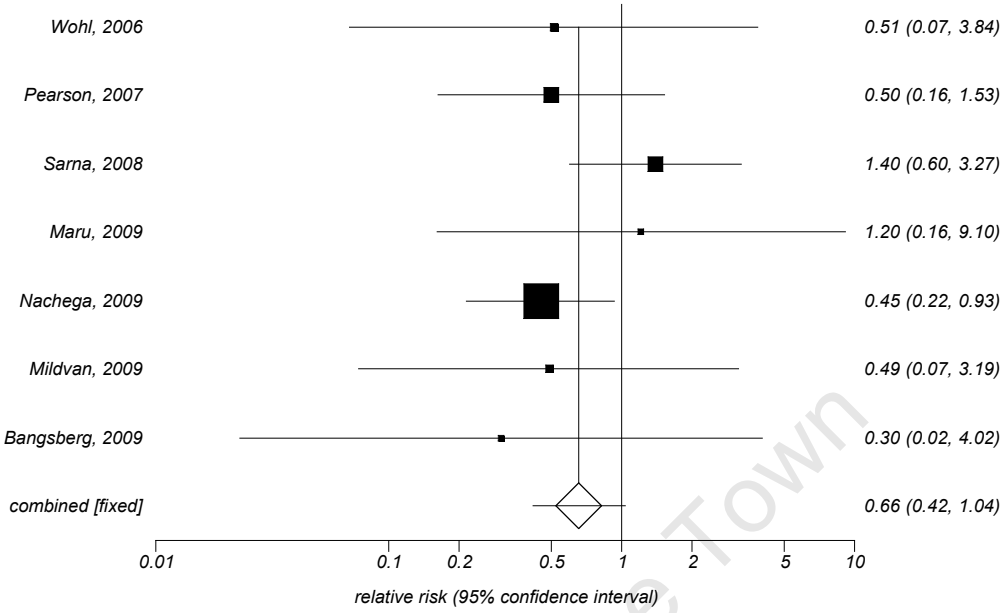
Bias assessment plot



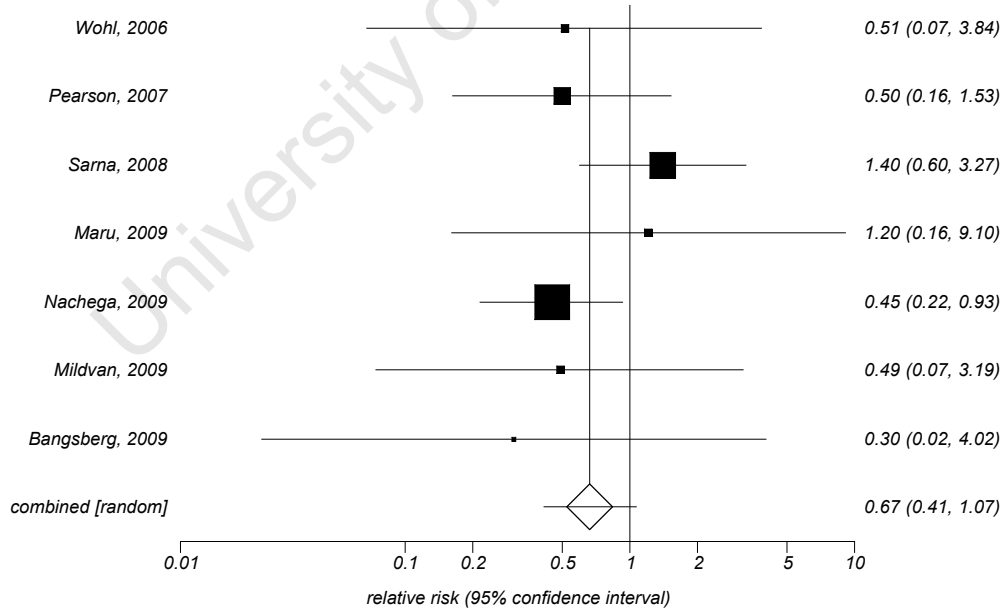
L'Abbe plot (symbol size represents sample size)



Relative risk meta-analysis plot (fixed effects)



Relative risk meta-analysis plot (random effects)



C.2.2.4. Development of new resistance mutations

Stratum	Table (xt, xc, nt, nc)				
1	5	0.5	65	44.5	Maru, 2009
2	8	10	14	25	Mildvan, 2009

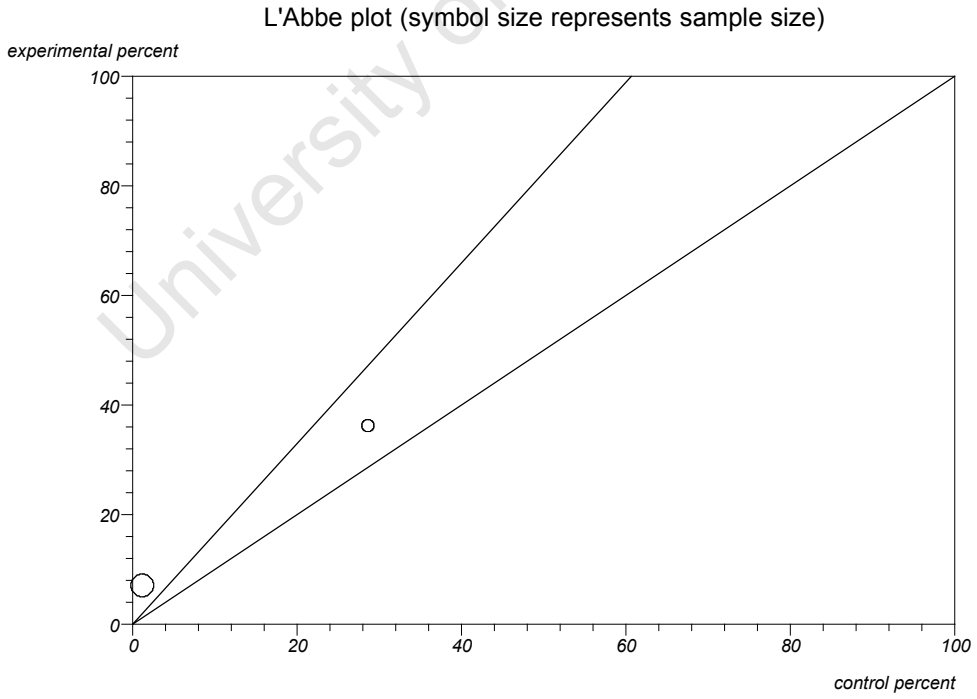
Stratum	Relative risk	95% CI (Koopman)		% Weights (fixed, random)		
1	6.428571	0.65214	66.121629	7.309031	16.575341	Maru, 2009
2	1.272727	0.58933	2.660259	92.690969	83.424659	Mildvan, 2009

Fixed effects (Mantel-Haenszel, Rothman-Boice)
Pooled relative risk = 1.64957 (95% CI = 0.781822 to 3.480435)
Chi² (test relative risk differs from 1) = 1.726248 (df = 1) P = 0.1889

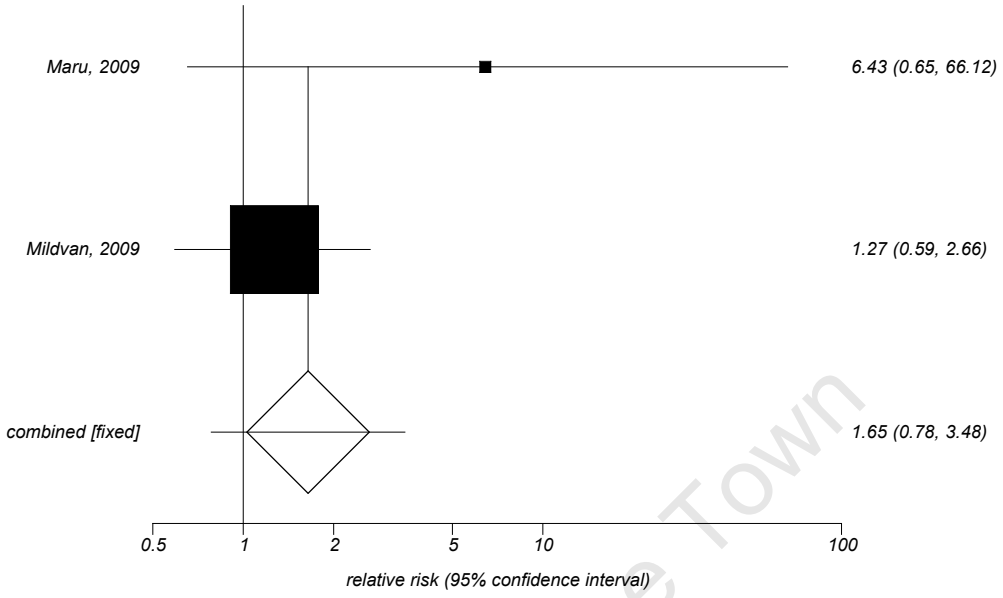
Non-combinability of studies
Cochran Q = 1.300744 (df = 1) P = 0.2541
Moment-based estimate of between studies variance = 0.348031
I² (inconsistency) = *% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled relative risk = 1.66465 (95% CI = 0.470025 to 5.895559)
Chi² (test relative risk differs from 1) = 0.623856 (df = 1) P = 0.4296

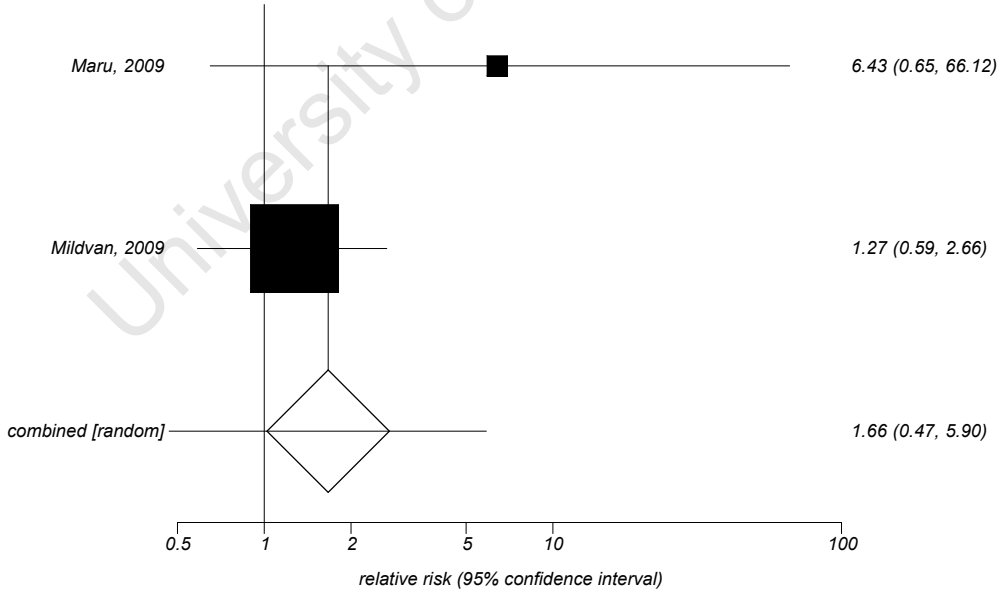
Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *
Horbold-Egger: bias = 2.244005 (92.5% CI = * to *) P = *



Relative risk meta-analysis plot (fixed effects)



Relative risk meta-analysis plot (random effects)



C.2.2.5. New or recurrent AIDS defining illnesses

Stratum	Table (xt, xc, nt, nc)				
1	12	8	70	76	Wohl, 2006
2	23	25	114	112	Nachega, 2009
3	1	11	81	150	Mildvan, 2009

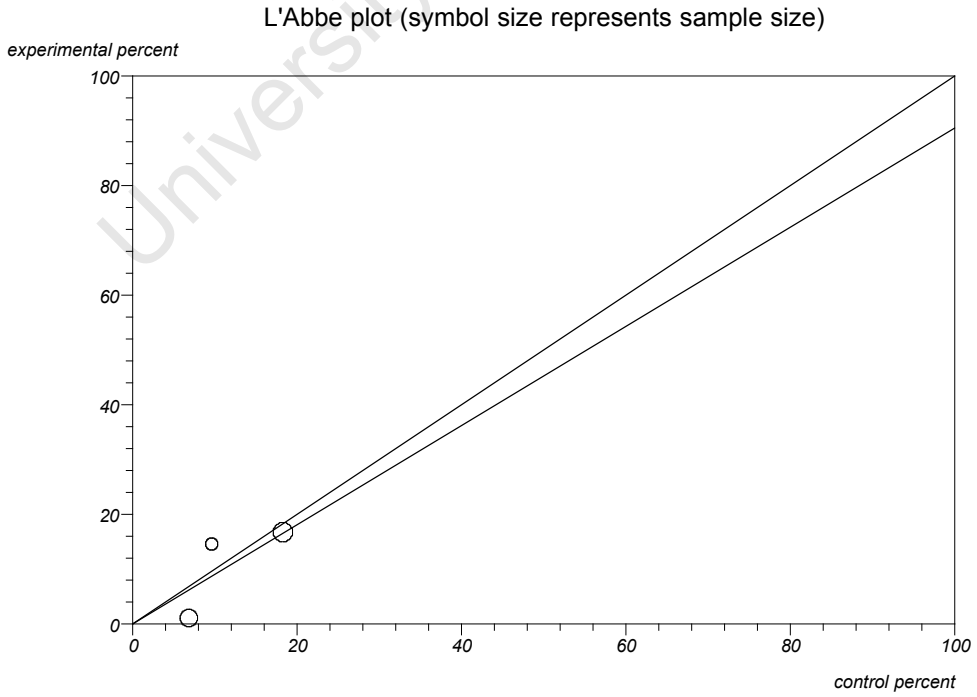
Stratum	Relative risk	95% CI (Koopman)		% Weights (fixed, random)		
1	1.536585	0.680283	3.498777	19.598581	36.78494	Wohl, 2006
2	0.92	0.552353	1.530403	61.992463	51.853827	Nachega, 2009
3	0.178492	0.029799	1.03656	18.408955	11.361233	Mildvan, 2009

Fixed effects (Mantel-Haenszel, Rothman-Boice)
Pooled relative risk = 0.904338 (95% CI = 0.593631 to 1.377669)
Chi² (test relative risk differs from 1) = 0.219193 (df = 1) P = 0.6397

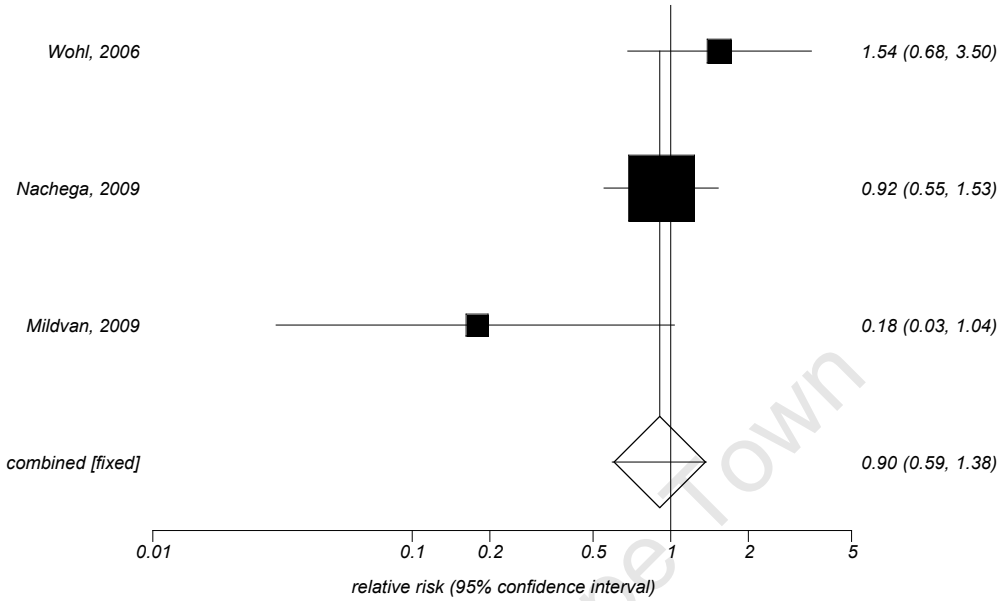
Non-combinability of studies
Cochran Q = 3.984659 (df = 2) P = 0.1364
Moment-based estimate of between studies variance = 0.212712
I² (inconsistency) = 49.8% (95% CI = 0% to 84.5%)

Random effects (DerSimonian-Laird)
Pooled relative risk = 0.922194 (95% CI = 0.436074 to 1.950221)
Chi² (test relative risk differs from 1) = 0.044933 (df = 1) P = 0.8321

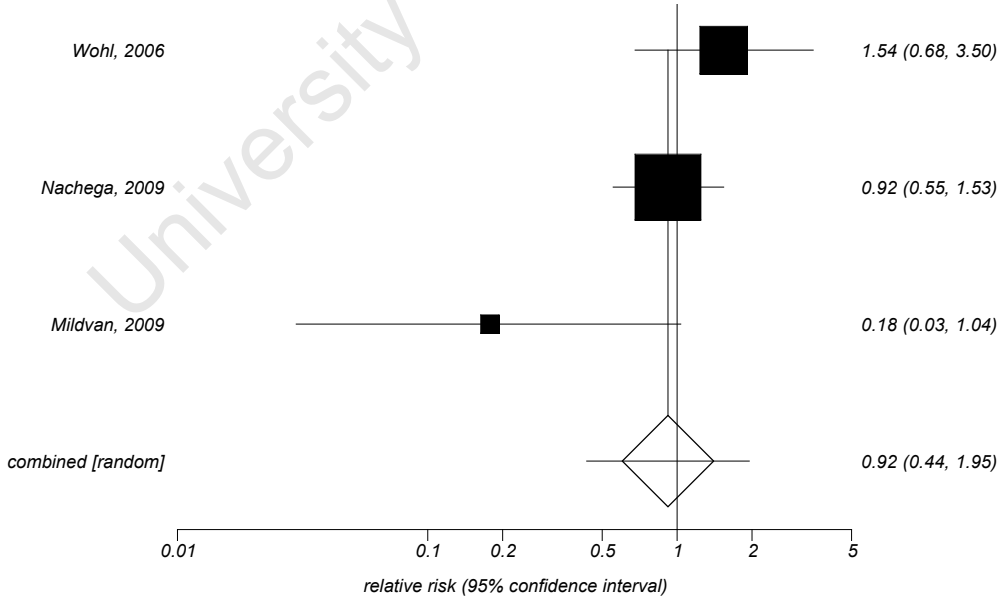
Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *
Horbold-Egger: bias = -1.720099 (92.5% CI = -30.949199 to 27.509001) P = 0.7063



Relative risk meta-analysis plot (fixed effects)



Relative risk meta-analysis plot (random effects)



Annex C.3. Overview of main search results

C.3.1. MEDLINE (via PUBMED)

#36	**Search #9 AND #19 AND #27 AND #35**	**66**
#35	Search **#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34**	983948
#34	Search **meta-analy* [tw]**	37210
#33	Search **meta analysis**	34485
#32	Search **clinical trial**	706135
#31	Search **single blind procedure**	19734
#30	Search **double blind procedure**	104920
#29	Search **random* [tw]**	596934
#28	Search **randomization**	73231
#27	Search **#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26**	99317
#26	Search **supervis* [tw]**	32942
#25	Search **DAART**	18
#24	Search **DOT**	16579
#23	Search **directly observ* [tw]**	2564
#22	Search **direct observ* [tw]**	4974
#21	Search **directly observed**	38925
#20	Search **direct observation**	11112
#19	Search **#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18**	178640
#18	Search **nonadher* [tw]**	4375
#17	Search **non-adher* [tw]**	2685
#16	Search **adher* [tw]**	90850
#15	Search **non-complian* [tw]**	2870
#14	Search **noncomplian* [tw]**	4767
#13	Search **complied [tw]**	1990
#12	Search **comply [tw]**	4899
#11	Search **complian* [tw]**	89669
#10	Search **patient compliance**	48171
#9	Search **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8**	276693
#8	Search **aids [tw]**	128030
#7	Search **acquired immune deficiency syndrome [tw]**	4428
#6	Search **acquired immunodeficiency syndrome [tw]**	76847
#5	Search **human immunodeficiency [tw]**	59636
#4	Search **hiv [tw]**	195015
#3	Search **anti human immunodeficiency virus agent**	1340
#2	Search **human immunodeficiency virus infection**	192209
#1	Search **human immunodeficiency virus**	238917

C.3.2. EMBASE

36	#9 AND #19 AND #27 AND #35	118
35	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	1,103,810
34	meta AND analy*	58,997
33	meta AND ('analysis'/exp OR 'analysis')	57,504
32	clinical AND trial	786,410
31	single AND ('blind'/exp OR 'blind') AND procedure	19,948
30	double AND ('blind'/exp OR 'blind') AND procedure	92,662
29	random*	574,002
28	'randomization'/exp OR 'randomization'	56,240
27	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	166,068
26	supervis*	34,275
25	daart	20
24	dot	19,082
23	directly AND observ*	46,778
22	direct AND observ*	72,958
21	directly AND observed	35,623
20	direct AND ('observation'/exp OR 'observation')	11,444
19	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	213,496
18	nonadher*	4,110
17	non AND adher*	10,502
16	adher*	94,357
15	non AND complian*	14,658
14	noncomplian*	5,356
13	complied	2,251
12	comply	5,917
11	complian*	120,829
10	('patient'/exp OR 'patient') AND ('compliance'/exp OR 'compliance')	74,103
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	378,476
8	'aids'/exp OR 'aids'	179,822
7	acquired AND immune AND deficiency AND ('syndrome'/exp OR 'syndrome')	105,343
6	acquired AND ('immunodeficiency'/exp OR 'immunodeficiency') AND ('syndrome'/exp OR 'syndrome')	108,140
5	('human'/exp OR 'human') AND ('immunodeficiency'/exp OR 'immunodeficiency')	331,394
4	'hiv'/exp OR 'hiv'	202,755
3	anti AND ('human'/exp OR 'human') AND ('immunodeficiency'/exp OR 'immunodeficiency') AND ('virus'/exp OR 'virus') AND agent	14,715
2	('human'/exp OR 'human') AND ('immunodeficiency'/exp OR 'immunodeficiency') AND ('virus'/exp OR 'virus') AND ('infection'/exp OR 'infection')	203,879
1	('human'/exp OR 'human') AND ('immunodeficiency'/exp OR 'immunodeficiency') AND ('virus'/exp OR 'virus')	236,548

C.2.3. CINAHL

#	Query	Limiters/Expanders	Results
S36	S9 and S19 and S27 and S35	**Search modes** - Boolean/Phrase	137
S35	S28 or S29 or S30 or S31 or S32 or S33 or S34	**Search modes** - Boolean/Phrase	110445
S34	TX meta-analy*	**Search modes** - Boolean/Phrase	11765
S33	meta AND analysis	**Search modes** - Boolean/Phrase	10819
S32	clinical AND trial	**Search modes** - Boolean/Phrase	27809
S31	single AND blind AND procedure	**Search modes** - Boolean/Phrase	149
S30	double AND blind AND procedure	**Search modes** - Boolean/Phrase	286
S29	TX random*	**Search modes** - Boolean/Phrase	95607
S28	randomization	**Search modes** - Boolean/Phrase	1494
S27	S20 or S21 or S22 or S23 or S24 or S25 or S26	**Search modes** - Boolean/Phrase	20346
S26	TX supervis*	**Search modes** - Boolean/Phrase	16718
S25	DAART	**Search modes** - Boolean/Phrase	6
S24	DOT	**Search modes** - Boolean/Phrase	481
S23	TX directly AND observ*	**Search modes** - Boolean/Phrase	2569
S22	TX direct observ*	**Search modes** - Boolean/Phrase	706
S21	directly AND observed	**Search modes** - Boolean/Phrase	1381
S20	direct AND observation	**Search modes** - Boolean/Phrase	932
S19	S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18	**Search modes** - Boolean/Phrase	36870
S18	TX nonadher*	**Search modes** - Boolean/Phrase	700
S17	TX non-adher*	**Search modes** - Boolean/Phrase	437
S16	TX adher*	**Search modes** - Boolean/Phrase	11406
S15	TX non-complian*	**Search modes** - Boolean/Phrase	626
S14	TX noncomplian*	**Search modes** - Boolean/Phrase	1314
S13	TX complied	**Search modes** - Boolean/Phrase	402
S12	TX comply	**Search modes** - Boolean/Phrase	1939
S11	TX complian*	**Search modes** - Boolean/Phrase	28440
S10	patient compliance	**Search modes** - Boolean/Phrase	11054
S9	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8	**Search modes** - Boolean/Phrase	60645
S8	TX aids	**Expanders** - Also search within the full text of the articles **Search modes** - Boolean/Phrase	41161
S7	TX acquired and immune and deficiency and syndrome	**Expanders** - Also search within the full text of the articles **Search modes** - Boolean/Phrase	538
S6	TX acquired and immunodeficiency and syndrome	**Expanders** - Also search within the full text of the articles **Search modes** - Boolean/Phrase	11055
S5	TX human and immunodeficiency	**Expanders** - Also search within the full text of the articles **Search modes** - Boolean/Phrase	6716
S4	TX hiv	**Expanders** - Also search within the full text of the articles **Search modes** - Boolean/Phrase	41531
S3	anti and human and immunodeficiency and virus and agent	**Search modes** - Boolean/Phrase	6
S2	human and immunodeficiency and virus and infection	**Search modes** - Boolean/Phrase	2498
S1	human and immunodeficiency and virus	**Search modes** - Boolean/Phrase	5872

C.5.4. COCHRANE

Search History

ID	Search	Hits
#1	(human immunodeficiency virus)	2662
#2	human immunodeficiency virus infection	2224
#3	anti human immunodeficiency virus agent	605
#4	(hiv)	7297
#5	(human immunodeficiency virus infection)	2224
#6	(acquired immunodeficiency syndrome)	1591
#7	(acquired immune deficiency syndrome)	862
#8	(aids)	9520
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	13610
#10	(patient compliance)	13224
#11	(complian*)	15704
#12	(comply)	1015
#13	(complied)	1015
#14	(noncomplian*)	655
#15	(non-complian*)	750
#16	(adher*)	5553
#17	(non-adher*)	214
#18	(nonadher*)	219
#19	(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)	20205
#20	(direct observation)	1591
#21	(directly observed)	1993
#22	(direct observ*)	5949
#23	(directly observ*)	2717
#24	(DOT)	833
#25	(DAART)	12
#26	(supervis*)	3126
#27	(#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)	10954
#28	(randomization)	17470
#29	(random*)	349074
#30	(double blind procedure)	16964
#31	(single blind procedure)	6242
#32	(clinical trial)	392464
#33	(meta analysis)	134293
#34	(meta-analy*)	13382
#35	(#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34)	479627
#36	(#9 AND #19 AND #27 AND #35)	389

C.4.4 PsychInfo

Searches	Results	Search
1	(human and immunodeficiency and virus).mp. [mp=title, abstract, heading word, table of contents, key concepts]	3310
2	(human and immunodeficiency and virus and infection).mp. [mp=title, abstract, heading word, table of contents, key concepts]	1527
3	(anti and human and immunodeficiency and virus and agent).mp. [mp=title, abstract, heading word, table of contents, key concepts]	3
4	hiv.mp. [mp=title, abstract, heading word, table of contents, key concepts]	22265
5	(human and immunodeficiency).mp. [mp=title, abstract, heading word, table of contents, key concepts]	3355
6	(acquired and immunodeficiency and syndrome).mp. [mp=title, abstract, heading word, table of contents, key concepts]	1561
7	(acquired and immune and deficiency and syndrome).mp. [mp=title, abstract, heading word, table of contents, key concepts]	2859
8	aids.mp. [mp=title, abstract, heading word, table of contents, key concepts]	25580
9	6 or 3 or 7 or 2 or 8 or 1 or 4 or 5	34941
10	(patient and compliance).mp. [mp=title, abstract, heading word, table of contents, key concepts]	3629
11	complian*.mp. [mp=title, abstract, heading word, table of contents, key concepts]	18380
12	comply.mp. [mp=title, abstract, heading word, table of contents, key concepts]	1654
13	complied.mp. [mp=title, abstract, heading word, table of contents, key concepts]	490
14	noncomplian*.mp. [mp=title, abstract, heading word, table of contents, key concepts]	2697
15	non-complian*.mp. [mp=title, abstract, heading word, table of contents, key concepts]	600
16	adher*.mp. [mp=title, abstract, heading word, table of contents, key concepts]	12011
17	non-adher*.mp. [mp=title, abstract, heading word, table of contents, key concepts]	375
18	nonadher*.mp. [mp=title, abstract, heading word, table of contents, key concepts]	688
19	11 or 17 or 12 or 15 or 14 or 18 or 10 or 13 or 16	29687
20	(direct and observation).mp. [mp=title, abstract, heading word, table of contents,	2983

	key concepts]	
21	(directly and observed).mp. [mp=title, abstract, heading word, table of contents, key concepts]	2445
22	(direct and observ*).mp. [mp=title, abstract, heading word, table of contents, key concepts]	8631
23	(directly and observ*).mp. [mp=title, abstract, heading word, table of contents, key concepts]	4400
24	DOT.mp. [mp=title, abstract, heading word, table of contents, key concepts]	2951
25	DAART.mp. [mp=title, abstract, heading word, table of contents, key concepts]	7
26	supervis*.mp. [mp=title, abstract, heading word, table of contents, key concepts]	30307
27	25 or 22 or 21 or 24 or 26 or 23 or 20	45518
28	randomization.mp. [mp=title, abstract, heading word, table of contents, key concepts]	1457
29	random*.mp. [mp=title, abstract, heading word, table of contents, key concepts]	79328
30	(double and blind and procedure).mp. [mp=title, abstract, heading word, table of contents, key concepts]	342
31	(single and blind and procedure).mp. [mp=title, abstract, heading word, table of contents, key concepts]	61
32	(clinical and trial).mp. [mp=title, abstract, heading word, table of contents, key concepts]	10082
33	(meta and analysis).mp. [mp=title, abstract, heading word, table of contents, key concepts]	8895
34	meta-analy*.mp. [mp=title, abstract, heading word, table of contents, key concepts]	9862
35	33 or 32 or 34 or 28 or 30 or 31 or 29	93933
36	35 and 27 and 19 and 9	9
37	**35 and 27 and 19 and 9**	**9**

C.5.6. NIH Clinical Trials Register

Title	Trial number	Status	Include/exclude Reason	Published Y/N
DOT-HAART for HIV-Infected South African Adults	NCT00076804	Terminated (futility)	Include	CROI 2009 #143
Directly Observed Therapy (DOT) in HIV-1 Infected Adolescents	NCT00259389	Active	Exclude Non-randomized	
Strategies for Delivering Anti-HIV Therapy in South Africa	NCT00080522	Completed	Include	
Directly Observed Therapy for Community-Released HIV+ Prisoners	NCT00786396	Recruiting	Include	
Depression Treatment to Improve Antiretroviral Adherence	NCT00338767	Recruiting	Exclude DOT is for anti-depressants	
The Adult Antiretroviral Treatment and Resistance Study (Tshepo)	NCT00197613	Completed	Include	Bussmann: JAIDS 2009
Effectiveness of Directly Observed Therapy in Combined HIV and Tuberculosis Treatment in Resource-Limited Settings	NCT00091936	Completed	Include	
Directly Observed Therapy in High Risk Populations in Newark, NJ	NCT00285883	Completed	Exclude Single arm trial	
A Study to Compare Anti-HIV Drugs Given Twice a Day or Once a Day, With or Without Direct Observation	NCT00036452	Completed	Include	
Directly Observed Antiretroviral Therapy Among Active Drug Users	NCT00367172	Completed	Include	Altice: CID 2007
Modified Directly Observed Therapy for Improving Antiretroviral Therapy Adherence in People With HIV	NCT00339092	Recruiting	Include	
Effectiveness of Enhanced Counseling and Observed Therapy on Antiretroviral Adherence in People With HIV	NCT00602758	Ongoing but not recruiting	Include	