Stavudine 20 mg BID or less versus stavudine 30 mg BID or more as a component of combination antiretroviral therapy for HIV infection

A Systematic Review

16 December 2009

Author
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Abstract

Background

Stavudine (d4T) continues to play a critical role in the scaling-up of combination antiretroviral therapy (ART) in low- and middle-income countries (LMIC). Initially, d4T generally is well tolerated. However, it causes cumulative mitochondrial toxicity (lipoatrophy, peripheral neuropathy, and lactic acidosis), which is of concern to people living with HIV (PLHIV) and to care providers, and is particularly troublesome for long-term management. Newer, patient friendly but currently more expensive ART regimens are available.

Since 2006, WHO has not recommended d4T as a preferred first-line ARV. The revised WHO guideline Antiretroviral Therapy for HIV Infection in Adults and Adolescents released as Rapid Advice in 2009 reaffirmed zidovudine or tenofovir as preferred ARVs in first-line regimens. Currently, however, d4T is included in 57% of first-line regimens in LMIC.

These less toxic but more expensive first-line ARVs need to be phased-in as they may not be feasible or affordable in many LMIC with less developed health systems, limited laboratory capacity, finite budgets and competing health priorities. Stavudine remains an inexpensive drug and its interim use may help current treatment programs to move forward, preserving and increasing access to PLHIV most in need and stretching a finite health budget. It may be considered as a suitable alternative drug when other drugs are not safe or available.

To inform policy makers whether a lower d4T dose than currently recommended is efficacious and appropriate, it is necessary to know if a reduced dose can result in suppression to and maintenance of viral load at an undetectable level and lessen mitochondrial toxicity.

Objectives

The primary objective of this systematic review was to assess the virological efficacy of doses of d4T of 20 mg BID or less compared to a dose of 30 mg BID.

Search methods

We developed a comprehensive electronic search strategy to identify all relevant, published studies on the efficacy of d4T at doses of 20 mg BID or less since 1995. We searched relevant conference proceedings to capture any relevant, unpublished data that might influence the recommendation. The references of published articles were hand searched for additional materials.

Selection criteria

Randomized controlled trials were selected. Titles, abstracts and descriptor terms from the searches were read. Full text articles were obtained for studies identified as potentially eligible for full review. These articles were inspected to establish their relevance in accordance with the review question. Four completed, randomized, controlled trials were identified for review.

Data collection and analysis

Data from the studies were extracted into a standardized data extraction form developed for this review.

Results

Four trials involving 8 381 participants were included. One study (McComsey) directly addressed the question regarding the efficacy of low-dose d4T, the others indirectly, and the evidence was of low quality (GRADE evidence profile). Data from two of the trials (McComsey and Ruxrungtham) were included in meta-analysis of viral load response. Low-dose d4T did not negatively impact achieving or maintaining undetectable viral load. One study (McComsey) found no difference between baseline and week 48 median CD4 count and another (Ruxrungtham) found a better CD4 response from those taking low-dose d4T but could not ascribe the dose of d4T to the CD4 response. One study (Petersen) reported adverse events in relationship to d4T dose. In this study, more peripheral neuropathy was reported with higher doses of d4T. Petersen also reported that disease progression was not associated with d4T dose. In the four studies, there were no reports of mortality associated with the dose of d4T. In the studies reviewed, meta analysis was not possible to assess the relationship between d4T dose and adverse events or mortality.

Authors’ conclusions

A dose of d4T 20 mg BID is not associated with loss of virological control and does not adversely affect CD4 count. In addition, data from these studies suggest a reduction of d4T-related adverse events and a lower rate of mitochondrial toxicity when using this low dose. The scarcity of available data and low quality of evidence suggest that these results should be interpreted with caution. Further clinical research is needed to examine the efficacy and safety of d4T 20 mg BID.
Plain language summary
Can doses of d4T lower than the current recommendations maintain viral efficacy while reducing side-effects?

Stavudine (d4T) is a potent antiretroviral drug commonly used in first-line combination therapy to treat HIV infection. Especially at higher doses, d4T has the potential to cause significant and potentially life-threatening adverse reactions, such as lactic acidosis, lipodystrophy, and peripheral neuropathy. Most industrialized countries no longer recommend d4T as an option in first-line antiretroviral therapy (ART). However, in many low- and middle-income countries (LMIC), d4T remains an important component of first-line ART. Many LMIC have decided on the progressive reduction in the use of d4T, but this is expected to take many years. To guide these countries, it would be useful to know if lower doses of d4T can be shown to achieve and maintain viral efficacy while reducing the incidence and intensity of known adverse reactions. A reduction in adverse events has the potential to increase adherence and reduce loss to follow-up.
Background

The World Health Organization (WHO) recently reported that approximately four million HIV-infected individuals in low and middle income countries (LMIC) were on antiretroviral treatment (ART) at the end of 2008. [WHO 2009] This report included data from 127 countries. This pace of scale up has been made possible by WHO’s public health approach that promotes standardized and simplified protocols, the use of fixed dose antiretroviral combinations (FDC) where possible, through decentralized services, and the shifting of less specialized tasks from physicians to other trained healthcare workers. [Gilks 2006] This approach was implemented to facilitate access to ART to the largest number of HIV-infected patients, and to slow the transmission rates of HIV. However, in 2007, there were 2.7 million new HIV infections and 6.7 million HIV-infected individuals still needing treatment. [UNAIDS 2008; UNAIDS 2008a]

Stavudine (d4T) is a synthetic thymidine nucleoside analogue active against the human immunodeficiency virus (HIV). Stavudine inhibits mitochondrial DNA polymerase of adipocyte tissue, heart, nerve, liver and pancreatic cells, [Makinson 2008] and this inhibition causes cumulative toxicity resulting in lipoatrophy, peripheral neuropathy (PNP), cardiomyopathy, lactic acidosis, and pancreatitis. [Subbaraman 2007; McComsey 2004] However, d4T has played a critical role in the scaling up of combination ART in LMIC. Currently, approximately 57% of HIV regimens in LMIC contain d4T. [WHO 2009a] It is a low-cost medication and is available in double- and triple-combination FDCs. Stavudine does not require administration with food or large amounts of liquids, requires limited or no laboratory monitoring, and has high initial adherence rates due to good gastrointestinal tolerance. Other nucleoside reverse transcriptase inhibitors (NRTI), such as tenofovir (TDF) and zidovudine (AZT), require more laboratory monitoring and have higher discontinuation rates when initiating therapy. [Gallant 2004; Gallant 2006]

Description of the condition

Stavudine dosing originally was recommended at 40 mg BID for body weight >60 kg and at 30 mg BID for body weight <60 kg. [BMS 1998] The prescribing information also recommended to halve each of these doses in the presence of adverse events, or to stop the medication for a period and to reintroduce it at the lower dose. Following a 2006 systematic review, WHO amended its guideline and recommended the use of d4T at a dose of 30 mg BID regardless of body weight. [WHO 2006] It is unclear whether doses lower than 30 mg BID can retain efficacy or impact the frequency and severity of adverse events. A lower dose of d4T may be a valid option in countries where reduction in the use of d4T will be progressive, including those with limited access to alternatives, limited laboratory capabilities, and as a back-up option in the presence of treatment-limiting toxicity due to AZT or TDF.

Description of the intervention

Doses of d4T of 20 mg BID or lower.

How the intervention might work

By taking lower doses of d4T, people living with HIV (PLHIV) may be able to tolerate an antiretroviral regimen that maintains virological efficacy with the potential to reduce mitochondrial toxicity or life-threatening adverse events that can result from higher doses of d4T. Reducing these adverse reactions has the potential to impact positively on adherence and reduce loss to follow-up.

Why it is important to do this review

To decide whether WHO Antiretroviral Therapy Guidelines for Adults and Adolescents can recommend the prescription of a lower than the currently recommended dose of d4T (30 mg BID regardless of weight), it is necessary to know if a reduced dose can result in suppression to and maintenance of viral load at an undetectable level. A secondary research question is whether a reduced dose of d4T is associated with fewer severe adverse events. Finally, reducing the dose of d4T may also reduce the cost and promote the production of new FDCs containing 20 mg of d4T.

WHO has recommended that countries plan for a progressive reduction in the use of d4T in first-line regimens. In the interim, countries where abrupt d4T phase-out risks compromising access to and/or scale-up of first-line ART, reducing the dose of d4T may be a useful option. [WHO 2009b]

Objectives

The primary objective of this systematic review was to assess the virological efficacy (measured by changes in CD4 count from baseline) of doses of stavudine of 20 mg BID or less compared to a dose of 30 mg BID.

The secondary objectives were to assess the immunological efficacy and the incidence of serious adverse events of doses of stavudine of 20 mg BID or less compared to a dose of 30 mg BID.

Methods

Criteria for considering studies for this review
Types of studies
Randomized, controlled clinical trials.
Observational studies (cohort and case-control) were not evaluated as a sufficient number of randomized, controlled trials (RCT) were identified.

Randomized, controlled trials that compare standard doses of d4T with reduced doses of d4T in treatment naive individuals initiating antiretroviral therapy provide the best evidence to determine if a reduced dose of d4T can achieve and sustain virological suppression. Systematic reviews and meta-analysis addressing interventions of interest were reviewed.

Types of participants
Adults and adolescents (15 years and older) with human immunodeficiency virus (HIV). As the numbers of RCTs in ART-naive individuals were few, data from RCTs that have enrolled treatment-experienced individuals were included in this review.

Types of interventions
Treatment with stavudine (d4T) 20 mg BID (or lower) of ART naive or pre-treated individuals, as compared to d4T 30 mg as monotherapy or as part of combined antiretroviral therapy (ART).

Types of outcome measures
Primary outcomes
Treatment response (undetectable viral load as defined by the study protocol), mortality and disease progression (CDC AIDS-defining events or as defined by the study protocol).

Secondary outcomes
Treatment response (changes in CD4 count from baseline) and treatment-limiting or serious adverse events (as defined by the study protocol).

Search methods for identification of studies
We developed a comprehensive search strategy in an attempt to identify all relevant, published studies on the efficacy of d4T at doses of 20 mg BID or less. Studies were reviewed for relevance, based on the inclusion/exclusion criteria. Irrelevant reports were discarded, and the fully published articles obtained for potentially relevant reports. We limited the date of publication year to 1995 onwards as this was the year that the parallel-track program for stavudine was launched in the United States.[Anderson 1995]

Systematic reviews and meta-analyses addressing interventions of interest were reviewed in detail.
The searches were performed without limits to language or setting.

We searched relevant conference proceedings from the Conferences on Retroviruses and Opportunistic Infections (CROI), International AIDS Conferences, International AIDS Society Conferences on HIV Pathogenesis, Treatment, and Prevention, and HIV/AIDS Implementers Meetings.

In addition, we contacted individual researchers, experts working in the field and authors of studies to ascertain if there were any newer data available for relevant cohorts and to address whether any relevant manuscripts are in preparation or in press. No new information was identified.
The references of published articles were hand searched for additional pertinent materials.

Electronic searches
The following databases were searched on 26 October 2009.

Medline/PubMed
This search was conducted 26 October 2009.

This yielded 12 studies from which we identified 6 abstracts for review.

The search strategy used was:

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This search was conducted on 26 October 2009.
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**EMBASE**

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This yielded 31 studies of which we identified 6 abstracts for review.

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**Cochrane Central Register of Controlled Trials (CENTRAL)**

This search was conducted 26 October 2009. This search did not reveal any different studies for review.

**Searching other resources**

Conference abstracts were searched using NLM gateway, eJIAS Conference Abstract Finder, and specific conference data bases, such as The International AIDS Society (IAS), the Conference on Retroviruses and Opportunistic Infections (CROI), the HIV/AIDS Implementers’ Meeting and the European AIDS Conference (EAC).
We searched the following databases to identify ongoing trials:

- ClinicalTrials.gov (http://clinicaltrials.gov/)
- Current Controlled Trials (www.controlled-trials.com/)
- Pan-African Clinical Trials Registry (www.pactr.org)

**Data collection and analysis**

**Selection of studies**

The titles, abstracts and descriptor terms of all downloaded material from the searches were reviewed. Full text articles were obtained for studies identified as potentially eligible for full review. These articles were inspected to establish their relevance in accordance with the review question.

**Data extraction and management**

Data from the studies were extracted into a standardized data extraction form developed for this review. The following characteristics were extracted and recorded from each of the included studies:

- Administrative details; trial identification, authors, published or not, year of publication, year study was conducted, and the details of any relevant papers referenced.
- Details of the study: study design, type, duration and completeness of follow-up, country and location of study, ethical considerations including informed consent and ethical approval.
- Details of participants: age, numbers, and relevant baseline characteristics, including demographic data, CD4 count and viral load measurements.
- Details of intervention: doses of stavudine and arms of the study.
- Details of outcomes: mortality, HIV disease progression, treatment response (changes in CD4 count and undetectable VL from baseline, as defined by the authors), and serious adverse events or toxicities.

**Assessment of risk of bias in included studies**

The components of each included trial were examined for bias using a standard form developed for this review. The methodological components of the trials were assessed and classified as adequate, inadequate or unclear. The GRADE approach for quality of evidence was applied and is presented where relevant and possible in summary tables.[Guyatt 2008] The GRADE approach assesses risk of bias in individual studies across five domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential biases.

The quality of evidence was assessed with the GRADE approach, defining the quality of evidence for each outcome as, “the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest”. [Higgins 2008] The quality rating across studies has four levels: high, moderate, low or very low. Randomized trials are categorized as high quality but can be downgraded; similarly, observational studies, which are initially classified as low quality, can be upgraded. Factors that decrease the quality of evidence include limitations in design, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, or high probability of publication bias. Factors that can increase the quality level of a body of evidence include a large magnitude of effect, if all plausible confounding would reduce a demonstrated effect and if there is a dose-response gradient.

**Measures of treatment effect**

Treatment effect was assessed based on the outcomes of interest. The outcomes for this review were treatment response as assessed by virological suppression and changes in CD4 cell count from base line as well as death, disease progression and serious adverse events. For dichotomous data, we calculated the overall measure of effect as a relative risk, with 95% confidence intervals, using the random effects model. We used an intention-to-treat analysis (analysing participants in their originally randomized groups, and using the initial number of randomized participants per group as the denominator). We analysed continuous data using the mean difference and standard deviation. Where the mean difference and standard deviation were not available from the publication, they were calculated from the median and interquartile range using the methods described by Hozo, which they developed for meta-analysis.[Hozo 2005]

**Unit of analysis issues**

Review Manager 5 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) was used to analyse and present results with 95% confidence intervals. Data are presented using GRADEProfiler 3.2.2
(GRADE Working Group 2004-2007), and GRADE Quality Assessments and Summary of Findings Tables have been generated. [GRADEpro]

**Dealing with missing data**

All relevant data were available from the publications.

**Assessment of heterogeneity**

Statistical assessment for heterogeneity was performed for two of the studies, pooling data for VL responses. Using Risk Ratio (RR) (Maentel-Hanzel, random effects analysis, 95% CI), the tests indicated that there was no heterogeneity in pooling the VL data ($\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 0.58$, df = 1 ($P = 0.45$); $I^2 = 0$%). McComsey reported only that there was no change from baseline in the median CD4 response so changes in CD4 could not be pooled with data from the Ruxrungtham study.

**Assessment of reporting biases**

Due to insufficient data, a formal assessment of reporting biases, by looking for asymmetry in a funnel plot of the standard error plotted against the risk ratio measured on a logarithmic scale, was not possible. In an attempt to minimize reporting bias in this review, multiple sources were searched as described above. Further, unpublished material from conference presentations and other material such as letters to the editor and short communications were reviewed. Three of the included studies were undertaken before the establishment of compulsory trial registries and so the reported outcomes could not be compared with registration details. No unpublished studies were identified.

**Data synthesis**

Meta-analysis was performed for two of the studies to examine VL response. Pooled estimates of relative risks (RR) for dichotomous data and mean difference for continuous data were performed.

GRADE Summary of Findings tables and profiles are presented.

**Subgroup analysis and investigation of heterogeneity**

There were no a priori subgroups of interest.

**Sensitivity analysis**

Sensitivity analysis was not performed.
Results

Description of studies

Of the 22 papers selected from the searches for abstract review, six completed, randomized, controlled trials were identified as meeting the inclusion criteria for this review. Two of these subsequently were rejected (see Excluded Studies). Full details for each study are provided in the Tables of Included Studies.

Included studies

McComsey 2008 was a randomized, controlled trial in the USA that evaluated the toxicity and safety of reduced dose d4T. This trial enrolled 24 participants (79% males and 79% African American, with a median age of 45 years). Included participants were HIV-infected, receiving standard dose d4T with undetectable VL for greater than 6 months. Nine participants were randomized to receive the same dose (continuation arm, 40 mg BID if over 60 kg and 30 mg BID if less than 60 kg) and 15 participants were randomized to receive one-half of the original stavudine dose (switch arm, 20 mg BID if over 60 kg and 15 mg BID if less than 60 kg). Outcomes measured were: fasting lactate, pyruvate, and lipid levels; results of whole-body dual-energy x-ray absorptiometry, and mitochondrial DNA measurements in fat and peripheral blood mononuclear cells. Change from baseline to week 48 was compared within and between groups.

Anderson 1995 was a randomized, double-blinded industry-sponsored study to evaluate the safety and efficacy of two weight adjusted dose levels of d4T monotherapy in patients with advanced HIV infection. All participants were either refractory or intolerant of both AZT and ddl. A total of 8127 participants were included, a majority of whom were from large metropolitan areas in the US (95% men, 85% white). Participants who weighed over 60 kg received 20 or 40 mg BID, those who weighed between 40 and 59 kg received 15 or 30 mg BID, and those who weighed less than 40 kg received either 10 or 20 mg BID. The primary efficacy endpoints were survival and time to clinical progression of HIV, while dose-limiting neuropathy was the primary safety endpoint.

Petersen 1995 was a dose-ranging study evaluating the activity of d4T after 10 weeks of therapy and safety after one year of therapy. It included 152 HIV-infected patients in a randomized, open-label trial and evaluated the effect of three different doses on CD4 count, weight gain, and other haematological variables. This trial compared three doses of d4T: 0.1 mg/kg (n=51), 0.5 mg/kg (n=53), and 2.0 mg/kg (n=48). Participants were predominantly from large metropolitan cities in the US (66% white, 87% male, with a median age of 36 years). Stepwise regression models to adjust for differences in baseline characteristics, to select covariates for adjustment of risk estimates, and square root transformation used for CD4 count to stabilize the variance were used to eliminate possible statistical bias.

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1 Peripheral neuropathy requiring narcotic analgesia, or repeat episodes of moderate neuropathy requiring nonnarcotic analgesia.
Ruxrungtham 2000 was a prospective, open-label, randomized study based in Thailand that assessed the safety and efficacy of combinations of different doses of ddI and d4T. Seventy-eight treatment-naive patients were randomized to one of five treatment arms containing either ddI monotherapy or a combination of low or high dose ddI (200 mg BID or 400 mg BID) and low or high dose d4T [20 (15) mg BID or 40 (30) mg BID] for 48 weeks (the numbers in round brackets are the weight adjusted doses for patients ≤60 kg).

Excluded studies

Two studies, one RCT (Pollard 1999) and one observational study (Pedrol 2007), initially were selected for review and later rejected. The Pollard study included 94 participants but there was a very high (58%) drop out. The Pedrol study was a retrospective review of 982 patients. As potential biases are likely to be greater for non-randomized studies compared with randomized studies, and there was no explicit method with respect to inclusion criteria, selection bias and reporting bias, it was decided not to include this study in the analysis.

Risk of bias in included studies

Details for risk of bias are shown in the Risk of Bias tables (Figure 2 and Figure 3) show graphical representations of the risk of bias for the four studies.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Figure 3 Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.
**Allocation**
All four studies demonstrated adequate sequence generation and allocation of randomization, generally by computer and isolated from the clinical context. Two of the studies, McComsey and Ruxrungtham did not provide adequate information regarding allocation concealment. Both of these studies were open-label and so it is assumed that the allocation was known, but it is not believed that this was a source of serious bias.

**Blinding**
Three of the studies were open-label and so there was no blinding to treatment allocation. The Andersen study was double-blinded but details of blinding were not given. All studies were marked down for possible bias due to non-blinding.

**Incomplete outcome data**
Three of the studies demonstrated that outcome data were reasonably complete and handled correctly. Attrition rates were low in each of the studies. The Anderson study was closed early for safety concerns in the high-dose arm. This may have contributed to the risk of bias as no data were presented for results or outcomes.

**Selective reporting**
Anderson presented scant data for results and outcomes and so it is possible that there is considerable risk of selective reporting bias in this study. The other studies seem free from reporting bias. Full statistical descriptions were presented. Ruxrungtham's analysis was intention to treat.

**Other potential sources of bias**
Anderson and Petersen were industry sponsored studies undertaken before stavudine was approved and marketed. This has the potential for bias. The other two studies declared some support from industry but it was not considered that this sponsorship would have contributed to bias.

**Effects of interventions**
Results were not available for all outcomes of interest.

**McComsey 2008** After 48 weeks, the median CD4 count in both arms remained unchanged from baseline. Six (4 of the 15 participants in the switch arm, and 2 of the 9 participants in the continuation arm) had a detectable viral load. However these 6 patients did report significant lapses in adherence, averaging less than 80% adherence compared to greater than 90% adherence for those participants who maintained virological control. Reducing d4T dose by half increased fat mtDNA and decreased lactate suggesting improvement in mitochondrial indices while preserving HIV virologic suppression in subjects who maintained adherence. A significant loss of bone mineral density (BMD) was seen in patients on standard-dose d4T but not in those on low-dose. Despite small numbers, this trial was significant. The results suggest that for those patients who were more than 90% adherent, switching to low-dose d4T may improve mitochondrial indices while maintaining virologic suppression.

**Anderson 1995** There was a paucity of data reported from this study. The data safety monitoring board stopped this study as there was a higher incidence of neuropathy in those receiving d4T high-dose (21% vs. 15%) and equivalent survival was seen in both arms (79%).

**Petersen 1995** Sustained improvement in CD4 counts was seen primarily with 0.5 mg/kg and 2.0 mg/kg dose groups. At this time, viral load analysis was not possible. In this trial, peripheral neuropathy was dose related; the 1-year rates were 6%, 17%, and 37% at 0.1, 0.5, and 2.0 mg/kg/day, respectively, with a statistically significant difference in frequency across groups (P=0.004). Peripheral neuropathy resolved within 1 to 9 weeks after interruption of d4T in 15 of 27 patients. The median time to resolution was 1.0, 1.4, and 3.0 weeks at 0.1, 0.5, and 2.0 mg/kg/day, respectively. Fifty-four participants permanently discontinued therapy with no significant relationship to dose (RR 1.12, P=0.85). There were 22 AIDS-defining events (with 3 deaths). In a stepwise Cox regression model, dose was not a significant predictor of time to AIDS-defining event or death (RR 0.80, P=0.48). Dose related peripheral neuropathy was the reason for first dose modification in 2%, 11%, and 21% of patients at 0.1, 0.5, and 2.0 mg/kg/day, respectively. The median times to first dose modification for any reason were 50 weeks at 0.1 mg/kg/day, 29 weeks at 0.5 mg/kg/day, and 21 weeks at 2.0 mg/kg/day, respectively. The authors concluded that the data demonstrated that the most favourable risk-benefit ratio in this trial was the d4T dose of 0.5 mg/kg/day.

**Ruxrungtham 2000** At 48 weeks, after logistic regression that excluded the ddI monotherapy arm (as these patients had d4T added at week 22), 68% in the d4T combined low-dose arms had viral load <500 copies compared to 50% in the combined high-dose arms (OR 0.48, CI 0.17-1.33). No evidence was found to indicate that the d4T dose (low or high) was related to the viral load outcome. A similar regression model of CD4 treatment response found that the CD4 count increased from baseline by a median of 135 cells in the combined
Data and analysis

Comparison: Low-dose d4T vs. high-dose d4T

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<td>Risk Ratio (M-H, Random, 95% CI)</td>
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<td>1.2 CD4 response</td>
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<td>63</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
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Primary outcomes

Treatment response viral load (detectable viral load as defined by the study protocol)

We pooled the data for two of these studies, McComsey and Ruxrungtham. We found that in the high-dose d4T group, the risk of virological failure was 0.71 (95% CI 0.40 to 1.225) compared to the low-dose d4T group [the risk of virological failure in the low-dose d4T group was 127 fewer per 1000 (from 263 fewer to 110 more), $\chi^2$ 0.58, df=1, $P=0.45$]. The number of participants and the number of events were very small and the results cannot be reliably interpreted. However, after logistic regression, no evidence was found that might indicate that the d4T dose (low or high) was related to the viral load outcome.

![Figure 4](https://example.com/figure4.png)

Figure 4 Forest plot of comparison: Low-dose vs. high-dose d4T, outcome: VL detectable

Disease progression

Anderson and McComsey did not present any data related to HIV disease progression. Petersen reported 22 AIDS-defining events according to the 1987 CDC definitions in use at the time of the study (including the 3 deaths). In a stepwise Cox regression model, d4T dose was not a significant predictor of time to AIDS-defining event. Ruxrungtham reported one case of extra pulmonary tuberculosis in the ddI monotherapy arm. The influence of the dosage of d4T on HIV disease progression cannot be ascribed.

Mortality

Anderson and Ruxrungtham did not present any mortality data. McComsey reported one death in the low-dose arm that was not study related. Petersen reported three deaths, one from each arm, but the relationship to study medication was not elucidated. It was not possible to analyse these events and the influence of the dosage of d4T cannot be ascribed.

Secondary outcomes

Treatment response CD4 (changes in CD4 count from baseline)

McComsey reported that after 48 weeks, the median CD4 count remained unchanged from baseline in both high- and low-dose d4T arms. Ruxrungtham reported that CD4 count increased from baseline by a mean of 135 cells (converted from the median of 135 cells) in the combined low-dose arms compared to a mean increase of 108 cells (converted from the median of 97 cells) in the combined high-dose arms ($P=0.00001$). Despite this difference, logistic regression did not identify evidence to indicate that the d4T dose (low or high) was related to the CD4 increase.
Discussion

Summary of main results

These four randomized, controlled trials provide low evidence that using a regimen of 20 mg BID of d4T (lower than the current WHO-recommended dose of 30 mg BID) does not adversely affect viral load outcomes or CD4 count response, and may reduce adverse effects. Only two of the studies were amenable to meta-analysis and only for the outcome of virological response. The data are limited and the numbers involved are small so the evidence should be interpreted with caution. The data mainly are from well-resourced settings, except for the Ruxruntham data, which are from Thailand, a middle income country. The participants from this trial were all Asian and half were female. Most of the participants from the other three trials were white and male.

Overall completeness and applicability of evidence

These four trials had different aims. Only McComsey was designed to examine a reduced dose of d4T of 20 mg BID, and this study aimed to investigate the effect of low-dose d4T on metabolic parameters. However, VL and CD4 response were examined and reported. Of the two industry-initiated trials from 1995, both were in the context of d4T monotherapy. One trial enrolled ART-naive patients and the other enrolled ART-experienced and failing patients. Anderson examined safety and efficacy of two weight-adjusted doses of d4T while Petersen aimed to determine an optimally active and well-tolerated dose of d4T. Ruxruntham in 2000 analysed the effects of high versus low doses of d4T as part of a study principally designed to evaluate ddi as monotherapy and in combination with d4T. For these reasons, the evidence must be used with caution and a generalizable recommendation is not possible. However, none of these studies found any virologically or immunologically detrimental effects from the low dose of d4T.

Quality of the evidence

The GRADE evidence profile was low to very low, and the risk of bias for these trials was moderate. All the trials reviewed were open-label. Three of the trials ran their full course and all data were available for analysis (Anderson was stopped due to safety concerns in the high-dose d4T arm and only discussed the process of the stavudine parallel-track program).

Potential biases in the review process

Figure 5 Forest plot of comparison: Low-dose vs. high-dose d4T, outcome: CD4 response

Treatment-limiting or serious adverse events (as defined by the study protocol)

The publications by Anderson and McComsey did not report any serious adverse events. Ruxruntham reported that there were no grade 4 events. Petersen reported that peripheral neuropathy requiring dose modification was the only adverse event that showed a statistically significant difference in frequency (P=0.004) across groups. The rates after 1 year were 6%, 17% and 37% at 0.1, 0.5, and 2.0 mg/kg/day respectively. In this trial, peripheral neuropathy was dose related and resolved after discontinuation of d4T.

Markers of mitochondrial function and metabolic parameters

McComsey reported that at week 48, although there were no significant between-group differences, both median fat-mtDNA and lactate improved in the switch (low-dose) group [+40 (range -49, 261) copies/cell; p=0.02 and -0.27 (range 0.25, -1.2) mmol/L; p=0.01, respectively]. The percent change from baseline to week 48 in fat-mtDNA levels also increased in the switch arm [+67% (-34 to 356); p=0.01]. No changes from baseline in levels of fat-mtDNA or lactate were seen in the continuation arm. At baseline, groups were similar with regards to total and regional body fat and BMD. There was a modest but statistically significant between-arm difference in the physician-generated lipohypertrophy score [median 0 (range -3, 3) vs. 0 (0, 3); p=0.04 in the switch vs. continuation arm]. In the continuation arm, a significant loss of BMD was observed at week 48 [-1.7% (-6.3% to 0.8%); p=0.02], while BMD remained stable in the switch arm [0.0 % (-1.2, 4); p=0.37]. The between-group difference in the change of BMD was significant (p=0.003).

Figure 5 Forest plot of comparison: Low-dose vs. high-dose d4T, outcome: CD4 response
We conducted comprehensive searches of journal and conference databases to ensure that all published and unpublished trials were identified. We did not limit the searches to a particular language. Authors were contacted to ascertain if any newer data were available since publication. All four studies included in the review were randomized, controlled trials. However, potential bias in this review exists as this review was undertaken by one person and the methodological quality of each study was not corroborated by another reviewer.

Agreements and disagreements with other studies or reviews
In general, these results are consistent with other published and unpublished studies.

A randomized, controlled trial [Pollard 1999] that examined various doses of d4T from 10 mg BID to 40 mg BID in combined antiretroviral therapy (cART) concluded that there were no clear dose-related differences among treatment groups with regards to suppression of plasma HIV RNA level, improvement in CD4 count or adverse effects. A retrospective chart review from Spain [Pedrol 2007] that examined the efficacy and safety of a reduced dose of stavudine in HIV-infected patients under immunological and virological stable conditions concluded that the d4T dose did not affect treatment efficacy. This was a large study that included 982 participants. After 6 months of follow-up, 97% of participants had a viral load less than 400 copies/mL (84% had less than 50 copies/mL) and a median increase in CD4 count of 38 cells/mm$^3$.

At the International AIDS Conference in Bangkok in 2004, Siangphoe et al. presented week-96 data on the efficacy and safety of half-dose (15 or 20 mg BID) compared to full-dose (30 or 40 mg BID) d4T and AZT in combination with ddI in 327 Thai HIV-infected patients. [Siangphoe 2004] They concluded that half-dose d4T showed a comparable efficacy compared to full-dose d4T, with no serious side effects. At the 3rd IAS Conference on HIV Pathogenesis and Treatment in Rio de Janeiro in 2005, Urbina et al. presented data from a retrospective chart review on 48 patients who received low-dose d4T.[Urbina 2005] After up to 8 years of follow-up, they concluded that the use of low-dose d4T was effective in achieving virological suppression and was well tolerated.

In a letter to the editor in 2004, data were presented from a retrospective study that analysed the long-term safety and efficacy of a cART containing NVP (200 mg BID), 3TC (150 mg BID) and d4T (20 mg BID, without regard to weight). [Shalit 2004] In this intent-to-treat analysis of 27 ART-naive patients from the USA, after 6 years of follow-up, the median viral load was <50 copies/mL and the median CD4 count was 492 cells/mm$^3$, and increase of 186 cells/mm$^3$ from baseline.

It is of note that a low dose of d4T has been used in HIV-positive patients with HIV-associated nephropathy. A letter to the Lancet reported on the use of d4T 20 mg BID as part of triple therapy with 3TC and NFV.[Wali 1998] The patient had a baseline CD4 of 40 cells/mm$^3$ and a viral load of 906,000 copies/mL. ART was commenced one week before 12 weeks of haemodialysis. Fourteen weeks after stopping dialysis, the CD count was 120 cells/mm$^3$ and the viral load was <500 copies/mL. A Short Communication from 2004 reports data concerning a 40-year-old man who underwent renal transplantation, who had been on a cART of d4T 20 mg/day with 3TC and SQV/r for 15 years.[Hardy 2004] This report states that the therapy was well tolerated; the patient had no opportunistic infections, a viral load of <20 copies/mL and a CD4 count above 700 cells/mm$^3$.

Authors' conclusions
Based on these four RCTs and low-quality of evidence, a dose of d4T 20 mg BID is not associated with loss of virological control, does not adversely affect CD4 count, and is associated with reduced d4T-related adverse events. In addition, McComsey reported that a switch to half dose d4T modestly but significantly improved markers of mitochondrial function but did not have significant impact on body composition. The switch was able to mitigate the loss of BMD seen over time with standard-dose d4T.

Implications for practice
In resource-limited settings, 57% of first-line ART regimens contain d4T. This is because of its low cost, wide availability and despite its toxicity profile. If the use of d4T continues, it is essential to reduce the incidence of side effects while maintaining virological efficacy. This review has shown, albeit with scarcity of data and low quality of evidence, that a dose of d4T of 20 mg BID is not associated with loss of virological control and does not adversely affect CD4 count. In addition, these data support a reduction of severe adverse events when using this low dose.

Implications for research
The scarcity of available data and the low quality of the data suggest that a randomized, clinical trial is required to adequately answer this question. Further research is very likely to have an important impact on the confidence of using d4T 20 mg BID and may change the current estimate.

Declarations of interest
Nil
Characteristics of studies

Characteristics of included studies

**Anderson 1995**

<table>
<thead>
<tr>
<th>Methods</th>
<th>A randomized, double blind, industry sponsored study of 8 months duration, conducted in the USA between October 1992 and July 1993 to evaluate the efficacy of 2 weight-adjusted doses of stavudine monotherapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>8127 severely immunocompromised, AZT-experienced adults in USA (baseline characteristics not presented). All patients were refractory or intolerant to AZT and ddI.</td>
</tr>
</tbody>
</table>
| Interventions | Weight-based doses of stavudine  

- ≥60 kg received either 20 mg or 40 mg BID  
- 40 to 59 kg received either 15 mg or 30 mg BID  
- <40 kg received either 10 mg or 20 mg BID |
| Outcomes | Mortality  ND  
- Disease progression  ND  
- Treatment response undetectable VL  ND  
- Treatment response changes in CD4 count from Baseline  ND  
- Serious adverse events  ND |
| Notes | No reported outcomes other than the study was closed following DSMB review. There was a higher incidence of neuropathy in the high-dose arm (21% vs. 15%), and equivalent survival (79%) was observed in both arms. |

**Risk of bias table**

<table>
<thead>
<tr>
<th>Item</th>
<th>Judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Centralized, computer-generated numbers from the industry sponsor.</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Centralized, computer-generated and randomly determined dose assignments from the industry sponsor.</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Unclear</td>
<td>This was called a double-blind study but details of how medicines were presented are not available. It is not clear whether or not the different doses looked the same.</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>No</td>
<td>Details of any exclusions or attrition were not presented.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>No</td>
<td>Scant data were presented for results and outcomes.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>This was an industry sponsored study. In addition, the study was closed early due to higher neuropathy in the high-dose d4T arm and equivalent survival in both arms.</td>
</tr>
</tbody>
</table>
A randomized, open-label, multi-centre, controlled study of 48 weeks to evaluate the toxicity and safety of reducing the dose of stavudine by half. This was the first RTC to examine a treatment switch to half the standard stavudine dose to alleviate metabolic toxicities in subjects with virological suppression. Randomization was 3:2 - nine continued full dose and 15 switched to half dose.

24 treatment experienced adults in USA, with a median age of 45 years, 79% male and 79% African American, median CD4 558 (207-1698), all with undetectable VL <50 copies (or <75 copies).

Weight-based doses of stavudine < or ≥ 60 kg. Patients were randomized to continue taking 40 mg or 30 mg BID (n=9) vs. switching to 20 mg or 15 mg (n=15).

Mortality 1 (not study related)
Disease progression ND
Treatment response undetectable VL: 4 (27%) of 15 (switch) vs. 2 (22%) of 9 (continuation) lost viral control. (Adherence for these 6 was <80% measured by pill count vs. >90% for those maintaining virological control.)
Treatment response changes in CD4 count from baseline: There was no change in the median CD4 count between baseline and week 48 (no details).
Serious adverse events ND
3 were lost to follow-up, including 1 death

This trial was significant as it showed, for those patients who were more than 90% adherent, and who had stable virological suppression, half-dose stavudine was equally as efficacious as the full dose while improving mitochondrial toxicities.
Petersen 1995

Methods
A randomized, open-label, dose-ranging, multi-centre, industry sponsored study to evaluate the efficacy of stavudine at 10 weeks and safety after 1 year.

Participants
152 ART naive (except for limited exposure to AZT) adults in USA, 87% male and 66% white with a median age of 36 years and with median baseline CD4 count of 250 cells (range 2-596 cells).

Interventions
Three weight-based doses of stavudine were compared: 0.1, 0.5, or 2.0 mg/kg daily in 3 divided doses (n=51, 53, 48 respectively).

Outcomes
Mortality. 3 deaths
Disease progression. There were 22 AIDS-defining events according to the 1987 CDC definitions in use at the time of the study, including 3 deaths, one in each dosage group. In a stepwise Cox regression model, d4T dose was not a significant predictor of time to AIDS-defining event or death.
Treatment response undetectable VL. Tests for VL were not available at the time of this study.
Treatment response changes in CD4 count from Baseline ND
Serious adverse events. Peripheral neuropathy requiring dose modification was the only adverse reaction that showed a statistically significant difference in frequency (P=0.004) across groups. The rates after 1 year were 6%, 17% and 37% at 0.1, 0.5, and 2.0 mg/kg/day respectively.

Notes
This was a 10-week dose-ranging study with follow-up safety data shown for up to 46 weeks. Peripheral neuropathy (PN) requiring dose modification was the only adverse reaction that showed a statistically significant difference in frequency across the groups. PN was determined to be dose related. The most favourable risk-benefit ration in this trial was 0.5 mg/kg/day.

Risk of bias table

<table>
<thead>
<tr>
<th>Item</th>
<th>Judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Randomly assigned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Industry centralised computer generated and randomly determined dosage assignments.</td>
</tr>
<tr>
<td>Blinding?</td>
<td>No</td>
<td>Open-label</td>
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<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>All enrolled participants were included in the presented analyses and results were well described.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear</td>
<td>This was an industry sponsored study.</td>
</tr>
</tbody>
</table>
### Methods
A prospective, randomized, open-label, dose-ranging study of 48 weeks duration to evaluate the efficacy and safety of four different regimens of ddI plus stavudine in HIV-infected Thais.

### Participants
78 adult Thais, ART naive, 50% of whom were female. The mean baseline CD4 count was 255 (SD 61) and the mean baseline VL was 4.3 logs (SD 0.8). 94% were infected through heterosexual contact and 77% were HIV subtype E.

### Interventions
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ddI monotherapy n=15</td>
<td></td>
</tr>
<tr>
<td>ddI LD + d4T LD n=16</td>
<td></td>
</tr>
<tr>
<td>ddI LD + d4T HD n=16</td>
<td></td>
</tr>
<tr>
<td>ddI HD + d4T LD n=15</td>
<td></td>
</tr>
<tr>
<td>ddI HD + d4T HD n=16</td>
<td></td>
</tr>
<tr>
<td>d4T dose was weight-based (doses for weight &lt;60 kg are given in parentheses)</td>
<td></td>
</tr>
<tr>
<td>Low dose (LD): 20 (15) mg BID</td>
<td></td>
</tr>
<tr>
<td>High dose (HD): 40 (30) mg BID</td>
<td></td>
</tr>
</tbody>
</table>

### Outcomes
- **Mortality**: ND
- **Disease progression**: 1 case of extra pulmonary tuberculosis in the ddI monotherapy arm.
- **Logistic regression**: Conducted excluding the ddI monotherapy group (as d4T had been added to this arm after 22 weeks).
- **Treatment response** undetectable VL: At week 48, 48 (50%) of those in the d4T HD arm had a VL <500 compared with 68% in the LD arm (OR 0.48, CI 0.17-1.33). There was no evidence that the d4T dose was related to viral outcome.
- **Treatment response changes in CD4 count from baseline**: At week 48, median CD4 count had increased by 97 cells (IQR 61-178) (mean 108) in the d4T HD arm compared with a median increase of 135 cells (IQR 71-199) (mean 135) in the d4T LD arm (P=0.38). There was no significant difference in d4T dose effects in changes in CD4 count.
- **Serious adverse events**: There were nil grade 4 events.

### Notes
Although this study was designed to compare ddI monotherapy with various combinations of high-dose and low-dose ddI and d4T, analysis was undertaken to test separately high-dose vs. low-dose ddI and high-dose vs. low-dose d4T. The results were able to demonstrate that low doses of d4T were not relevant to CD4 outcome and was not associated significantly with VL outcome.

### Risk of bias table
<table>
<thead>
<tr>
<th>Item</th>
<th>Judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Patients were allocated to the treatment arms by the industry sponsor according to a random number table designed by the Thai US-CDC Collaboration in a 1:1:1:1:1 allocation.</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>No information provided.</td>
</tr>
<tr>
<td>Blinding?</td>
<td>No</td>
<td>Open-label</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>71 of 78 completed the study and the dropouts were spread throughout the arms. Stated outcomes were addressed in the paper.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>ITT analysis was used and a full description of the statistical analyses was provided.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear</td>
<td>There was some industry sponsorship.</td>
</tr>
</tbody>
</table>
Characteristics of excluded studies

Pedrol 2007

Reason for exclusion: This was a retrospective chart review of 982 Spanish patients. It showed that, in this large number of patients, a lower than standard dose of d4T did not compromise virological efficacy. However, as this was a retrospective, non-randomized study, it was excluded from the GRADE review.

Pollard 1999

Reason for exclusion: This RTC was excluded as the numbers involved were small (N=86) and the dropout rate was very high (58%). It found no clear dose related differences among treatment groups (d4T 10 mg, 20 mg, 40 mg BID) with regard to suppression of plasma HIV RNA.

References to studies

Included studies

Anderson 1995

McComsey 2008

Petersen 1995

Ruxrungtham 2000

Excluded studies

Pedrol 2007

Pollard 1999
Pollard, RB, Peterson, D, Hardy, D, Pottage, J, Murphy, RL, Gathe, J, Beall, G, Rutkievicz, V, Reynolds, L, Cross, AP, Dunkle, LM. Safety and antiretroviral Effects of Combined ddI and D4T Therapy in HIV-infected Individuals with CD4 Counts of 200 to 500 cells/mm³. JAIDS 1 September 1999:22(1):39.

Other references

Anderson 1995

BMS 1998

Cochrane 2008

**WHO 2009a**

**WHO 2009b**

---

**Sources of support**

WHO HQ Dpt of HIV/AIDS Antiretroviral Treatment and HIV Care Team, Switzerland

This review was undertaken while the reviewer was a consultant to the WHO HIV/AIDS Antiretroviral Treatment and HIV Care Team
### Appendices

#### 1. GRADE Table

**Author(s):** John C Liddy  
**Date:** 2009-12-03  
**Question:** Should Low-dose d4T vs High-dose d4T be used for HIV infection?  
**Settings:** Resource and resource-limited settings  
**Bibliography:**  
- Ruxrungtham. A randomized, dose-finding study with ddI plus d4T versus ddI alone in antiviral-naive, HIV-infected Thai patients. AIDS 2000, 14:1375-1382

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td>VL detectable (follow-up median 48 weeks)</td>
<td>2 randomised trials</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious²</td>
</tr>
<tr>
<td>CD4 response (Better indicated by higher values)</td>
<td>1 randomised trials</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious²</td>
</tr>
</tbody>
</table>

¹ Both of these studies were open-label and allocation concealment was not detailed. There was some industry sponsorship but the risk of bias was considered minimal.  
² Studies involved low numbers of participants with few outcome events. Studies were not directly designed to answer the question of the efficacy of low-dose d4T. However, analyses in the studies did address this question.  
³ This study was open-label and there was some industry sponsorship (supply of antiretrovirals).
### 2. Summary of Findings Table

Low-dose d4T compared to high-dose d4T for HIV infection

**Patient or population:** patients with HIV infection  
**Settings:** Resourced and resource-limited settings  
**Intervention:** Low-dose d4T  
**Comparison:** High-dose d4T

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL detectable</td>
<td>Assumed risk 439 per 1000 (176 to 549) followed-up: median 48 weeks, Corresponding risk 312 per 1000 (176 to 549)</td>
<td>RR 0.71 (0.4 to 1.25)</td>
<td>87 (2 studies)</td>
<td>low²</td>
<td></td>
</tr>
<tr>
<td>CD4 response</td>
<td>The mean CD4 response in the intervention groups was 4.81 standard deviations higher (3.81 to 5.8 higher)</td>
<td>63 (1 study)</td>
<td></td>
<td>low²</td>
<td></td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence  
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.  
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.  
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.  
**Very low quality:** We are very uncertain about the estimate.

1 Both of these studies were open-label and allocation concealment was not detailed. There was some industry sponsorship but the risk of bias was considered minimal.  
2 Studies involved low numbers of participants with few outcome events. Studies were not directly designed to answer the question of the efficacy of low-dose d4T. However, analyses in the studies did address this question.  
3 This study was open-label and there was some industry sponsorship (supply of antiretrovirals).