The clinical role of therapeutic drug monitoring of antiretrovirals - A Cochrane systematic review

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Declaration page

I, Tamara Kredo, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise). 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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Statement of authors' role

A Cochrane systematic review is a collaborative process. The following describes contributions of the author and co-reviewers:

- The author conceptualized the research question and wrote the first draft of protocol. Dr Jan-Stefan van der Walt (JSW), Dr Nandi Siegfried (NS) and Dr Karen Cohen (KC) gave input to the final protocol.
- The author developed the search strategy together with the Cochrane HIV/ AIDS Group Trial Search co-ordinator who implemented the search.
- The author developed the abstract eligibility forms to assess the abstracts identified by the search, (NS) gave input into the final form.
- The author was responsible for developing the article data extraction form – KC and JSW provided input into the final form.
- The author and JSW performed data extraction independently.
- The author analysed and interpreted the data.
- The author wrote the review report.

Signature:

Date:

List of abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral
cART	Combination antiretroviral therapy
GIQ	Genotypic inhibitory quotient
HIV	Human Immunodeficiency Virus
LTFU	Lost-to-follow-up
MEMS	Medication Event Monitoring Systems
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
PCR	polymerase chain reaction
PI	Protease inhibitor
PIQ	Phenotypic inhibitory quotient
RNA	Ribonucleic acid
SOC	Standard of care
TDM	Therapeutic drug monitoring
WHO	World Health Organisation

Abstract

Background

Despite the proven efficacy of combination antiretroviral therapy (cART) and the resultant improvement in prognosis of those living with HIV/AIDS, a large proportion of individuals on cART does not achieve or maintain virological suppression. Several tools have been proposed to enhance virological outcomes, including therapeutic drug monitoring (TDM) of antiretrovirals (ARVs). ARV TDM can identify elevated, potentially toxic ARV concentrations and low, potentially sub-therapeutic concentrations. ARV TDM may optimise efficacy and minimise toxicity of ARVs.

Objectives

To evaluate whether ARV TDM reduces mortality and morbidity of adult patients on cART.

Search strategy

We conducted a comprehensive search including both published and unpublished studies in all languages in MEDLINE, EMBASE and The Cochrane Library, between the 18th and 25th of January 2008. Databases listing conference abstracts, and reference lists of articles were searched. Additional data were sought from relevant authors, however no additional data were provided.

Selection criteria

Only randomized-controlled trials conducted subsequent to the introduction of cART were included in this systematic review. Participants could be on either a protease inhibitor (PI)-based regimen or non-nucleoside reverse transcriptase (NNRTI)-based regimen and be either ARV-naïve or experienced.

Data collection & analysis

Two reviewers independently assessed and extracted data for analysis. Meta-analysis was conducted where appropriate. Where study outcomes could not be combined, a narrative review was performed. Outcome measures for dichotomous data were reported as a relative risk with 95% confidence intervals. Continuous data were analysed using the weighted mean difference and standard deviations. Stratified analyses were conducted by ARV regimen and treatment groups. Heterogeneity between studies was anticipated; therefore random effects models

were chosen to generate pooled effects. Differences in the findings were assessed by using the Chi Square test for heterogeneity ($p < 0.1$) that was quantified by the Higgins I^2 statistic.

Main results

1408 records were identified and 8 trials with a total of 1181 participants were included in the review. Trials were conducted in higher income earning countries between 2002 and 2007. Sample sizes ranged between 40 and 230. The methodological quality of the studies was judged to be generally good, although allocation concealment was reported in only 3 of the 8 studies. A meta-analysis including 3 studies did not show any significant effect on virological suppression <500 HIV-RNA copies/mL at one year (RR 1.28 [0.86, 1.92] $chi^2 = 11.55$ ($P = 0.003$), $I^2 = 83\%$). Two trials including participants predominantly treated with unboosted PI-based regimens, had a 49% increased likelihood of achieving a HIV-RNA viral load < 500 copies/mL at 52 weeks (RR 1.49 [1.20, 1.83] chi^2 0.69 ($P = 0.4$), $I^2 = 0\%$). Safety outcomes were reported in 4 studies, and were similar between TDM and standard of care. Uptake of expert advice based on TDM results was good in 2 trials (>70%), but low (<35%) in the remaining 3 studies that reported uptake of the recommendations.

Reviewers' conclusions

Our review does not support routine ARV TDM in ARV-naïve or -experienced patients on either boosted PI or NNRTI cART regimens. TDM in treatment-naive participants on a PI-based cART regimen, particularly if unboosted, may improve virological outcomes. Trials were underpowered with small sample sizes, short duration of follow up and generally poor uptake of TDM recommendations. As these trials were conducted in higher income earning countries, results may not be generalisable to resource-limited countries where the burden of HIV is heaviest.

Introduction

This mini-dissertation reports the results of a Cochrane systematic review and meta-analysis evaluating the clinical role of antiretroviral (ARV) therapeutic drug monitoring (TDM) for adults on combination antiretroviral therapy (cART).

Overview of systematic reviews

Clinicians, researchers and policy makers rely on literature reviews to provide comprehensive overviews of current evidence. Systematic reviews are a means of synthesizing all available evidence on a clearly defined research question. By necessity a review is retrospective observational research, with inherent potential for both systematic and random error in its compilation (Cook 1997). For this reason, systematic reviews require transparent methodology in order to minimise the systematic errors (bias) introduced in their compilation.

The key aspects of a systematic review are (Green 2008, Pai 2004, Greenhalgh 1997):

- The methodology is explicit and reproducible
- There are pre-defined objectives with clear descriptions of the eligibility criteria for included studies
- There is a comprehensive search strategy which can identify all studies fitting the eligibility criteria
- There should be a thorough appraisal of the validity of the findings, including assessment of the risk of bias in each study

Systematic reviews may contain quantitative reports combining data from studies, by means of meta-analyses. Meta-analysis is a statistical method for pooling data from two or more studies and providing a more precise estimate of the magnitude of the effect of the intervention. This is appropriate in studies that are clinically and methodologically similar. Meta-analyses also explore consistency of the evidence between studies and can facilitate further investigation of differences across included studies (Cook 1997, Green 2008).

Traditional narrative reviews differ from systematic reviews. The methodology is generally not reproducible, using subjective means for searching and compiling the evidence. The approach to appraisal of the content and quality of the literature is often not explicit. Empirical research has shown that narrative reviews tend to be of poorer quality (McAlister 1999).

Cochrane systematic reviews differ from narrative literature reviews by using a transparent standardized design; extensive searches to minimise language and publication bias; they are current and require regular updating and they use meta-analysis where combinable outcomes measures are found. Both the Cochrane protocol and full review are peer-reviewed after which they are published online by the Cochrane Collaboration (Wiley publishers) in the Cochrane Library.

Background

Antiretroviral (ARV) therapy aims to durably suppress HIV viral replication to allow immune system recovery. The introduction of combination antiretroviral therapy (cART) has been shown to reduce both morbidity and mortality of individuals living with HIV (Palella 1998, Lohse 2007). However, despite the efficacy of the ARV agents and the improvements in prognosis, a large proportion of individuals on cART does not achieve or maintain virological suppression. In one large systematic review of antiretroviral naive patients (3257 participants, 23 clinical trials, including both cohort and randomised studies), a total of 47% of patients on cART were adequately virologically suppressed (viral load ≤ 50 HIV-RNA copies/mL) at 48 weeks (Bartlett 2001). In a large Swiss cohort, EUROSIDA (2674 patients), 66% of the treatment-naive patients remained virologically suppressed (viral load ≤ 400 HIV-RNA copies/mL) at 30 months (Ledergerber 1999).

Measuring success in HIV drug therapy

HIV viral load decreases in response to ARV therapy. The viral load is quantified using a technique known as polymerase chain reaction (PCR) that specifically amplifies and quantifies HIV genetic material (RNA). As technology has improved in sensitivity, so the definition of virological suppression has changed. In the early 1990's, achieving a viral load < 1000 or 500 HIV-RNA copies/mL was accepted as a successful response. Current technology is able detect concentrations as low as <20 HIV-RNA copies/mL. Clinicians and researchers accept a viral load below 50 HIV-RNA copies/mL as appropriate virological suppression, and therefore treatment success. HIV viral loads greater than this signify virological failure. Maximal suppression of HIV viral load is associated with a lower risk of virological failure over time (Raboud 1998) and hence becomes a goal of antiretroviral therapy and auxiliary HIV interventions.

Virological failure

There are numerous potential causes of virological failure including non-adherence; drug toxicity; factors related to the action of the drugs in the body (pharmacokinetic factors) and the emergence of viral resistance. Small elevations in HIV viral concentrations may result in the development of resistance to ARVs, hence the need to maintain therapeutic drug concentrations at all times (Back 2002).

Defining therapeutic drug monitoring

Therapeutic drug monitoring (TDM) is defined as the analysis of in vivo drug concentrations and adjusting dosage regimen on the basis of these concentrations (Back 2002). For the majority of medicines on the market acceptable clinical outcomes and safety margins are achieved without TDM. However certain agents with defined therapeutic ranges, notably anticonvulsants, aminoglycosides, immunosuppressants and certain cardiac drugs such as digoxin, benefit from monitoring of concentrations to ensure acceptable safety and efficacy (Gibbon 2005).

Characteristics of drugs for TDM

Several characteristics are necessary for a drug to be considered an appropriate candidate for TDM (Rayner 2006). An essential requirement is the presence of a dose-response relationship i.e. plasma concentrations should correlate with either drug efficacy or toxicity. There should also be a recognised defined therapeutic range. Another important requirement is that there should be significant inter-patient variability that is unpredictable and low intra-patient variability in plasma concentrations. Importantly, a reliable drug assay with acceptable sensitivity and high specificity should be available (Rayner 2006).

TDM of antiretrovirals

Current ARV therapy combines three or more drugs to minimise the risk of drug resistance (Hammer 1997): a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs e.g. lamivudine or zidovudine) with the addition of either a non-nucleoside reverse transcriptase inhibitor (NNRTI e.g. nevirapine or efavirenz) or a protease inhibitor (PI e.g. lopinavir boosted with ritonavir or indinavir). Current guidelines recommend that protease inhibitors be coupled with a small dose of ritonavir to enhance their efficacy. A nucleotide reverse transcriptase inhibitor (NtRTI e.g. tenofovir) may be included in place of a NRTI and a fusion inhibitor may be included as add-on therapy in ARV-experienced patients on salvage therapy. The drug regimen may be altered according to patient response, toxicity and the development of resistance. The ARVs are typically administered in standard fixed doses, without dose adjustment for factors that may affect drug concentrations in specific individuals, such as sex, diet, genetic polymorphisms or altered pharmacokinetics (i.e. drug absorption, distribution, metabolism and elimination).

TDM of ARVs aims to improve cART efficacy and safety by maintaining individual patients ARV plasma concentrations within a therapeutic range. Many review articles suggest that ARV TDM may be a useful tool for improving outcomes for HIV-infected individuals (Back 2001, Back 2002, Kappelhoff 2004, Molto 2004, Boffito 2005, Back 2006). They suggest that TDM of ARVs can potentially identify patients with sub-therapeutic, toxic or appropriate drug concentrations. In patients with advanced HIV disease, a retrospective analysis found an association between sub-therapeutic drug concentrations at the commencement of cART and poorer immunological outcomes and failure to achieve virologic suppression in the first year of treatment (Alexander 2003). ARV TDM is therefore theoretically a rational tool to optimise efficacy and minimise toxicity of ARV therapy.

PIs as potential candidates for TDM

PIs and efficacy

PI-based therapy has substantial retrospective observational evidence to support the association between drug exposure and virological suppression (Back 2002, Boffito 2005). This association is seen across a spectrum of patients, ranging from antiretroviral-naïve to those on salvage therapy on dual-PI regimens. However in patients who have been heavily pre-treated with ARVs, who have multiple resistance mutations, this association is less clear. In this situation the therapeutic range for drug concentrations is poorly defined (Back 2006, Boffito 2005).

PIs and toxicity

The link with PI plasma concentrations and toxicity is described in small retrospective observational studies. There are conflicting results regarding the association with drug concentrations and the long-term toxicities such as lipodystrophy and hypercholesterolaemia. Well-known short-term adverse effects of the PIs such as diarrhoea and nausea may be associated with higher peak plasma concentrations (Boffito 2005).

Boosting PIs with ritonavir

PIs may be prescribed with a small non-therapeutic dose of another PI, ritonavir. Its function is to inhibit the metabolic breakdown of the primary protease inhibitor, thereby increasing the therapeutic drug concentration. Boosted drug concentrations have in some studies been found to exceed the necessary therapeutic concentrations (Murphy 2001). In ritonavir-boosted regimens the clinical value of TDM in preventing virological failure is still to be determined (Boffito 2005).

The NNRTIs as candidates for TDM

Two NNRTIs are most commonly recommended as part of cART in international guidelines, nevirapine and efavirenz (WHO 2006). Retrospective data from several cohorts propose an association between nevirapine concentration, and a rapid-onset and long-lasting virological response to ARV therapy (Veldkamp 2001, De Requena 2005, Van Leth 2006). Contrary to this, in the prospective 2NN study, trough concentration measurements of nevirapine were poor predictors of virological failure (van Leth 2006). The association between elevated nevirapine concentrations and toxicity remains conflicting, and therefore early TDM when nevirapine therapy is initiated is not currently advocated (Back 2006, Kappelhoff 2005, De Maat 2003).

Efavirenz concentrations have data supporting a correlation with virological outcomes. In a subgroup analysis in the 2NN study, *not* having an efavirenz trough plasma concentration of less than 1.1mg/L had an 89% negative predictive value. That is, participants achieving plasma EFV concentrations above 1.1mg/L, had an 89% likelihood of not failing virologically (van Leth 2006). In addition, neuropsychiatric adverse effects, such as insomnia, have been associated with supra-therapeutic efavirenz concentrations (Hasse 2005, Back 2006).

The NRTIs as candidates for TDM

The NRTIs are pro-drugs that require intracellular activation to their active form. The process of measuring intracellular concentrations of the NRTIs is both complex and costly. Although early small prospective studies suggested a concentration-effect relationship for NRTIs (Fletcher 2000) these agents are generally not considered amenable to TDM (Back 2002, Boffito 2005).

The potential role of TDM in the management of HIV

To date eight randomised studies have evaluated the benefit of monitoring drug ARV concentrations in adults (Clevenbergh 2002, Fletcher 2002, Burger 2003, Bossi 2004, Crommentuyn 2005, Torti 2005, Khoo 2006, Best 2007). However, a large study supporting routine use of TDM is still outstanding.

International HIV management guidelines and TDM

The debate regarding the clinical utility of ARV TDM is reflected by the conflicting recommendations of HIV management guidelines internationally. Western Europe

and United Kingdom centres favour the use of TDM in specific clinical situations (Delfraissy 2000, Carosi 2006, BHIVA 2006, Yeni 2006). The British HIV Association supports the use of TDM in clinical scenarios where drug concentrations may be difficult to predict (BHIVA 2006). These clinical situations include pregnancy, paediatric patients, management of drug-interactions and in salvage therapy, when TDM can be integrated with genotyping of the viral DNA to assess resistance. These guidelines also support TDM in renal and hepatic dysfunction; in cases with ARV toxicity and with new regimens whose efficacy and safety are not yet well defined. Guidelines from the United States are supportive of ARV TDM without providing specific recommendations (DHHS 2006). The International AIDS Society guidelines suggest that expert clinical pharmacology advice should be sought when using TDM and they are concerned about the lack of prospective studies that demonstrate an impact on clinical outcomes of patients (IAS-USA 2006, IAS-2008). South African National guidelines do not include use of TDM (SADOH 2004). The World Health Organisation (WHO 2006) guidelines for adults and adolescents of resource-limited settings do not advocate the use of TDM, particularly in the context of poor access to immunological and virological testing. None of the guidelines specify recommendations for the implementation of TDM - such as appropriate time points or intervals for testing. HIV management guidelines that do mention TDM agree that large randomised controlled trials are needed to refine the population who would most benefit from ARV TDM.

Objectives

Aims

This systematic review aims to comprehensively examine the current evidence for the use of ARV TDM in both ARV-naïve and -experienced adults.

Primary objectives

To evaluate the effect of ARV TDM on:

- Morbidity and mortality of adult patients on cART
- Improving the virological suppression of HIV replication, as defined by respective authors

Secondary objectives

To evaluate the effect of ARV TDM on:

- Change in HIV-RNA viral loads
- Immunological responses in the CD4+ cell count
- Quality of life
- Discontinuation of cART due to virological failure.

Safety objectives

- To determine the proportion of patients discontinuing or switching ARV therapy due to ARV toxicity
- To describe the differences in adverse effects as a result of ARV TDM

Methods of the review

Criteria for considering studies for inclusion in this review

Types of studies

Randomised controlled trials were included in this review. Only trials conducted subsequent to the introduction of cART have been included.

Types of participants

HIV-infected adult patients on cART that must include either a NNRTI or PI as part of their treatment regimen. Study populations may include antiretroviral-naïve, antiretroviral-experienced or a combination of these.

Types of interventions

Therapeutic drug monitoring of the NNRTIs and PIs will be evaluated. The intervention arm may include TDM alone or TDM plus an additional intervention (e.g. genotyping, adherence support etc). The control arm includes participants who have had no TDM or are receiving the current standard of care or an alternative intervention. TDM has no set standard guiding the monitoring of plasma concentrations including ideal timing of blood sampling or number of specimens. TDM will be included when plasma concentrations are measured at least once in a study that is examining the clinical utility of TDM.

Types of outcome measures

Primary outcome measures include:

- Death (all cause)
- Occurrence of new HIV-related events (death or AIDS-defining illness)
- Proportion of patients achieving and maintaining an undetectable viral load, as defined by the authors

Secondary outcome measures include:

- Change in mean CD4+ cell count (mean relative change (percent) or mean absolute change, compared with baseline, and standard deviation)
- Change in HIV-RNA concentrations (mean relative change (percent) or mean absolute change, compared with baseline mean, and standard deviation)
- Quality of life indicators as reported in the studies
- Proportion of patients discontinuing or switching ARV therapy due to virological failure, as defined by the authors (e.g. HIV-RNA <50 or <400 copies/mL)

Safety outcomes

- Proportion of patients discontinuing or switching ARV therapy due to ARV toxicity
- Adverse events, as defined by authors

Search methods for identification of studies

A comprehensive, reproducible search strategy was developed to minimise bias and to ensure all relevant studies are found. Studies were sought regardless of language and publication status (published, unpublished, in press or in progress). All searches were conducted between the 18th and 25th of January 2008.

The following electronic journal databases were searched for relevant trials:

1. Cochrane Central Register of Controlled Trials (CENTRAL)
2. Cochrane Database of Systematic Reviews
3. EMBASE
4. PubMed
5. Meta Register of Controlled Trials

The following electronic conference databases were searched:

AIDSearch - this platform covers abstracts from a number of relevant international conferences including:

a. Conferences on Retroviruses and Opportunistic Infections

b. International AIDS Conference

Hand searches of the reference lists of all the relevant reviews and studies found were undertaken. Investigators of identified trials and other experts were contacted to identify any additional studies that were not yet identified. The WHO International Clinical Trials Registry Platform was searched for possible identification of ongoing trials, not yet in the public domain.

The search strategy for randomised controlled trials of TDM of NNRTIs and PIs used standardised approaches, which will be repeated for future updates. The search strategy included the following relevant terms for therapeutic drug monitoring: Therapeutic drug monitoring; concentration-controlled; drug concentration monitoring; drug monitoring (table1. Example of search strategy).

Table 1. Example of search strategy: Pubmed 18th January 2008

Search	Most Recent Queries	Result
#13	Search **#9 AND #10 AND #11** Limits: **Publication Date from 1996 to 2008**	716
#12	Search **#9 AND #10 AND #11**	811
#11	Search **HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency**	226577

	virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]	
#10	Search **randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR (comparative study) OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])**	3428752
#9	Search **(MONITORING, DRUG) OR (DRUG MONITORING) OR (THERAPEUTIC DRUG MONITORING) OR (DRUG MONITORING, THERAPEUTIC) OR (MONITORING, THERAPEUTIC DRUG) OR (CONCENTRATION-CONTROLLED) OR (CONCENTRATION CONTROLLED) OR (DRUG CONCENTRATION CONTROLLED)**	56649

Data collection and analysis

Data extraction

The literature search was conducted with the assistance of the Trials Search Coordinator of the Cochrane HIV/AIDS Group, South African Cochrane Centre. All study abstracts yielded by the search were reviewed independently by two reviewers (TK, JSW) for inclusion in the analysis. We used the specifically designed eligibility form (Appendix 1). For those studies meeting the inclusion criteria detailed above, full reports were obtained. Any disagreement regarding study eligibility was resolved by discussion with the HIV/AIDS mentor (NS) or third reviewer (KC).

The included studies were then assessed in detail by two reviewers (TK, JSW). The reviewers were not blinded to the names of the trial investigators, their institutions and journals of publication. A Data abstraction form was developed (TK) and piloted (TK, JSW), improvements were made prior to further data extraction. Data was abstracted independently by these two reviewers using the standardised pre-tested data abstraction form (Appendix 2).

The data abstraction forms include the following details:

- Administrative details: Trial identification number; author(s); published or unpublished; year of publication; number of studies included in paper; year in which study was conducted; details of other relevant papers cited.

- Details of the study: study design; type, duration and completeness of follow-up; country and location of study (e.g. higher income vs. resource-limited country).
- Details of participants: setting, numbers, relevant baseline characteristics (e.g. treatment naïve or -experienced).
- Details of intervention: which drug concentrations were measured, additional interventions.
- Details of outcomes: mortality; HIV-related morbidity; HIV-RNA viral load measurements and proposed concentrations for suppression, as defined by the authors; CD4+ cell counts; adverse events and toxicity.

Quality assessment

The risk of bias was assessed using the following Cochrane guidelines (Altman2008):

- Sequence generation: inadequate randomisation sequence generation may result in groups that are unequal at baseline, therefore resulting in *selection bias.*
- Allocation concealment: inadequate allocation sequence concealment in advance of, or during enrolment. This may result in unequal groups at baseline, and therefore *selection bias*.
- Blinding (masking) of participants, personnel and outcome assessors: knowledge of the intervention group to which an individual is allocated may result in systematic differences between in the care that is provided, or in the exposure factors other than the intervention of interest, and therefore *performance bias*.
- Description of the completeness of outcome data for each main outcome: This is done to assess whether all participants randomised were included in an intention-to-treat analysis so as to minimise bias that occurs with loss-to-follow up, *attrition bias*.
- Assessment of selective reporting: This evaluates whether each of the pre-specified outcomes was reported, if not done, this is described as *reporting bias.*
- Other potential sources of bias, specific to the study were assessed (e.g. uptake of recommendations in the trials; adherence to ARV therapy)

Data synthesis

Meta-analysis was conducted where trials were found to be methodologically or clinically comparable. Where studies did not have combinable outcomes, a narrative review was undertaken.

Analysis

Data analysis was conducted using Review Manager (RevMan) version 5.0.15 (Copenhagen: the Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Outcome measures for dichotomous data (e.g. death, virological suppression) were reported as a relative risk with 95% confidence intervals. Continuous data (e.g. CD4+ cell counts, HIV-RNA viral loads) were analysed using the weighted mean difference and standard deviations. Stratified analyses were conducted by ARV regimen and differing treatment groups (e.g. treatment-naïve vs. treatment-experienced). Heterogeneity between studies was anticipated and therefore the random effects models were used to generate pooled effects. Differences in the findings were assessed using the Chi Square test for heterogeneity ($p<0.1$) which was quantified by the Higgins I^2 statistic. Statistical heterogeneity was explored using the following subgroups:

- Patients on NNRTIs vs. PIs
- Patients who were treatment-naïve vs. treatment-experienced.

There was insufficient data to conduct a sensitivity analysis to evaluate bias introduced by variability in allocation concealment in the included studies.

Results

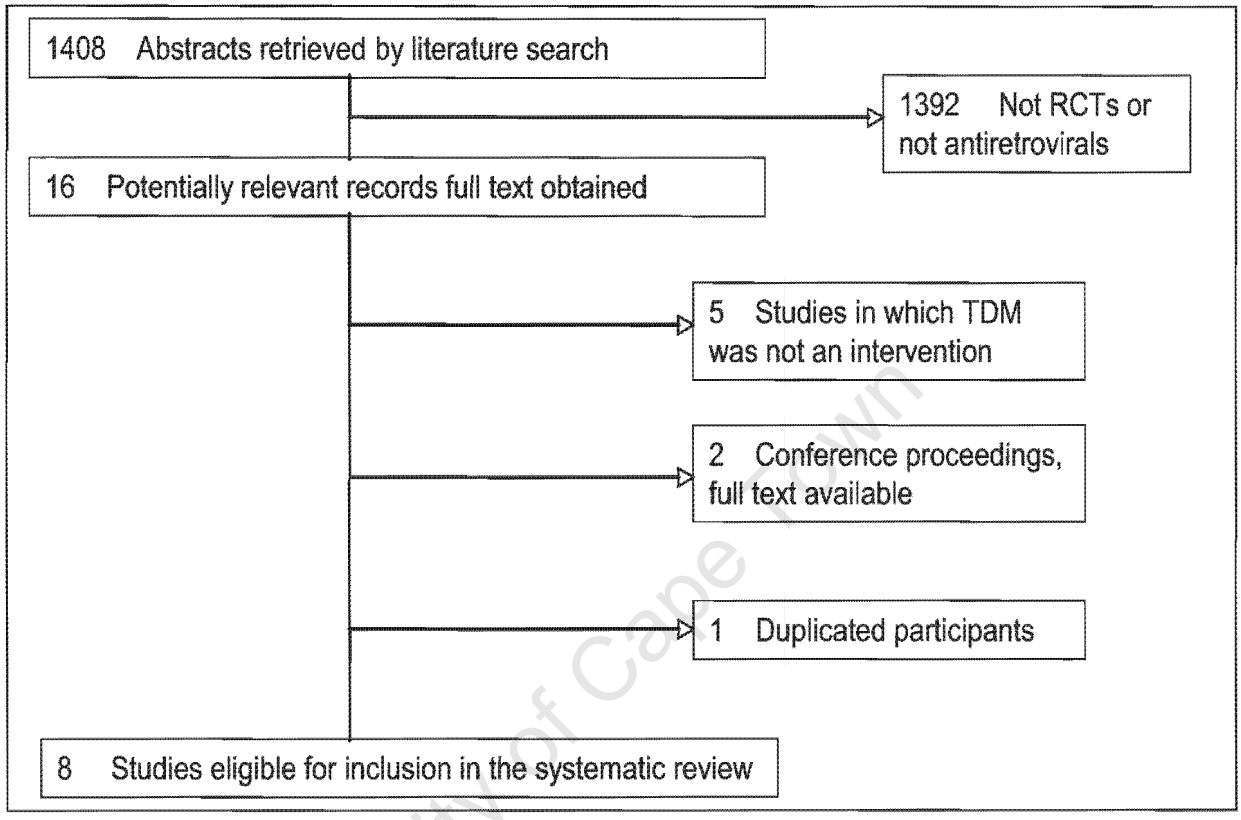
Description of studies

Results of the search

Using the standardised eligibility form with pre-specified criteria (Appendix 1), JS and TK independently reviewed 1408 abstracts for eligibility. Of these, 16 abstracts were identified as potentially fitting the criteria for inclusion and the full text articles were retrieved. Eight of the selected studies were excluded for the following reasons: TDM was not an intervention (5 studies: Clevenbergh 2003, Durant 2000, Fletcher 2005, Hugen 2002, Van Leth 2006); conference proceedings which were

subsequently published (2 studies: Kakuda 1999; Clevenbergh 2001); report of an interim analysis (Kakuda 2001) (figure 1).

Figure 1. Flow diagram of search results



Included studies

The current review includes 8 trials with a total of 1181 randomised participants. All studies included were randomised controlled trials (table 2 table of characteristics of included studies).

The trials were conducted between 2002 and 2007 in several countries: France (Clevenbergh 2002, Bossi 2004); United States of America (Fletcher 2002, Best 2007); The Netherlands (Burger 2003, Crommentuyn 2005); Italy (Torti 2005) and the United Kingdom (Khoo 2006). Details of the settings with respect to socio-economic status were not described in any of the studies. The sample sizes ranged from 40 to 230 participants. The median duration of follow-up was 24 weeks (range 12 to 72 weeks).

Table 2. Characteristics of included studies

Clevenbergh 2002	
Methods	*Random sequence generation:* Centralized open-label randomisation was performed, using a permuted block approach with assignments sequentially numbered. *Allocation concealment:* Sequentially numbered assignments were provided from central site. *Blinding:* Open-label *Inclusion of all participants:* Loss to follow up was not reported. However, the losses to follow up were not large or different between groups and not expected to impact on results. *Duration of follow-up:* 12 weeks
Participants	*Inclusion criteria:* Treatment-experienced patients with viral loads > 2000 HIV-RNA copies/mL despite 6 months of cART. *Exclusion criteria:* Not reported
Interventions	At baseline, all had genotype tests done and their antiretroviral treatment changed according to the results. Participants were then assigned to either TDM or standard of care. Both groups had TDM taken at weeks 4 and 8, only those in TDM arm had expert advice.
Outcomes	*Primary endpoints:* (i) Change in HIV-RNA level from baseline at week 12 (ii) Proportion of patients with HIV RNA concentrations < 200 copies/ml at 12 weeks. No secondary or safety endpoints were reported.
Notes	*Location:* Not reported *Duration of study:* October 1999 to October 2000 *Uptake of recommendation:* Poor - 29% *Funding:* This study was supported by sponsorship by Visible Genetics, France; Bristol Myers-Squibb, France; Dupont Pharma, France; Glaxo-Wellcome, Roche, France; and Virco, Belgium
Fletcher 2002	
Methods	*Random sequence generation:* Performed using a permuted block approach with assignments contained in sealed, opaque envelopes sequentially numbered. The randomisation cards were prepared by the protocol statistician and only handed out on a case-by-case basis. *Allocation concealment:* Allocation assignments were contained in sealed, opaque envelopes that were sequentially numbered. *Blinding:* Open-label *Inclusion of all participants:* A clear description of the treatment discontinuations prior to 8 weeks is given. It is not clear to which arm they were assigned. All drop-outs after 8 weeks were included in a modified intention-to-treat analysis. *Duration of follow-up:* 52 weeks

Participants	*Inclusion criteria:* All participants were HIV positive, antiretroviral-naïve, between 18-60 years old. They had to have an HIV RNA level > 5000 copies/mL. *Exclusion criteria:* The participants would be excluded if they had an opportunistic infection or documented non-adherence to treatment or clinic visits.
Interventions	All participants had TDM done, but only the TDM arm received advice following these results. Serial sampling was done at 2 and 28 weeks. Single samples 2-5hrs post-dose were obtained at each visit (weeks 2, 4 and every 4 weeks after that).
Outcomes	Primary outcomes: (i) Proportion achieving desirable drug concentrations at week 28 (ii) Proportion of participants with HIV-1 RNA concentrations <50 copies/mL at 52 weeks (iii) Safety and tolerance of conventional compared with concentration-controlled therapy
Notes	*Location:* University- based general clinical research centre, out patients department, at the University of Minnesota *Duration of study:* Enrolment June 1997 to September 1999. The last participant completed follow up in September 2000. *Uptake of recommendation:* Not reported *Funding:* A grant from the National Institute of Allergy and Infectious Diseases and The National Institute for Health, Center for Research Resources General Clinical Research Centres Program and from the manufacturers of the ARVs, Glaxo-Smith Kline and Merck and Co.
Burger 2003	
Methods	*Random sequence generation:* Groups were 'randomly assigned' but there is no detail given for the randomisation process. *Allocation concealment:* No details of allocation concealment given. *Blinding:* Open-label *Inclusion of all participants:* Discontinuation was one of the primary endpoints and was therefore well reported. Intention-to-treat analysis is performed where non-completer = failure. *Duration of follow-up:* 12 months
Participants	*Inclusion criteria:* Treatment-naïve patients starting antiretrovirals with either Nelfinavir or Indinavir. They must have signed an informed consent document. *Exclusion criteria:* Not reported
Interventions	TDM was conducted at clinical visits at weeks 4, 12 and every 12 weeks thereafter in all participants. Only those randomised to TDM received advice regarding drug concentrations within 4 weeks of the sample.
Outcomes	*Primary endpoints:* (i) Treatment discontinuation - the reason for stopping would be recorded (ii) Virological response to treatment after 6 and 12 months of enrolment Secondary endpoints and safety endpoints were not reported in the manuscript.

Notes	*Location:* The study was conducted at 22 centres around the Netherlands as part of the ATHENA Cohort. *Duration of study:* Unclear, recruitment was completed as of 1st November 1999. *Uptake of recommendations:* This was not described. *Funding:* Not described
Bossi 2004	
Methods	*Random sequence generation:* Randomisation list was obtained using the SAS procedure plan at the data statistical analysis centre. Randomisation was on a one to one basis with block size of 6. *Allocation concealment:* The randomisation list was created at the statistical data centre, but further description of allocation is not included. *Blinding:* Open-label *Inclusion of all participants:* Losses to follow up were disclosed and the analyses were conducted a modified intention-to-treat analysis in which missing = failures and on an observed basis. Although the authors describe an intention-to-treat analysis, the 139 participants initially randomised were not all included, as 5 were excluded due to 4 withdrawals and 1 lung cancer diagnosis. This is a negligible attrition and not expected to bias results. *Duration of follow-up:* 24 weeks
Participants	*Inclusion criteria:* > 18 years of age, antiretroviral-experienced with a viral load in excess of 1000 HIV-RNA copies/mL within 1 month of baseline and at baseline. They were required to be on an antiretroviral regimen including at least 3 drugs including either one or more protease inhibitors and/or one or more non-nucleoside reverse transcriptase inhibitors and this regimen should not have been changed over the last 3 months. *Exclusion criteria:* Participants with active opportunistic infections, previous resistance testing and/or those who were pregnant were not eligible to participate.
Interventions	Resistance testing was performed on all participants at baseline. TDM recommendations could be made at each time point (4, 8, 12, 18, 24 weeks) for the group assigned to TDM, and from 12 weeks to both arms.
Outcomes	*Primary outcome:* (i) Proportion of patients with plasma HIV-RNA concentrations <200copies/mL at 12 weeks. *Secondary outcomes:* (i) Changes in plasma HIV-RNA concentrations and (ii) CD4 count from baseline to 12 weeks and 24 weeks (iii) Changes in plasma drug concentrations during study. Safety outcomes were reported.
Notes	*Location:* Paris, France *Duration of study:* November 2000 to November 2001 *Uptake of recommendations:* Not reported. *Funding:* Funding support came from SIDACTION (Paris, France) and a grant from Bristol-Myers Squibb (Paris, France)
Crommentuyn 2005	
Methods	*Random sequence generation:* Details of randomisation not provided.

	Allocation concealment: Details of allocation concealment not provided. *Blinding:* Open-label *Inclusion of all participants:* Modified intention-to-treat analysis was performed using non-completer = failure. *Duration of follow-up:* 24 months
Participants	*Inclusion criteria:* Not described in detail, participants were HIV positive and antiretroviral naïve. *Exclusion criteria:* Not reported
Interventions	After randomisation, those in the TDM arm had nevirapine concentrations measured (at weeks 4, 12 and every 12 weeks thereafter) and an interpretation reported to the treating physician. The control arm also had drug concentrations measured, however not reported.
Outcomes	*Primary endpoints:* (i) Treatment discontinuation and (ii) Virologic response (HIV-1 RNA level less than 500 copies/mL) *Secondary endpoints:* Not reported
Notes	*Location:* Participants included from one the of the 22 treatment centres included in the ATHENA cohort in The Netherlands *Duration of study:* Not reported *Uptake of recommendation:* Not reported *Funding:* Not reported
Torti 2005	
Methods	*Random sequence generation:* Simple randomisation lists were generated at a central site and distributed to each study centre. *Allocation concealment:* Not described. *Blinding:* Open-label *Inclusion of all participants:* 265 participants randomised, 35 losses-to-follow-up were accounted for. *Duration of follow-up:* 24 weeks
Participants	*Inclusion criteria:* Patients on a failing regimen with ≥ 3 antiretrovirals. Defined as - (i) HIV-1 RNA ≥ 1000 copies/mL on stable treatment for 6 months or (ii) HIV-1 RNA ≥ 1000 copies/mL on treatment for 3 months with less than 1 $\log_{10}$ decrease in their viral load. *Exclusion criteria:* Not reported
Interventions	TDM at baseline, and weeks 1, 4, 12 and 24
Outcomes	*Primary outcomes:* (i) The proportion of participants with virological success at 24 weeks (HIV-RNA < 400 copies/mL) *Secondary outcomes:* (i) Change from baseline of viral load and CD4 count

	(ii) Proportion of participants with persistent virological response (i.e. HIV-RNA <400 copies/mL before 24 weeks and sustained until the 24 week assessment)
Notes	*Location:* Multiple clinic sites in Italy *Duration of study:* May 2002 to September 2003 *Uptake of recommendation:* Poor, only 8 of 27 dose increase recommendations implemented at week 1 (29.6%); 7 of 29 at week 4 (24.1%); 0 of 29 patients at week 12 and 2 of 29 at week 24 (6.8%). *Funding:* Not reported
Khoo 2006	
Methods	*Random sequence generation:* Randomisation was conducted in a block-permuted manner stratified by treatment centre. *Allocation concealment:* No detail is given regarding allocation concealment. *Blinding:* Open-label *Inclusion of all participants:* 132 participants were randomised, 10 did not return for assessment, and therefore the remaining 123 participants were included in a modified intention-to-treat analysis. Reasonable loss-to-follow-up. *Duration of follow-up:* 24 weeks
Participants	*Inclusion criteria:* HIV positive, > 18 years old and have good attendance at clinic. The participant had to be willing to attend a nurse-led clinic and have a life-expectancy > 24 months. 2 groups including both antiretroviral-naïve and –experienced participants: Study 1 - patients commencing or switching to a new regimen were included. Study group 2 - patients on a stable regimen for > 6 months with virological suppression < 50 copies/mL. *Exclusion criteria:* Liver dysfunction, pregnant or on NRTIs alone or those who did not give consent.
Interventions	Participants were assigned to either adherence support and TDM or SOC. TDM was conducted on early morning plasma samples. Study group 1 - samples taken baseline, 2, 4 and 12 weeks and 12 weekly thereafter. The group 2 - samples at baseline and 12 weekly.
Outcomes	*Primary endpoints:* (i) Failure to achieve viral load < 50 copies/mL at 24 weeks (ii) Viral rebound after suppression (rebound > 400 copies/mL) (iii) Occurrence of any treatment limiting toxicity Secondary outcomes: (i) Failure to achieve a viral load < 400 copies/mL at 24 weeks (ii) Other toxicities (liver enzymes, raised cholesterol concentrations or use of cholesterol lowering agents; raised pancreatic enzymes)
Notes	*Location:* Nurse-led clinics at 3 treatment centres in Northwest England. There was one large clinic (> 1000 patients); one medium sized clinic (> 400 patients) and a smaller clinic (200 patients) *Duration of study:* March 2000 to October 2003 *Uptake of recommendation:* Poor, modifications undertaken in 9 of 26 patients where changes were recommended (35%) *Funding:* North West Regional Health Authority R & D Reactive Funding Scheme

Best 2007	
Methods	*Random sequence generation:* Central factorial randomisation was computer generated, block approach and stratified by clinic site (5 sites) and prior treatment (treatment-naive vs. treatment- experienced). *Allocation concealment:* Computer generated, block approach, no further detail given. *Blinding:* open-label. A committee of ARV pharmacologists and HIV treatment specialists were blinded to the participants' allocation. *Inclusion of all participants:* 241 patients were assessed for eligibility, 230 were randomised and 199 were finally included in a modified intention-to-treat analysis. Explanations are given for loss-to-follow up and these were equal between arms. *Duration of follow-up:* 48 weeks
Participants	*Inclusion criteria:* HIV RNA level > 3000 copies/mL with the intention of starting a new PI- or NNRTI-based regimen. Participants could be either ARV naïve, treatment-experienced and on a stable regimen or treatment-experienced and off ARV therapy for ≥ 2 months; ≥ 18 years old; have a life expectancy of ≥ 12 months; if female, should be willing to use contraception. *Exclusion criteria:* Any sign of an active opportunistic infection or cancer, chronic diarrhoea, malabsorption, treatment-limiting toxicity to the current ARV regimen, severe cognitive impairment, active drug or alcohol abuse, and currently pregnant or breast-feeding.
Interventions	Pharmacokinetic serial sampling was conducted at 2 weeks and 48 weeks. ARV TDM concentrations for the PIs and NNRTIs were taken at each clinical visit in all participants and pharmacokinetic parameters were estimated from the week 2 evaluation, and re-estimated from samples collected between weeks 2 and 12, 12 and 24, and 24 and 48 visits. Recommendations were provided at week 4, 12 and 24 visits.
Outcomes	*Primary endpoints:* (i) Proportion of participants who had a TDM recommendation to change PI and or NNRTI dosing (ii) Proportion of recommended changes that were carried out (TDM arm only) *Secondary endpoints:* (i) Proportion of recommended interventions that achieved the target concentration in the TDM arm (ii) Proportion of patients with an HIV RNA level < 400 copies/mL at 48 weeks compared between arms (iii) Proportion of patients experiencing grade III/IV and/ or treatment limiting toxicity compared between arms
Notes	*Location:* 5 clinic sites in California, United States *Duration of study:* Recruitment took place between September 2001 and December 2003. Follow up was complete by January 2005 *Uptake of recommendations:* Good – 76% *Funding:* University wide AIDS Research Program of the University of California, the National Institute of Mental Health, the National Institute of Allergy and Infectious Disease, the National Institute for Child Health and Human Development and the University of California, San Diego Centre for AIDS Research, National Institute for Allergy and Infectious Diseases

Participants

The studies were conducted in adults with an age range of 22 to 68 years (7 studies) (table 3). Sex was reported in 7 of the 8 included studies, representing 742 male and 175 female participants. This 4:1 male predominance, likely reflects the distribution of HIV-infection in the developed countries from which the participants are sampled (WHO 2008).

In six of the studies the baseline CD4+ cell counts and HIV-RNA viral loads are described. In these studies the CD4+ cell counts were all below 400 cells/μL, and the viral loads range from 3 $\log_{10}$ copies/mL to 6.7 $\log_{10}$ copies/mL.

Three studies were conducted in antiretroviral-naïve participants exclusively (Fletcher 2002; Crommentuyn 2005; Burger 2003); three studies recruited antiretroviral-experienced patients (Clevenbergh 2002; Bossi 2004; Torti 2005). Two of the most recent studies included both antiretroviral-naïve and -experienced participants (Khoo 2006; Best 2007).

Table 3. Baseline Characteristics - included studies

(Results presented as reported by authors)

Study ID	Age	Sex	Prior AIDS	CD4 count (cells/μL)	Viral loads ($\log_{10}$ copies/mL)
Clevenbergh 2002	Not reported	Not reported	Not reported	median 300 vs. 300	median 4.2
Fletcher 2002	median (range) 37 (22-57) vs. 39 (28-59)	36 male; 4 female	Not reported	median (range) 267 (20-666) vs. 70 (52-105)	median (range) 4.57 (3.79-5.88) vs. 4.56 (3.88-5.7)
Burger 2003	median (IQR) 36 (33-43) vs. 39 (34-45)	131 male; 16 female	Not reported	median (IQR) 180 (55-320) vs. 232 (91-380)	median (IQR) 5.2 (4.9-5.5) vs. 5.1 (4.5-5.5)
Bossi 2004	mean (range) 42 (27-65) vs. 40 (18-56)	107 male; 27 female	31% vs. 34%	median (range) 294 (60-826) vs. 292 (6-844)	median (range) 4 (3-5.3) vs. 4.1 (3-5.4)

Crommentuyn 2005	mean (range) 41(28-68) vs. 41 (22-59)	43 male; 2 female	Not reported	mean (range) 309 (30-696) vs. 296 (20-660)	mean (range) 4.74 (3.94 - 5.87) vs. 4.5 (3.57-5.04)
Torti 2005	mean (SD) 40.2+_ 6.5 vs. 40.9 +_8.2	158 male; 72 female	27.7% vs. 37.9%	mean (SD) 370+_197 vs. 402+-242	Mean (SD) 3.8+_0.7 vs. 3.8+_o.7
Khoo 2006	Not reported	106 male; 16 female	56% vs. 58%; overall 57%	median (95%CI) 280 (282-409) vs. 430 (358-483); overall 325 (337-426)	median (95%CI) 4.04 (3.03-4.64) n=18 vs. 4.9 (3.59-5.05) n=20; overall 4.61 (3.52-4.58) n=37
Best 2007	mean (SD) 40+-8 vs. 39±8 ;overall 40±8	161 male; 38 female	65 (48%) vs. 26 (40%); overall 90 (45%)	Median (range) 151(20-675) vs. 190 (20-570); overall 176 (20-675)	Median (range) 5.2 (3.4-6.7) vs. 5.2 (3.6-6.4); overall 5.2 (3.4-6.7)

Interventions

TDM alone was the intervention in four studies (Fletcher 2005; Burger 2003; Crommentuyn 2005; Best 2007). TDM was combined with genotypic testing at baseline in two studies (Clevenbergh 2002; Bossi 2004), with genotypic testing or virtual phenotypic testing in one study (Torti 2005) and with adherence support in one study (Khoo 2006) (table 4).

TDM of PIs was assessed in three studies: all available PIs (Clevenbergh 2002), nelfinavir and indinavir (Burger 2003), indinavir only (Fletcher 2002). Only Crommentuyn 2005 included participants on NNRTIs alone. The remaining 4 studies included participants on either PIs or NNRTIs and their outcomes were not reported by treatment regimen.

Two studies included participants on predominantly unboosted PIs (Fletcher 2005; Burger 2003), a therapeutic recommendation no longer in common clinical practice (IAS-USA 2008, WHO 2006).

TDM assessments differed between studies. In the studies assessing genotypic or virtual phenotypic testing at baseline, Clevenbergh 2002; Bossi 2004 and Torti 2005, TDM samples were collected at weeks 4,8 and for the Torti 2005 study, at 12 weeks. Outcome was assessed at 12 weeks, within one month of implementing the TDM recommendations. TDM assessments were conducted over a longer duration of follow up in the remaining five studies.

Uptake of TDM recommendations differed between studies. In the Best 2007 study the uptake of recommendations was 76% (95% CI 68% - 84%). In three studies, Clevenbergh 2002; Khoo 2006; Torti 2005, the uptake ranged between 0%, at one of the described time points, and 35%.

Table 4. Summary of Intervention vs. Control in included studies

Study ID	Intervention	Control
Clevenbergh 2002	TDM and genotypic testing	Genotypic testing only
Fletcher 2002	TDM	SOC
Burger 2003	TDM	SOC
Bossi 2004	TDM and genotypic testing	Genotypic testing only
Crommentuyn 2005	TDM	SOC
Torti 2005	Genotypic testing and TDM; or virtual phenotype and TDM	Genotypic testing and SOC; or virtual phenotype and SOC
Khoo 2006	TDM and adherence support tool	SOC and standard adherence support
Best 2007	TDM	SOC

Outcomes

We aimed to collect data on mortality (all cause); HIV related events and quality of life data, however these were not recorded or reported in any of the studies.

- All studies provided data on the proportion of participants achieving or maintaining virological suppression as defined by the respective authors, and these were described at different time points (Clevenbergh 2002: 12 weeks; Fletcher 2002: 52 weeks; Burger 2003: 24 and 52 weeks; Bossi 2004: 12

and 24 weeks; Crommentuyn 2005: 24 and 52 weeks; Torti 2005: 12 weeks; Khoo 2006: 72 weeks; Best 2007: 24 and 52 weeks).

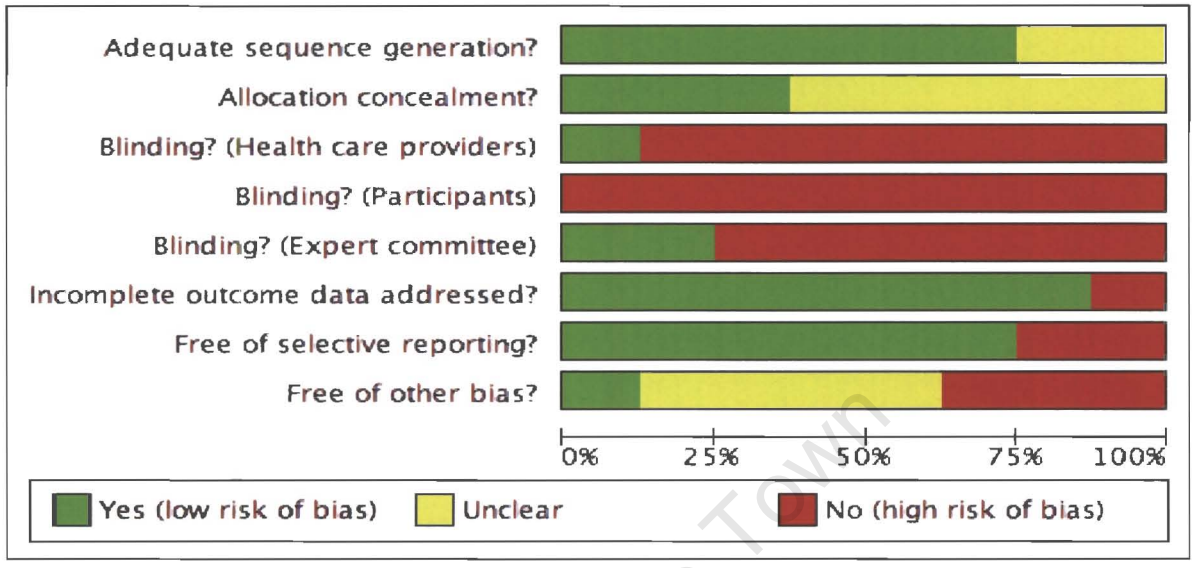
- Adequate suppression ranged from <50 HIV-RNA copies/mL to <500 HIV-RNA copies/mL. The change in mean CD4 cell count was described in two trials at different time points (Fletcher 2002: 52 weeks; Bossi 2004: 12 and 24 weeks).
- The changes in HIV-RNA concentrations were included in 2 studies at different time points (Clevenbergh 2002: 12 weeks; Bossi 2004: 12 and 24 weeks).
- The proportion of participants stopping or switching ARV regimens due to virological failure was described in two studies (Fletcher 2002, Burger 2003).
- The safety outcomes included the proportion of participants stopping or switching due to toxicity (2 studies: Fletcher 2002, Burger 2003) and the reporting of any adverse events (4 studies: Fletcher 2002, Bossi 2004,Khoo 2006, Best 2007).

Risk of bias in included studies

Selection bias:

Generation of the randomisation sequence was unclear in 2 studies (Burger 2003, Crommentuyn 2005) and adequate in the remaining six trials (figures 2 and 3). The allocation concealment was unclear in five of the studies (Bossi 2004, Burger 2003, Crommentuyn 2005, Khoo 2006, Torti 2007) the remaining 3 were adequate. Both sequence generation and allocation concealment were clearly adequate in 3 studies (Best 2007, Clevenbergh 2002, Fletcher 2002).

Figure 2. Methodological quality graph: Judgements regarding each methodological quality item presented as percentages across all included studies



Performance bias:

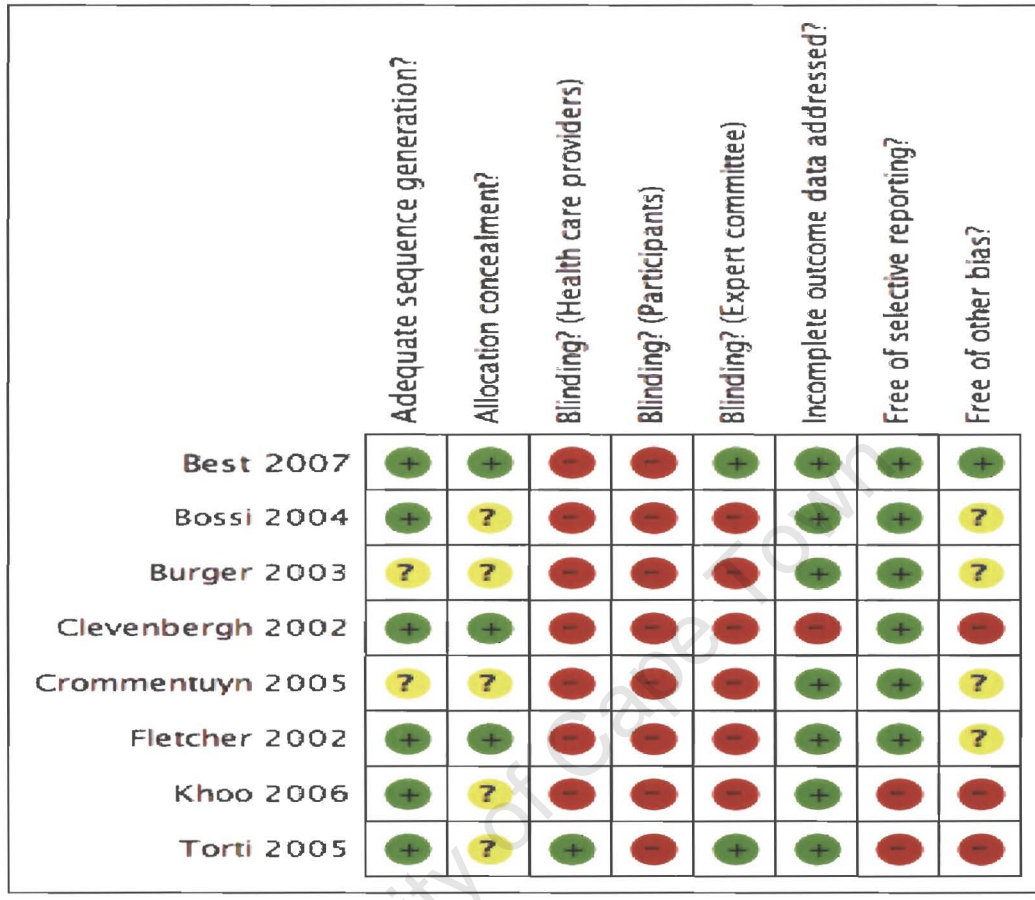
All of the studies were open-label, resulting in potential risk of bias in performance, however, as the intervention relies on expert advice, it is not practicable to blind participants or health care providers. In two studies the expert committees were blinded to participant allocation and were required to comment on results in both TDM and standard of care (SOC) arms (Best 2007; Torti 2005).

A major source of potential bias introduced in these studies is the uptake of the expert advice regarding the TDM results. In only one study was the uptake of recommendations described as good 76% (95% CI 68% - 84%) Best 2007. In 3 studies the uptake ranged between (0% at one of time periods) and 35% overall (Clevenbergh 2002, Khoo 2006, Torti 2005). There was no description of uptake of the TDM advice in 4 of the studies, and therefore the level of bias is unclear.

Attrition bias:

In three studies (Clevenbergh 2002, Burger 2003, Crommentuyn 2005) the outcome data was not clearly described, however the proportion lost-to-follow-up (LTFTU) was not excessive and this is therefore unlikely to impact on the results. The attrition was accounted for in the remaining 5 studies (Fletcher 2002: LTFU =7%; Bossi 2004: LTFU = 7%; Torti 2005: LTFU = 13%; Khoo 2006: LTFU = 7%; Best 2007: LTFU = 13%). In the reported studies, attrition was similar between arms.

Figure 3. Methodological quality summary: Judgements regarding each methodological quality item for each included study



Reporting bias:

Two of the studies have missing primary endpoint data (Khoo 2006, Torti 2005). The primary endpoints as described in the studies were omitted from the results sections of the reports. Khoo 2006 reported on actuarial results of virological outcomes at 72 weeks on treatment. Torti 2005 reported on secondary outcomes only. This selective reporting is a potential source of bias.

Effects of interventions

Primary Outcomes

The primary objective of this review was to assess the effects of ARV TDM on mortality, morbidity and the proportion of HIV-infected adults on cART achieving and maintaining an undetectable viral load, as defined by the authors. The first two outcomes were not reported in any of the included studies. The proportion of HIV-infected adults on cART achieving and maintaining an undetectable viral load is

reported in all of the studies at varying time points (e.g. 12 weeks, 24 weeks or 52 weeks).

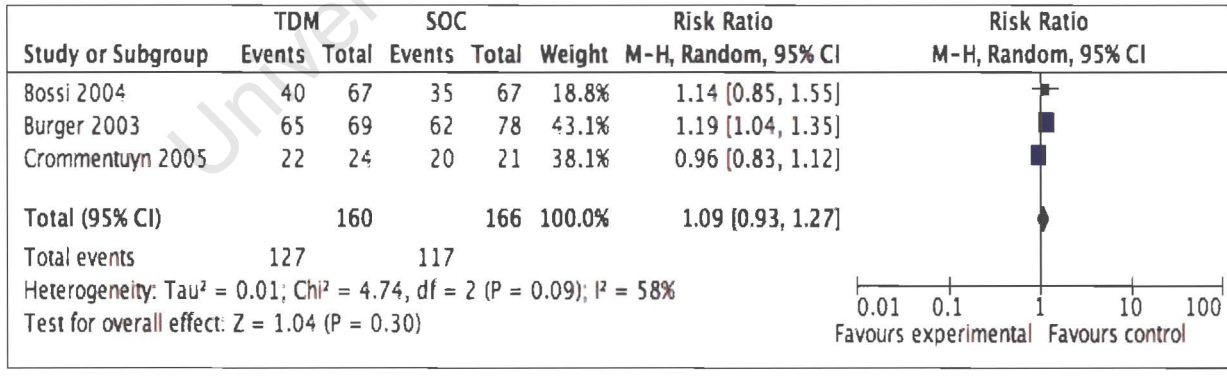
Virological suppression

The definition of virological outcomes varied between studies, viral load 'cut-offs' included <50 HIV-RNA copies/ml in Fletcher 2002; Best 2007 and Khoo 2006, <200 HIV-RNA copies/ml in Bossi 2004 and Clevenbergh 2002 and < 400 HIV-RNA copies/ml in Best 2007; Torti 2005, and < 500 HIV-RNA copies/ml in Burger 2003 and Crommentuyn 2005. For the purposes of this review, all results less than 500 HIV-RNA copies/ml were accepted as virologically suppressed.

All participants on either PIs or NNRTIs

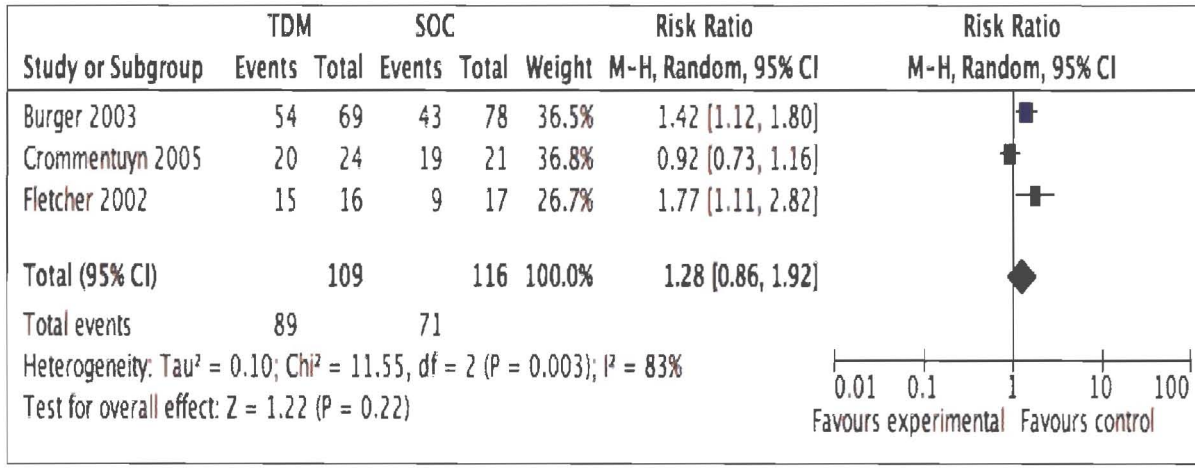
Comparing TDM of all ARVs to standard of care (SOC), in both ARV-naïve and -experienced participants, indicated a non-significant trend to increased risk of virological failure at 24 weeks (RR 1.09 [0.93, 1.27], 326 participants, 3 trials, figure 4) As expected, due to clinical differences in the populations included in the analysis, there was significant heterogeneity between studies as reflected by a chi^2 statistic = 4.74 (P = 0.009) and Higgins' I^2 statistic of 58% indicating a moderate degree of inconsistency between studies.

Figure 4. All participants: TDM of all ARVs vs. SOC at 24 weeks



The same comparison of TDM at one year of follow-up, resulted in a non-significant trend to increased failure (RR 1.28 [0.86, 1.92], 225 participants, 3 trials, figure 5). Again there was significant heterogeneity between studies with chi^2 = 11.55 (P = 0.003), with Higgins' I^2 statistic indicating high degree of heterogeneity (I^2 = 83%).

Figure 5. All participants: TDM of all ARVs vs. SOC at 52 weeks

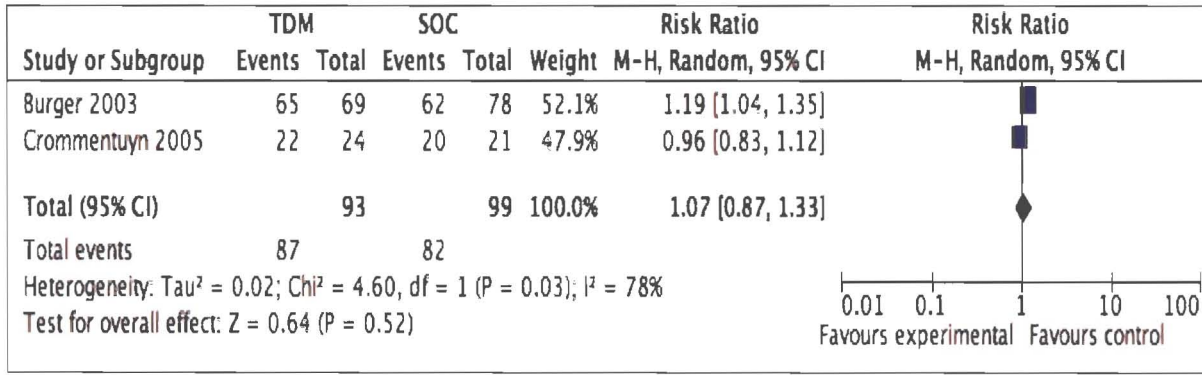


No significant effect of TDM was seen on meta-analysis including all ARVs. In light of significant heterogeneity, it may be inappropriate to pool results of the above studies. Therefore we proceeded to analyse in the subgroups according to the pre-specified treatment groups (antiretroviral-naïve and –experienced) and further according to their ARV treatment regimen (NNRTI and PI).

Antiretroviral-naive participants on either PIs or NNRTIs

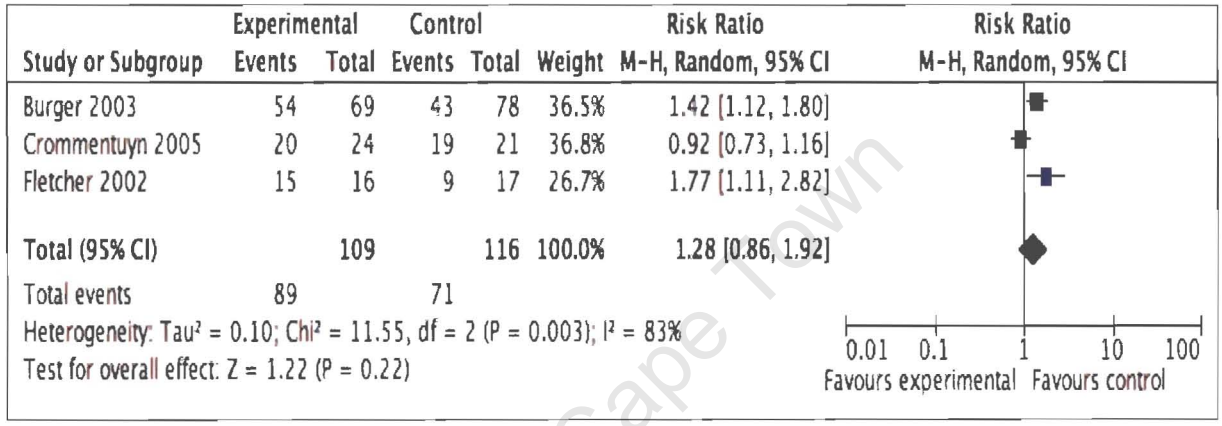
The subgroup analysis of antiretroviral-naïve particiants on either PIs or NNRTIs did not reach significance at a viral load cut-off of <500 HIV-RNA copies/mL at 24weeks of follow up (RR 1.07 [0.87, 1.33], 192 participants, 2 trials, figure 36), again with significant heterogeneity, I^2 = 78% indicating a high degree of inconsistency between groups.

Figure 6. Antiretroviral-naïve participants: TDM of all ARVs vs. SOC at 24 weeks



This same subgroup analysed at 52 weeks revealed consistent results (RR 1.28 [0.86, 1.92], 225 participants, 3 trials, Figure 7, I^2 = 83%). This indicates, that there is insufficient evidence to support the use of TDM for all antiretroviral-naive participants on all regimens, even with the longer duration of treatment and implementation of the TDM.

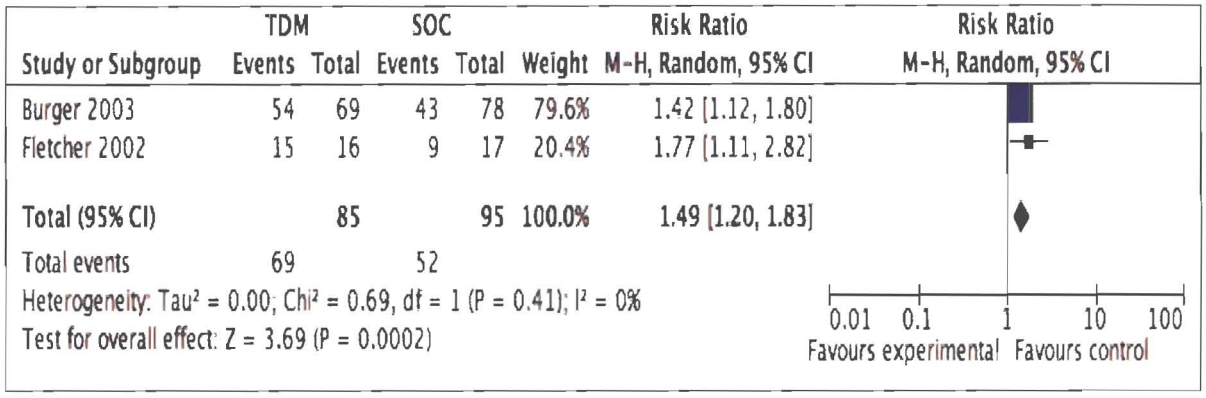
Figure 7. Antiretroviral-naïve participants: TDM of all ARVs vs. SOC at 52 weeks



Antiretroviral naive on PIs

This subgroup including only antiretroviral naïve participants, predominantly on unboosted PI-based cART is clinically homogeneous. Therefore meta-analysis was conducted. Participants on PIs had a 50% increased likelihood of achieving a HIV-RNA viral load < 500 copies/mL at 52 weeks of follow up (R 1.49 [1.20, 1.83], 180 participants, 2 trials, Figure 8). Low heterogeneity, and therefore consistency between trials, is indicated by the chi^2 0.69 (P = 0.4), I^2 = 0%.

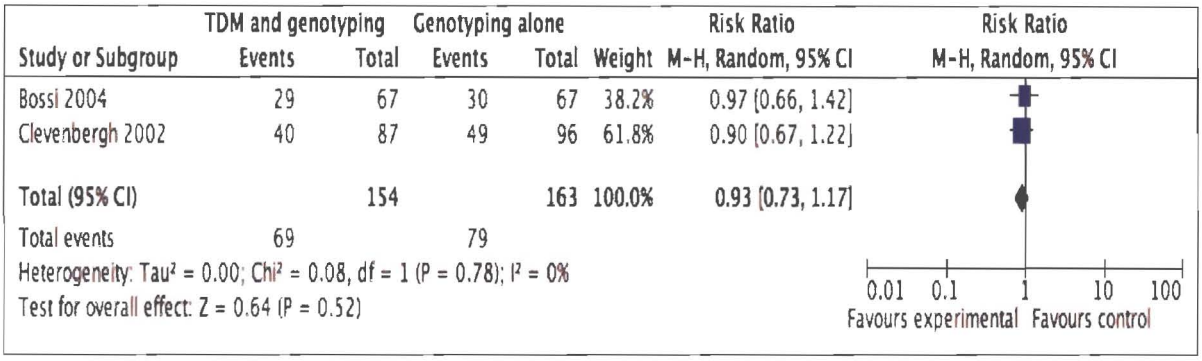
Figure 8. Antiretroviral-naïve participants: TDM of protease inhibitors vs. SOC



ARV experienced participants

Three studies included ARV experienced participants only, Bossi 2004; Clevenbergh 2002 and Torti 2005. In these ARV-experienced participants the baseline ARV regimens were guided by genotypic or virtual phenotypic testing. Genotypic testing was conducted in all participants at baseline in Clevenbergh 2002 and Bossi 2004; whereas Torti 2005 included a factorial design, randomising participants to either genotype testing or virtual phenotypic testing prior to randomisation to TDM or SOC. These studies had short durations of follow up with outcomes reported 12 weeks after a TDM intervention at either week 4 or 8. Torti 2005 did not find any significant virological suppression <400 HIV-RNA copies/mL at 12 weeks in TDM and SOC for 74 vs. 63.6% respectively (P = 0.1). Clevenbergh 2002 and Bossi 2004 when analysed showed no significant effect of TDM vs. SOC on the background of genotype testing (RR 0.93 [0.73, 1.17], 317 participants, 2 trials, figure 9). Here there was good consistency between trials, chi^2 = 0.08 (P = 0.78) and the Higgins' I^2 = 0%. Although we analysed these clinically and methodologically similar studies, the evidence did not support routine TDM in ARV experienced patients.

Figure 9. Antiretroviral-experienced: Genotypic testing plus TDM vs. genotypic testing alone at 12 weeks



Secondary outcomes

Change in mean CD4+ cell count

Two studies (Fletcher 2002, Bossi 2004) reported a change in CD4+ cell count, at varying time points and in different populations. This was not amenable to further analysis. Neither study showed significant changes in CD4+ cell counts. In Fletcher 2002, the mean change in CD4+ cell count from baseline was 214 cells/μL and 167 cells/μL in the TDM and SOC arms respectively (P = 0.26). In Bossi 2004 the change in CD4+ cell count from baseline was 29 vs 49 cells/ml (p=0.278) and 63 vs. 75 cells/ml (p=0.510) at 12 and 24 weeks respectively.

Change in mean HIV-RNA concentrations

Results for the change in mean HIV-RNA concentrations are available from two studies (Clevenbergh 2002, Bossi 2004). In both studies results were reported at 12 weeks, after plasma drug concentrations were measured at 4 and 8 weeks and recommendations were implemented where appropriate. Bossi 2004 does further TDM and HIV-RNA assessments, however, from 12 weeks the TDM results are available to both arms of the study. In Clevenbergh 2002 the non-significant changes seen were (-1.7$\log_{10}$ copies/mL) vs. (-2.0 $\log_{10}$ copies/mL) in the TDM plus genotypic testing arm and the genotypic testing arm respectively. In Bossi 2004, the results were (-1.4 $\log_{10}$ copies/mL) and (-1.3 $\log_{10}$ copies/mL) in the TDM and genotypic intervention arm and the genotypic testing arm (P = 0.412). The Clevenbergh 2002 study does not report results of a test for a difference between

TDM and non-TDM groups, or confidence intervals, and therefore results of these two studies could not be combined.

Quality of life indicators

This outcome was not reported in any of the studies.

Proportion of patients discontinuing or switching ARV therapy due to virological failure

Two studies report on this outcome (Fletcher 2002 and Burger 2003). In the Fletcher 2002 study there were 1/16(6%) vs. 4/17 (20%) switches to alternative therapy by 6 months due to virological failure (HIV-RNA < 200 copies/ml) in the TDM and SOC arms, respectively. In Burger 2003 there was a non-significant difference between groups, with 2/69 (3%) vs. 6/78 (11%) stopping due to virological failure at one year of follow-up in the TDM and SOC arms, respectively. This study evaluated participants on nelfinavir- or indinavir-based cART. When analysed by treatment regimen, there was a significant discontinuation for failure in those on nelfinavir-based cART (12% vs. 35% in TDM and SOC group, respectively (P = 0.001)).

Safety outcomes

Proportion of patients discontinuing or switching ARV therapy due to ARV toxicity

Two studies (Fletcher 2002 and Burger 2003) report on this outcome. In Fletcher 2002 equal proportions of participants stopping due to toxicity was reported in the TDM vs. SOC groups respectively, 3/21 (14%) vs. 3/19 (16%), no P-value or confidence interval is provided in the report. Burger 2003 results showed discontinuations due to toxicity were 7/69 (10%) vs. 12/78 (16%), not significantly different between the TDM and SOC groups. There was a trend to significant differences between TDM and SOC resulting in stopping for toxicity in a subgroup of participants on indinavir-based cART (P = 0.07).

Adverse events

Adverse events were described in 4 studies (Fletcher 2002; Bossi 2004; Khoo 2006; Best 2007), there were no statistically significant differences found between the TDM and SOC arms.

Discussion

Summary of main results

Therapeutic drug monitoring of antiretrovirals has been proposed as a means to optimise efficacy of cART while minimising toxicity. A comprehensive search was conducted and 1408 abstracts reviewed for eligibility. This systematic review included 8 randomised-controlled studies evaluating the clinical value of antiretroviral TDM.

TDM in ARV-naïve and experienced participants on PIs or NNRTIs

A meta-analysis of TDM in all participants (ARV-naïve and experienced; on either PIs or NNRTIs) showed no effect on virological outcomes at 52 weeks (RR 1.28 [0.86, 1.92]). There is strong evidence of heterogeneity between studies suggesting that the clinical differences in the participants enrolled in these studies, and the methodological differences in study designs minimise the value of combining these groups.

TDM in ARV-naïve participants

A sub-group analysis was performed to evaluate virological outcomes in ARV-naïve participants only (Burger 2003, Crommentuyn 2005 and Fletcher 2002). No effect of TDM was found at 52 weeks of follow-up (RR 1.28 [0.86, 1.92]). Although participants are clinically similar in these small studies, the drug regimens they were assigned, either NNRTIs or PIs, may differ in utility of TDM. Crommentuyn 2005 was the only trial enrolling participants on an NNRTI-based (nevirapine) regimen. Fletcher 2002 and Burger 2003 included participants on predominantly unboosted PI-based regimens. Despite observational data supporting TDM in this subgroup, heterogeneity suggests they should not be combined in analysis.

TDM in ARV-naïve participants on PIs only

In the subset of antiretroviral-naïve participants on a PI-based regimen, there was a 49% increased likelihood of achieving an HIV-RNA viral load < 500 copies/mL at 52 weeks of follow-up, with low heterogeneity between studies (RR 1.49 [1.2 to 1.83]). The two studies in this analysis included participants on predominantly unboosted PI-based therapy, including indinavir or nelfinavir. However, nelfinavir and unboosted indinavir have fallen out of favour in clinical practice, largely due to alternative agents with better efficacy and tolerability, and the introduction of ritonavir boosting of PIs (IAS-2008, WHO 2006).

Ritonavir, when added in a small dose to PI-based cART, slows the metabolism of the associated PI thereby increasing its potential therapeutic drug concentration. Boosted PIs offer the advantage of simpler dosing regimens and improved efficacy (Flexner 2000). Torti 2005 supports this in his trial of antiretroviral-experienced participants, where use of boosted-PIs was an independent predictor of virological success.

TDM in ARV-experienced participants

In this review three studies included participants who had been exposed to multiple prior ARVs (Clevenbergh 2002; Bossi 2004; Torti 2005). Two studies (Bossi 2004, Clevenbergh 2002) were clinically and methodologically similar and could be included in meta-analysis. No significant virological effect of TDM vs. SOC was found at 12 weeks of follow-up (RR 0.93 [0.73, 1.17]). The included studies had short follow-up periods of 12 weeks. HIV virological responses are unlikely to be seen within this short interval, and therefore this does not reflect a clinically meaningful period in which to assess virological outcomes.

The studies were conducted in France, where national guidelines support the use of routine TDM as their accepted SOC. Therefore, despite clinical equipoise because of lack of evidence, it was deemed unethical to withhold TDM in these patients for longer than 12 weeks. This reveals the difficulty of studying TDM in countries already incorporating this intervention into their HIV management.

In these studies, TDM was performed at 4 or 8 weeks after randomization and a recommendation implemented 4 weeks later. A concern with this study design is that participants with sub-therapeutic drug concentrations for 4 weeks may already be accruing HIV resistance mutations (Deeks 2003, Jackson 2000).

In this analysis, the ARV-experienced participants may have extensive previous exposure to several classes of ARVs resulting in high-level resistance. This makes choices regarding therapy challenging. Salvage therapy for these patients may be guided by viral resistance testing. In these trials, all participants received HIV resistance testing at baseline, either genotype testing or virtual phenotype testing, and were subsequently randomised to TDM vs. SOC. In ARV-naïve people on ritonavir boosted-PIs evidence supporting TDM is uncertain, as the drug concentrations achieved far exceed that required to inhibit 50% of susceptible HIV viral replication (IC_{50}) (Flexner 2000, Murphy 2001). However, in this subgroup, with resistant virus, higher drug concentrations are required to inhibit viral replication, and there may be benefit of TDM if appropriate target plasma ARV concentrations are attained and resistance overcome (Back 2006).

Target ARV concentrations for this subgroup requiring salvage therapy are poorly delineated (Boffito 2005). This may complicate results of studies in salvage therapy, where incorrect reference ranges were applied and participants managed inappropriately. Future research addressing target therapeutic ranges for this subgroup may guide more accurate evaluation of TDM.

Finally, regarding this subgroup, there is growing interest in integrating information from drug concentration measurements and resistance testing, referred to as the genotypic inhibitory quotient (GIQ) or phenotypic inhibitory quotient (PIQ). To date there are no prospective randomised studies of these interventions to guide current HIV salvage therapy management (Durant 2000, Boffito 2005). An ongoing study in this area will be incorporated into the future update of this Cochrane review (Demeter 2008).

Challenges to assessing ARV TDM

ARV efficacy and under-powered studies

Combination ART is an effective intervention for the management of HIV, and therefore add-on therapies or interventions would require large, adequately powered studies to demonstrate benefit. Khoo 2006 describes that two-thirds of the heterogeneous cohort enrolled in the POPIN study were already virologically suppressed at baseline. This is reflected by other published cohorts (Ledergerber 1999; Paredes 2000). TDM may only be expected to contribute marginally to outcomes of ARV therapy. Therefore it is anticipated that large, adequately

powered studies are required to evaluate efficacy and safety. In Khoo 2006, a power calculation for sample size is presented. It proposes that 1000 patients (500 per arm) will be required to reach a mortality endpoint if the uptake of expert recommendations regarding TDM is at 75%. Alternatively, a total of 1720 participants are required if there is poor uptake of recommendations, around 35%. Sample sizes in this review ranged between 40 and 230 participants.

Optimal timing for TDM sampling

At the time of recruitment for all included studies there were limited guidelines regarding the best method and timing for measuring drug concentrations. Trough concentrations, taken close to next dosing time; sparse sampling - measuring several samples around the time of a dose or intensive serial sampling, were all considered possible approaches for TDM.

Studies in the review also incorporated varying target therapeutic ranges for the same drugs, creating a heterogeneous group to compare in meta-analysis. The first TDM guidelines were presented in 2003 (Back 2003) with a further update in 2006 (La Porte 2006). The recommendation for measuring trough samples is suggested (efavirenz is an exception as mid-dosing concentrations are recommended). The trough sampling approach is supported by empirical *in vivo* and *in vitro* evidence, and is simpler to introduce in a busy clinic setting.

The guidelines for use of TDM provide target plasma concentrations of the various antiretrovirals based on current best evidence. There is pharmacokinetic and pharmacodynamic data underlying the target ranges in antiretroviral-naïve participants. However, in antiretroviral experienced where there may be multiple resistance mutations and limited choices of antiretrovirals, target ranges are still poorly delineated (Back 2006).

Uptake of expert TDM recommendations

A limitation of the studies to date is the apparent poor uptake of expert recommendations by treating clinicians. An intervention was recommended in approximately 20 - 35% of participants across studies; however, high-level implementation was described only in Best 2007 (76%) and Clevenbergh 2002 (71%). Low uptake of the intervention results in bias, as the true effect of TDM cannot be assessed in the absence of the advice being implemented.

There are multiple potential reasons for poor physician adherence to advice. There is a need to evaluate patients holistically, changes to therapy based on a laboratory result alone, may undermine the assessment made by an experienced clinician. In particular, despite low or high drug concentrations, the participant may be clinically well, virologically suppressed and not experiencing adverse effects, and therefore it is inappropriate to implement a change in therapy. Other explanations include participants' refusal to alter dose; and the finding that adherence was enhanced in concentration-controlled groups, simply by highlighting their low drug measurements, and therefore dose adjustments were not necessary (Torti 2005).

The high uptake of recommendations in two studies may reflect the manner in which the advice was given. Best 2007 incorporated extensive clinical information into the process, aiming to optimise overall patient care, not simply responding to a single drug concentration result.

Adherence

Adherence to ARV therapy

An obstacle to investigating the clinical utility of TDM is knowledge of participants' adherence to their prescribed therapy. A sub-therapeutic TDM concentration may indicate poor adherence in the days immediately preceding sampling. A recommendation to alter ARV therapy based on a low concentration should have a means of assessing drug adherence at the time of blood sampling (e.g. pill count, pharmacy refill, electronic monitoring). Dose adjustments made in the face of unidentified poor adherence may put the patient at risk of increased drug concentrations and hence toxicity. Further, these circumstances will compromise the true evaluation of TDM.

Adherence monitoring in the review

Adherence assessments varied between studies. Best 2007 included validated electronic tablet bottles that capture and centrally record the number of times the medicine container is opened (MEMS - Medication Event Monitoring Systems, *Aprex*). Adherence questionnaires were used in three trials, whereas there was no description of adherence monitoring in three studies.

Generalisability of results

These trials were conducted in higher-income earning settings in Western Europe and America. These countries differ considerably from the communities in sub-

Saharan Africa where the burden of disease is heaviest. Access to health-care in many African countries is constrained by resource-limitations, both technical and financial. This impacts directly on HIV management where basic medicines and monitoring tests (e.g. viral loads and CD4+ counts) may not available. Results of the included studies cannot be generalised to resource-limited countries. Antiretroviral TDM should be studied where HIV prevalence is highest in order to assess its practical applicability where ARV roll-outs are largest and where small improvements in care may have significant impacts on population health.

Potential limitations of this review

Minimising systematic errors in the review methodology

The retrospective design of a review creates the risk of systematic errors in data capturing and the assessment of methodological quality of the studies. Guided by Cochrane methodology standards, a comprehensive, reproducible search was constructed and performed. Independent data extraction by two reviewers was employed to minimise potential bias. It is possible that unpublished literature may not have been captured. Attempts were made to contact each of the authors in the review and enquiries were made regarding further studies that may not be in the public domain. No further studies were identified.

Combining outcomes for meta-analysis

Assessment of heterogeneity between studies is important prior to considering met-analysis. The internal validity of the trials was good, although key aspects of quality, such as allocation concealment were not reported in several studies. Trials differed in terms of included participant populations, durations of follow-up, virological cut-off points and adherence to recommendations, making comparison difficult. Where populations were similar, such as the antiretroviral naïve populations on PIs, good consistency between the two studies was found, as confirmed by the Higgins I^2 statistic.

Virological cut-offs differed between studies, from < 50 to < 500 HIV-RNA copies/mL. The choices of viral load cut-off most likely reflect the timing of protocol development and the technology used in each study. HIV-RNA quantitative testing has evolved and is increasingly sensitive, able to provide values for HIV-RNA < 20 HIV-RNA copies/mL. For the purposes of the meta-analysis, as pre-specified in the protocol, the viral loads indicating virological success were grouped to include all results below 500 HIV-RNA copies/mL. This may be a limitation as there is

evidence that achieving a viral load below 20 copies/mL on ARVs is predictive of longer-term durability of ARV therapy (Raboud 1998, Mocroft 2007). A future review of this topic, given more trials are available, may choose to separate these virological cut-off points for a more accurate result.

Choice of primary outcomes

The primary outcomes chosen for this review include all-cause mortality, HIV-related morbidity and the proportion of participants achieving virological end points. The first two endpoints are not described in any of the included studies. Studies in HIV that do report on these clinical endpoints are often large studies with prolonged follow-up, conducted at great expense. For an intervention such as TDM, they may not be appropriate outcomes to assess and therefore virological outcomes are chosen as surrogate markers of the intervention. HIV viral load is a well validated marker of successful treatment and has been associated with long-term successful ARV therapy (Raboud 1998, Mocroft 2007)

Conclusion

A challenge to health-care practitioners, public health strategists and people taking antiretroviral therapy, is ensuring the durability of life-long HIV therapy. This requires treatment regimens that are accessible and simple to use, with maximal efficacy and minimal adverse drug effects. TDM of ARVs has been proposed as one tool for improving HIV management. Drug concentrations have been recommended for practitioners to individualise appropriate therapy by ensuring that ARV plasma concentrations are neither too low and therefore sub-therapeutic, nor too high and potentially toxic. However, this systematic review found little evidence to support routine use of ARV TDM.

Reviewers' conclusions

Implications for practice

The studies evaluating TDM may be underpowered to assess virological, immunological and safety outcomes. This review does not support routine use of TDM in ARV-naïve patients on either boosted PIs or NNRTIs. TDM in naïve participants on a PI-based regimen, particularly if unboosted, may improve virological outcomes.

Indications for TDM

Routine TDM has little place in clinical practice, however it is critical to identify individual patient categories that will benefit from this intervention. Current TDM guidelines recommend TDM for the following specific clinical indications in which the ARV concentration is expected to fall outside of the therapeutic range (La Porte 2006):

- Significant drug-drug or drug-food interactions
- Patients with alterations in their organ function (e.g. gastrointestinal, hepatic and renal dysfunction)
- Treatment-experienced patients with resistant virus ad possible reduced susceptibility to cART
- Patients with adverse effects that are known to be due to increased drug concentrations (e.g. insomnia with efavirenz)
- ARV-naïve patients with poor response to treatment despite apparent good adherence
- Monitoring adherence
- Patients who are pregnant and paediatric patients

These indications require appropriately powered studies to confirm their role in improving outcomes for patients on ARVs.

Generalisability of results

The studies included in this review were conducted in Western Europe and America and as such do not reflect conditions in resource-constrained environments. The greatest burden of HIV exists in resource poor settings where access to basic HIV-related care, such as ARVs, immunological and virological testing, may not be adequately addressed (Tassie 2003). In these environments, the value of additional TDM has not been evaluated and can therefore not be recommended as a routine intervention. Where TDM is available and accessible, the merits of measuring drug concentrations for specific indications should be balanced against the cost and potential benefit to the individual patient.

Optimising TDM sampling

Clinical practice must be guided by current evidence-based guidelines for the TDM sampling times (i.e. generally trough sampling) and target therapeutic ranges. Where these have not yet been elucidated, there is no value in performing TDM.

Implications for research

1. All of the included studies were underpowered to show outcomes of TDM compared with standard of care, therefore future studies should include larger study populations, with longer durations of follow-up
2. Studies of routine TDM should consider investigating its role in particular patient groups where there is evidence of biological plausibility for its effectiveness (e.g. salvage therapy, paediatrics, concurrent treatment with anti-tuberculosis therapy, pregnancy).
3. There should be close co-ordination between clinicians and expert pharmacologists in TDM to ensure full clinical details are known prior to making recommendations based on TDM and to ensure implementation of these recommendations.
4. It is essential to monitor adherence to antiretroviral therapy (pill counts, 3 or 7 day recall, MEMS).
5. Research should be conducted where the burden of disease is greatest. In resource-limited countries, there are concurrent epidemics (e.g. tuberculosis, HIV and malaria) putting patients at risk of multiple drug-interactions that may benefit from TDM.
6. Sampling times for TDM and the relevant target therapeutic ranges for antiretroviral-naïve and experienced participants should conform to current best evidence.

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Potential conflict of interest

None to declare.

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Appendix 1. Eligibility form

Systematic review of ARV TDM

Study eligibility form _____ (Reviewer ID)

Type of study			
Is the study a Randomised Controlled Trial?	Yes ⇩	Unclear ⇩	No ⇩
	Go to next question		Exclude Study type: ⇨
Trial Intervention			
Was the intervention ARV TDM at least once in people infected with HIV on an NNRTI or PI as part of cART?	Yes ⇩	Unclear ⇩	No ⇩
	Go to next question		Exclude
Trial participants			
Were the trial participants adults?	Yes ⇩	Unclear ⇩	No ⇩
	Go to next question		Exclude
Any other reasons for excluding study? Specify:	No ⇩		Yes ⇩
	Include, subject to clarification of 'unclear' points		Exclude
Final decision	Include	Unclear	Exclude

Appendix 2. Data Abstraction Form

Data extraction form

ARV TDM in HIV – Cochrane review

General identifying information

Study ID _____ Reviewer ID _____ Date _____

Journal (name, year, vol, issue, pgs) Published ☐ Unpublished ☐

_____

_____

Title

_____

_____

_____

Authors

_____

_____

_____

Location of trial (e.g. hosp/ OPD and city/ country etc) Not specified ☐

_____

Setting: high income ☐ low income ☐ unclear ☐

Date of trial: Start / end _____

Duration of study _____

Methodological quality

Risk of bias	Description	Risk (L,M,H)
Selection		
Performance		
Attrition		

Detection		
Reporting		

Randomisation method clear ☐ unclear ☐ not specified ☐

Describe:_____

_____

_____

Allocation concealment

Adequate ☐

i.e Centralized randomization by telephone; randomization schemes controlled by a off site; on-site computer systems which can be assessed after entering the characteristics of an enrolled participant, where allocations are locked on unreadable file, and sequentially numbered, sealed envelopes.

Inadequate ☐

i.e any allocation procedure transparent before assignment (e.g. open list of random numbers, alternation, date of birth, day of week, case record number)

Unclear ☐

i.e. sealed envelopes, but not sequentially numbered or opaque; description suggests concealment, but other features are suspicious (e.g. notable unequal baseline characteristics, randomization stated but no detail given)

Not reported ☐

Blinding yes ☐ no ☐ not described ☐

Describe who was blinded

_____

_____

_____

Follow up

Type_____

_____

Frequency (in weeks)_____

_____

Duration (total) _____

Ethics approval yes ☐ no ☐ unclear ☐

If yes, which REC _____

Informed consent oral ☐ written ☐ not done ☐ not described ☐

_____

_____

Participants

Proposed sample size (if given) _____

Inclusion criteria

_____

_____

_____

Exclusion criteria

_____

_____

_____

Interventions (draw diagram below if desired)

Arm 1 _____

Duration of treatment _____

Arm 2 _____

Duration of treatment _____

Description of outcomes

Primary outcomes

_____

_____

_____

Secondary outcomes

_____

_____

_____

Baseline characteristics		
Number recruited	n=	Unclear
Number randomised		
	Arm 1	Arm 2
Intervention		
Total number included in ITT		
Male n(%)		
Female n(%)		
Age Mean (SD) Median (IQR)		
Weight (SD) BMI		
WHO stage		
CDC stage		
Prior AIDS (%)		
Baseline CD4 (cells/mcL)		
Baseline viral load (log copies/mL)		
Duration on ARVs		
Previous Rx hist		
ART Naïve (%)		
ART exp. (%)		
Drug [] measured PI NNRTI		

Outcomes		
	Arm 1	**Arm 2**
ARV [name]		
Intervention		
PRIMARY		
Death (all cause)		
New HIV events (death or AIDS defining illness)		
Prop achieving and		

maintaining LDL		
SECONDARY		
Change in mean CD4 cell count		
Change in HIV-RNA concentrations		
QOL indicators		
Prop stopping or switching due to viral failure		
SAFETY		
Prop stopping or switching due to toxicity		
Any adverse effects (give detail below)		

Details of other relevant papers cited

Additional information required from authors