Changes in hematologic parameters and efficacy of thymidine analogue-based, highly active antiretroviral therapy: a meta-analysis of six prospective, randomized, comparative studies

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CRD summary
This review assessed the effects of zidovudine- and stavudine-based triple regimens on haematological outcomes, CD4+ T-cell counts and viral load in patients infected with the human immunodeficiency virus. The authors concluded that zidovudine regimens reduced haemoglobin and increased neutropenia events in comparison with stavudine-based regimens. Since most of the studies used different co-treatments and did not assess validity, it is difficult to judge the reliability of the conclusions.

Authors' objectives
To assess the effects of thymidine analogue-based triple therapy on haemoglobin (Hb) levels and neutrophil counts in patients infected with the human immunodeficiency virus (HIV), and to compare the efficacy of different regimens using CD4+ T-cell counts and viral load.

Searching
MEDLINE, PubMed, EMBASE, and the Cochrane Database of Systematic Reviews were searched; the keywords were reported. There were no restrictions on language, date or publication type.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared triple-therapy regimens containing stavudine (d4T) with those containing zidovudine (AZT) were eligible for inclusion. All of the included studies used AZT in combination with lamivudine (3TC); studies combined d4T with didanosine (ddI) or 3TC. The third agent in the treatment regimens was either a protease inhibitor (indinavir or nelfinavir) or a non-nucleoside (nevirapine).

Participants included in the review
Studies of treatment-naive adult patients were eligible for inclusion. In the included studies, the baseline CD4 values ranged from 267 to 449 cells/mm3, the mean viral load from 4.5 to 5.2 log copies/mL, and Hb levels from 13.8 to 14.5 g/dL.

Outcomes assessed in the review
Studies that assessed haematological outcomes were eligible for inclusion. The review assessed CD4+ count, viral load, Hb and neutrophil counts at 24 and 48 weeks. In the review, haematological outcomes were classified from grade 1 (mild) to 4 (potentially life threatening) using the World Health Organization/AIDS Clinical Trials Group toxicity criteria.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
Three employees of Bristol-Meyers Squibb Company extracted the trial data. Data on changes in Hb levels (by last observation carried forward), CD4+ cell counts and viral loads from baseline to weeks 24 and 48 were extracted for each treatment group, then used to calculate a standardised mean difference (SMD) for each time point. Data on frequencies of changes in Hb and neutrophils by toxicity grade were also extracted. The results for two of the RCTs were reported as one set of results. Study groups, authors and pharmaceutical companies were contacted for additional information.

Methods of synthesis
How were the studies combined?
SMDs for changes in Hb levels, CD4 counts and viral loads at 24 and 48 weeks were pooled in a meta-analysis, weighting by study size. Data on neutrophilic events were tabulated for individual studies. Overall mean values and standard errors (SEs) were also calculated, weighting by sample size for each treatment.

How were differences between studies investigated?
The authors did not report that they investigated heterogeneity between the studies. Any differences in haematological events between regimens containing 3TC and those containing ddI as the second agent were compared.

Results of the review
Six RCTs were included (n=1,663 at 24 weeks: 679 AZT-treated and 984 d4T-treated patients; n=1,595 at 48 weeks: 649 AZT-treated and 946 d4T-treated patients).

The mean Hb levels decreased with AZT by 0.4 g/dL (SE=0.05) at 24 weeks and by 0.2 g/dL (SE=0.06) at 48 weeks. However, the mean Hb levels increased with d4T by 0.45 g/dL (SE=0.03) and 0.58 g/dL (SE=0.04), respectively.

AZT-based regimens were associated with significantly reduced Hb levels at 24 and 48 weeks in comparison with d4T-based regimens (SMDs 0.87 and 0.79, respectively).

All studies found that AZT increased anaemia and grade 1 to 4 neutropenic events in comparison with d4T (the results for the individual studies were tabulated), although no statistical analysis was reported.

There were no statistically significant differences between the treatments in terms of CD4 counts at 24 or 48 weeks (respective changes in cells/mm3: +147 with AZT versus +158 with d4T; +193 with AZT versus +199 with d4T), or in viral load at 24 or 48 weeks (respective changes in log copies/mL: -2.33 with AZT versus -2.44 with d4T; -2.35 with AZT versus -2.44 with d4T).

There was no significant difference in haematological events between regimens containing 3TC and those containing ddI as the second agent (no data were reported).

Authors' conclusions
Compared with highly active antiretroviral therapy regimens containing d4T, regimens containing AZT reduced Hb and increased anaemia and neutropenia events.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched but the search strategy was not completely described; it was unclear whether the studies were restricted by publication type or language after the initial search had been conducted. The methods used to select the studies were not described, so it is not known whether any efforts were made to reduce errors and bias. Three employees of a pharmaceutical company that manufactured one of the drugs of interest (d4T) extracted the data; it was not reported whether they extracted the data independently or not. Only RCTs were included but validity was not assessed. Attrition rates were not reported.
The studies were combined in a meta-analysis. Statistical heterogeneity was not assessed, although meta-analysis graphs suggested the absence of statistical heterogeneity for changes in Hb levels. Since only studies reporting haematological outcomes were eligible, it is possible that other relevant studies that only assessed the efficacy of the treatments might have been omitted from the analysis of CD4 counts and viral loads. Only one of the studies comparing AZT with d4T used the same co-treatments in both treatment arms, which makes comparisons of AZT with d4T problematic. In view of the limitations discussed, the authors’ conclusion about the relative effects of AZT-based and d4T-based triple regimens on haematological measures may not be reliable.

One of the authors is employed by PharmaNet Ltd.

**Implications of the review for practice and research**

Practice: The authors stated that differences in the effect on haematologic parameters of d4T-based and AZT-based regimens may influence drug choice in certain patient populations.

Research: The authors did not state any implications for further research.

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