Co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV infection and AIDS (Review)

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T A B L E   O F   C O N T E N T S

[Intervention Review]

Co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV infection and AIDS

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A B S T R A C T

Background

UNAIDS estimates that 34 million people are currently living with the human immunodeficiency virus (HIV) worldwide. Currently recommended regimens for initiating HIV treatment consist of either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or ritonavir-boosted protease inhibitor (PI) combined with two nucleoside reverse transcriptase inhibitors (NRTIs). However, there may be some patients for whom NNRTIs and PIs may not be appropriate. This is an update of the review published in the Cochrane Library Issue 3, 2009.

Objectives

To evaluate the effects of any fixed-dose combination of three NRTIs (co-formulated abacavir-lamivudine-zidovudine) for initial treatment of HIV infection.

Search methods

Between December 2010 and July 2011, we used standard Cochrane methods to search electronic databases and conference proceedings with relevant search terms without limits to language or publication status.

Selection criteria

We selected randomised controlled trials (RCTs) with a minimum follow-up time of six months which compared co-formulated abacavir-lamivudine-zidovudine with either PI-based or NNRTI-based therapy among antiretroviral-naive HIV-infected patients aged at least 13 years.

Data collection and analysis

Three authors independently selected eligible studies, assessed risk of bias, and extracted data; resolving discrepancies by consensus. We calculated the risk ratio (RR) or mean difference (MD), as appropriate, with its 95% confidence interval (CI) and conducted meta-analysis using the random-effects method because of significant statistical heterogeneity (P<0.1).

Main results

We identified 15 potentially eligible RCTs, four of which met our inclusion criteria. The four included RCTs were conducted in the United States of America (USA); USA, Puerto Rico, Guatemala, Dominican Republic, and Panama; USA and Mexico; and Botswana, respectively. The RCTs compared co-formulated abacavir-lamivudine-zidovudine to treatment based on efavirenz (NNRTI), nelfinavir (PI), atazanavir (PI), and co-formulated lopinavir-ritonavir (PI), respectively. Overall, there was no significant difference in virological suppression between co-formulated abacavir-lamivudine-zidovudine and NNRTI- or PI-based therapy (4 trials; 2247 participants: RR 0.73, 95% CI 0.39 to 1.36). However, the results showed significant heterogeneity (I^2=79%); with co-formulated abacavir-lamivudine-zidovudine inferior to NNRTI (1 trial, 1147 participants: RR 0.35, 95%CI 0.26 to 0.49) but with a trend towards co-formulated abacavir-lamivudine-zidovudine being superior to PI (3 trials, 1110 participants: RR 1.07, 95%CI 1.00 to 1.16; I^2=0%). We found no significant differences between co-formulated abacavir-lamivudine-zidovudine and either PI or NNRTI on CD4+ cell counts (3 trials, 1687 participants: MD -0.01, 95%CI -0.11 to 0.09; I^2=0%), severe adverse events (4 trials: RR 1.22, 95%CI 0.78 to 1.92; I^2=62%) and hypersensitivity reactions (4 trials: RR 4.04, 95% CI 0.41 to 40.02; I^2=72%). Only two studies involving PIs reported data on the lipid profile. One study found that the mean increase in total cholesterol from baseline to 96 weeks was significantly lower with co-formulated abacavir-lamivudine-zidovudine than with nelfinavir, but there were no differences with triglyceride levels. The second study found the fasting lipid profile to be comparable in both co-formulated abacavir-lamivudine-zidovudine and atazanavir arms at 48 weeks.

The significant heterogeneity of effects for most outcomes evaluated was largely due to differences in the control therapy used in the included trials (i.e. NNRTIs or PIs). Using the GRADE approach, we rated the overall quality of the evidence on the relative effects of co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV infection as moderate. The main reason for downgrading the quality of the evidence was imprecision of the findings. The estimate of the treatment effect for each outcome has wide confidence intervals, which extend from the fixed-dose NRTI combination regimen being appreciably better to the regimen being appreciably worse than PI- or NNRTI-based regimens.

Authors' conclusions

This review provides evidence that co-formulated abacavir-lamivudine-zidovudine remains a viable option for initiating antiretroviral therapy, especially in HIV-infected patients with pre-existing hyperlipidaemia. The varied geographical locations of the included trials augment the external validity of these findings. We are moderately confident in our estimate of the treatment effects of the triple NRTI regimen as initial therapy for HIV infection. In the context of the GRADE approach, such moderate quality of evidence implies that the true effects of the regimen are likely to be close to the estimate of effects found in this review; but there is a possibility that they could be substantially different. Further research should be geared towards defining the subgroup of HIV patients for whom this regimen will be most beneficial.

P L A I N   L A N G U A G E   S U M M A R Y

Co-formulated abacavir-lamivudine-zidovudine for treating HIV infection and AIDS

The primary objective of this review was to evaluate the antiviral efficacy of co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV infection. The secondary objectives were to evaluate the safety and tolerability of the triple drug combination. We identified 15 potentially eligible studies, four of which met our inclusion criteria. Our findings indicate that co-formulated abacavir-lamivudine-zidovudine remains a viable option for initiating antiretroviral therapy, especially in HIV-infected patients with pre-existing hyperlipidaemia and those who do not tolerate ritonavir.

Co-formulated abacavir-lamivudine-zidovudine compared to NNRTIs or PIs for initial treatment of HIV infection and AIDS				
Patient or population: Antiretroviral-naive HIV infected patients **Settings:** Any country setting (i.e. low-, middle-, or high-income) **Intervention:** Co-formulated abacavir-lamivudine-zidovudine **Comparison:** Non-nucleoside reverse transcriptase inhibitor (NNRTI)- or protease inhibitor (PI)-based therapy				
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	NNRTIs or PIs	**Co-formulated abacavir-lamivudine-zidovudine**			
Virologic failure 2 successive HIV-1 RNA >= 200copies/ml at 16+ weeks after randomisation Follow-up: mean 48 weeks	115 per 1000	131 per 1000 (64 to 266)	RR 1.14 (0.56 to 2.31)	1687 (3 studies)	⊕⊕⊕◯ moderate[1]
Virologic suppression Viral load <50 copies/ml Follow-up: mean 48 weeks	732 per 1000	710 per 1000 (549 to 915)	RR 0.97 (0.75 to 1.25)	2247 (4 studies)	⊕⊕⊕◯ moderate[1]
CD4 cell count Follow-up: mean 48 weeks	The mean CD4 cell count ranged across control groups from **415-634 cells per cubic millimetres**	The mean CD4 cell count in the intervention groups was **0.01 lower** (0.11 lower to 0.09 higher)		1687 (3 studies)	⊕⊕⊕◯ moderate[1]
Severe adverse events Follow-up: mean 48 weeks	116 per 1000	142 per 1000 (90 to 223)	RR 1.22 (0.78 to 1.92)	2247 (4 studies)	⊕⊕⊕◯ moderate[1]
Hypersensitivity reactions Follow-up: mean 48 weeks	44 per 1000	178 per 1000 (18 to 1000)	RR 4.04 (0.41 to 40.02)	2247 (4 studies)	⊕⊕⊕◯ moderate[1]

*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] The estimate of effect has wide confidence intervals, which extend from appreciable benefit to appreciable harm

BACKGROUND

The human immunodeficiency virus (HIV) pandemic poses one of the greatest challenges to global public health. In 2011, an estimated 34 million people were living with HIV and 1.7 million died of the acquired immunodeficiency syndrome (AIDS) (UNAIDS 2012). Prevention is commonly advocated to curb the spread of HIV infection, and although preventive methods have considerably slowed the spread of HIV in most parts of the world, people who are already infected need care and treatment.

The goal of antiretroviral therapy is to achieve prolonged suppression of HIV replication. The ideal antiretroviral drugs should be effective in suppressing viral replication, affordable, available in simplified regimens, well tolerated, and have no dietary interactions. The use of monotherapy and dual therapy has often led to mutations and long-term resistance (Eron 1995; Pialoux 1998; Rutherford 2003), necessitating the development of combination therapy with three drugs taken separately (Carpenter 2000; Hammer 2008). In well-resourced countries (Ledergerber 1999) and, recently, Brazil (Hacker 2004; Teixeira 2004), antiretroviral therapy has contributed substantially towards delaying HIV progression to AIDS and death. However, these combinations are complex and difficult to take due to high pill burden, stringent intake schedules, and food and fluid restrictions They may also be associated with drug-drug interactions and numerous side effects, including various lipid abnormalities (Mehta 1997; Gifford 2000). This complexity also makes antiretroviral therapy less accessible to patients in most resource-constrained regions of the world, which currently are hardest hit by the pandemic, such as sub-Saharan Africa. This area is inhabited by approximately 10% of the world's population but is home to 60% of all people currently living with HIV (UNAIDS 2012).

Concern over toxicity, adherence, and drug-drug interactions has led to the development of simpler antiretroviral regimens, including co-formulated abacavir-lamivudine-zidovudine (Anon 2000; Saez-Llorens 2001). Three NRTIs simplify PI-based therapy by easing dosing regimens (only one tablet twice daily) and avoiding lipid abnormalities (Seaton 2003). Although treatment simplification could help patients maintain adherence, continued virologic suppression must be ensured. Therefore, clarification of the role of this simplified antiretroviral therapy on prolonged suppression of HIV replication is of considerable importance. Because all three antiretroviral drugs are of the same class, the use of co-formulated abacavir-lamivudine-zidovudine (if proven to be effective) potentially preserves NNRTIs and PIs for later use, thereby avoiding resistance to all classes of antiretroviral agents at the same time, and allows for effective second-line treatment regimens (Staszewski 2001). There are concerns, however, about hypersensitivity reactions to abacavir (Staszewski 1998). Cross resistance between drugs of the same class should also be considered. Also, entecavir used for hepatitis B virus (HBV) treatment, may select for M184V mutation which confers resistance to lamivudine in individuals co-infected with HIV and HBV (McMahon 2007).

The aim of this review was to combine all high-quality RCTs comparing co-formulated abacavir-lamivudine-zidovudine with PI- or NNRTI-based therapy to assess the antiviral potency and tolerability of the simplified triple nucleoside combination in initial therapy for HIV.

OBJECTIVES

The primary objective of this review was to evaluate the antiviral efficacy of co-formulated zidovudine-lamivudine-abacavir for initial treatment of HIV infection. The secondary objectives were to evaluate the safety and tolerability of the triple nucleoside combination.

METHODS

Criteria for considering studies for this review

Types of studies

Only RCTs with a minimum follow-up time of six months were included. Six months of treatment was considered enough time to detect significant differences in the suppression of viral activity after initiation of therapy.

Types of participants

HIV-infected, antiretroviral-naive patients aged at least 13 years. We chose only studies that focused on adolescents and adults.

Types of interventions

Treatment of HIV infection with co-formulated abacavir-lamivudine-zidovudine as initial therapy compared with treatment based on PIs or NNRTIs

Types of outcome measures

The primary outcome measure was suppression of viral activity, as defined by the authors.
The secondary outcome measures included:
1- CD4 cell count
2- Severe adverse events
3- Clinical lipodystrophy manifestations
4- Total cholesterol
5- Triglyceride level
6- Treatment adherence

Search methods for identification of studies

See: HIV/AIDS Collaborative Review Group search strategy.

Between February 2008 and May 2009, we searched PubMed, EMBASE, Cochrane Database of Systematic Reviews, and the York Database of Abstracts of Reviews of Effectiveness (DARE) for previous reviews and meta-analyses of antiretroviral therapy for treatment of HIV that included co-formulated abacavir-lamivudine-zidovudine; and searched the references of these reviews for reports of eligible trials. We then carried out an exhaustive search of the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, NLM GATEWAY, and AIDSearch, for randomised controlled trials of co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV, using standardised methodological filters (Higgins 2011) where appropriate. We also searched reference lists of identified articles. There were no time or language restrictions to our search.

We updated the search in December 2010 by searching EMBASE, ISI Web of Science, PsycINFO, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/search/en/). In addition, in July 2011, we finalised the update by searching CENTRAL, and PubMed.

See Appendix 1 for all search strategies.

Data collection and analysis

See: Cochrane HIV/AIDS Group methods used in reviews.

Selection of studies

The Trials Search Coordinator of the Cochrane HIV/AIDS Group (http://www.igh.org/Cochrane/) conducted the electronic database searches. For the original version of the review and this update, three authors (MS, EJK, and CSW) independently conducted the selection of potentially relevant studies by scanning the titles and abstracts of all material downloaded from the electronic searches. Irrelevant reports were discarded and the full articles were obtained for all potentially relevant or uncertain reports. From this pool of potentially eligible studies, we selected studies for inclusion in the review if they were RCTs (study design) comparing any fixed-dose combination of abacavir, lamivudine and zidovudine (NRTI) with PI- or NNRTI-based antiretroviral therapy (intervention) in antiretroviral-naive, HIV-infected adults (participants). Disagreements between the review authors were resolved by discussion and consensus. When no consensus could be reached, SMA and JS arbitrated.

Data extraction and management

The three authors (MS, EJK, and CSW) extracted data independently using pre-established data collection forms. We extracted information from included studies on study details (i.e.

how the allocation sequence was generated, method used to conceal treatment allocation, blinding of those receiving and providing care and those assessing outcomes, losses to follow-up and how they were handled), participant characteristics (i.e. setting, number of patients randomised, baseline HIV-1 RNA and CD4 cell levels), interventions (i.e. treatment and control, length of treatment), and outcomes (virological failure/suppression, CD4+ cell count, cholesterol level, clinical lipodystrophy manifestations, other side effects). Disagreements between the review authors were resolved by discussion and consensus. When no consensus could be reached, SMA and JS arbitrated.

Assessment of risk of bias in included studies

We assessed risk of bias as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Three review authors (MS, EJK, and CSW) independently assessed the risk of bias in each included study by addressing seven specific domains, namely, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and 'other issues'. For each included trial, the authors independently described what the study authors reported that they did for each domain and then made a decision relating to the risk of bias for that domain by assigning a judgement of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias. The review authors compared the results of their independent assessments of risk of bias and resolved any discrepancies by discussion and consensus. When no consensus could be reached, SMA and JS arbitrated.

For study selection, data extraction, and risk of bias assessment we were not blinded to the names of the trial authors, their institutions, nor the journals of publication.

Data synthesis

We undertook meta-analysis using RevMan 5. We analysed all participants in the groups to which they were randomised, irrespective of whether they received the allocated intervention, and assessed heterogeneity between study results using the chi-square test of homogeneity, with significance defined at the 10% level (www.cochrane-handbook.org). We expressed each trial result as a risk ratio (RR) for dichotomous data and mean difference (MD) for continuous data, with 95% confidence intervals (CIs), and combined the results using the random-effects method because of significant heterogeneity. We also used the I^2 statistic to describe the percentage of between-study variability in effect estimates, which is attributable to true heterogeneity rather than chance (Higgins 2011).

We used the GRADE method to rate the quality of evidence on the effectiveness of the triple NRTI regimen (Guyatt 2008; Balshem 2011), and have presented these ratings in Summary of findings for the main comparison. The GRADE approach results in an assessment of the quality of a body of evidence as high, moderate,

low, or very low. High quality evidence implies that "further research is very unlikely to change our confidence in the estimate of effect". Moderate quality evidence means "further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate". Evidence is considered of low quality if "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", and very low quality if "we have very little confidence in the effect estimate". In this review we considered five factors when grading the quality of evidence on the relative effects of fixed-dose NRTI regimen for initiating HIV treatment; namely, risk of bias in included RCTs, unexplained heterogeneity of effects, indirectness of the evidence, imprecision of the findings, and possibility of publication bias. Regarding risk of bias, we were most concerned with lack of allocation concealment, lack of blinding of outcome assessment, and a large loss to follow-up. Heterogeneity of effects across studies for which there were no compelling explanations would also have reduced our confidence in the evidence. Indirectness refers to differences between the population, intervention, comparison group and outcome of interest to us, and those reported by the included RCTs. For imprecision, if we found that studies included relatively few participants and few events and thus had estimates of effects with wide confidence intervals, we rated down the quality of the evidence. Finally, we would also have rated down the quality of evidence if there was a high likelihood of publication bias (Balshem 2011).

R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
After scanning the titles and abstracts of all material obtained from the searches conducted from February 2008 to July 2011 (Table 1; Table 2; Table 3; Table 4; Table 5; Table 6; Table 7; Table 8; Table 9; Table 10; Table 11), and discarding clearly irrelevant reports, we obtained 15 potentially eligible studies. We reviewed the full-text articles of the 15 randomised controlled trials (Gulick 2004; Kumar 2006; Kumar 2009; Shapiro 2010; Ait-Khaled 2002; Cahn 2004; d'Ettorre 2009; Feinberg 2003; Matheron 2003; Munderi 2010; Ndembi 2010; Shao 2009; Sprenger 2010; Staszewski 2001; Vibhagool 2004) and four met our inclusion criteria (Gulick 2004; Kumar 2006; Kumar 2009; Shapiro 2010).
The Gulick 2004 trial recruited 1147 participants from 33 units of The AIDs Clinical Trials Group (ACTG) in the United States

of America (USA); the Kumar 2006 trial recruited 261 participants from 34 sites in the USA, Puerto Rico, Guatemala, Dominican Republic, and Panama; the Kumar 2009 study recruited 279 participants from 46 sites in the USA and Mexico; and the Shapiro 2010 trial recruited 560 women in both urban and rural areas in Botswana. The four trials only included participants who were antiretroviral-naive. The Gulick 2004 and Kumar 2009 trials recruited predominantly male participants (81% and 79%, respectively), while only 50% of participants in the Kumar 2006 trial were men. Finally, all participants in the Shapiro 2010 trial were women.
Participants in the Gulick 2004 trial had mean age 38 years (SD 9 years), were 40% white, 36% African American, and 21% Hispanic and had mean HIV-1 RNA level of 4.85 $\log_{10}$ copies/mL (SD 0.70) and mean CD4+ cell count of 234 cells/mm^3 (SD 187). Participants in the Kumar 2006 trial had median age 34 years (range 18-60 years), were 21% white, 40% African American, and 37% Hispanic, and had median HIV-1 RNA level of 4.44 $\log_{10}$ copies/mL (range 2.23 to 5.77) and median CD4 cell count of 339 cells/mm^3 (range 19 to 1269). Participants in the Kumar 2009 study had median age 37 years (range 18 to 68 years), HIV-1 RNA levels between 2.3 and 5.6 $\log_{10}$ copies/mL, and CD4+ cell counts from 103 to 889 cells/mm^3. Participants in the Shapiro 2010 trial were pregnant women, aged 18 years or older, were presumably all black Africans, and had median HIV-1 RNA levels of 13,300 copies/mL in the NRTI arm and 9,100 in the PI arm, and a CD4+ cell count of at least 200 cells/mm^3 (median 393 cells/mm^3 in the NRTI arm and 403 cells/mm^3 in the PI arm).
The participants in the Gulick 2004 trial were randomised to either zidovudine (ZDV)-lamivudine(3TC)-abacavir (ABC) [Trizivir®], or ZDV-3TC [Combivir®] + efavirenz [a NNRTI] or Trizivir® + efavirenz. Participants took a total of seven pills per day, including placebo tablets, divided into two doses. In the Kumar 2006 trial, participants were assigned to either Trizivir® twice daily, or Combivir® + nelfinavir [a PI] 1250 mg twice daily, or stavudine [d4T] 40 mg + 3TC 150 mg + nelfinavir 1250 mg twice daily. In Kumar 2009, participants were randomised to receive either Trizivir® or atazanavir plus lamivudine and zidovudine. In Shapiro 2010, participants were randomised to receive Trizivir® twice daily in the NRTI arm, or 400 mg of lopinavir and 100 mg of ritonavir [co-formulated as Kaletra®] twice daily in the PI arm. The Shapiro 2010 trial also had a third group of participants (observational arm) who received Combivir® twice daily. This observational arm was not included in our analysis.

Risk of bias in included studies

Our judgements about the risk of bias in each included study are summarised in Figure 1 and Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
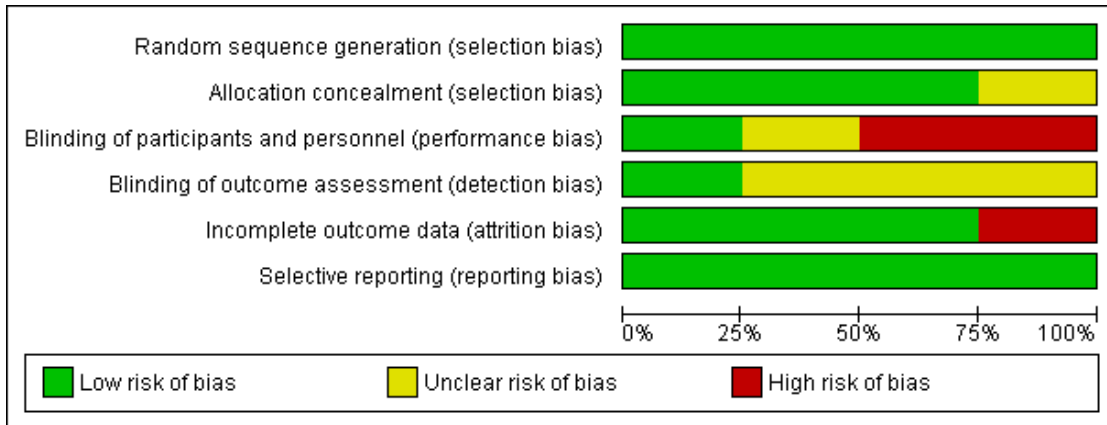
Figure 2.   Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Generation of allocation sequence

Three trials did not provide an adequate description of the methods used for generating the allocation sequence, but all were described as randomised [Gulick 2004; Kumar 2006; Kumar 2009]. However, the equal allocation of participants suggests that a computer-generated block randomisation process was used. In the Shapiro 2010 trial, participants were randomly assigned to treatment groups based upon computer-generated lists (Shapiro 2010).

Allo cation concealment

The Gulick 2004, Kumar 2009, and Shapiro 2010 trials used central randomisation, suggesting that allocation concealment in all three trials was adequate. The Kumar 2006 trial did not provide sufficient detail to describe the allocation concealment process.

Blinding

In the Gulick 2004 trial, participants, providers, and outcome assessors were all blinded. In the Kumar 2006 and Kumar 2009 trials, the participants and providers were not blinded, but it was not clear if the outcome assessors were blinded. In the Shapiro 2010 trial, no details were given about blinding of participants, providers, or outcome assessors.

Loss to follow-up

When the triple-nucleoside arm was stopped in the Gulick 2004 trial after a median of 32 weeks, 83 participants (7%) had discontinued the study for various reasons, including withdrawal of consent (2%) and loss to follow-up (2%). In the Kumar 2006 trial, loss to follow-up at 96 weeks was 26.4% for Trizivir[®], 24.2% for COM/NFV, and 14.5% for d4T/3TC/NFV groups. In the Kumar 2009 trial, 9% and 10% of the participants were lost to follow-up in the Trizivir[®] and ATV + 3TC/ZDV arms, respectively. In the Shapiro 2010 trial 15(5.2%) women in the Trizivir[®] and 13(5.1%) in Kaletra[®] arms left the study for reasons that are not stated.

Effects of interventions

See: **Summary of findings for the main comparison** Co-formulated abacavir-lamivudine-zidovudine compared to NNRTIs or PIs for initial treatment of HIV infection

There was significant heterogeneity between the included trials in the incidence of virological failure (3 trials, 1687 participants, heterogeneity P=0.009, I^2=79%; Analysis 1.1). The Kumar studies (Kumar 2006; Kumar 2009) did not find a significant difference in the incidence of virological failure between participants on NRTIs and those on a PI (i.e. nelfinavir or atazanavir) (two trials, 540 participants: RR 0.82, 95% CI 0.50 to 1.36; heterogeneity P= 0.21, I^2=35%). Gulick and colleagues found that participants on NRTIs had a significantly higher incidence of virological failure than did those on the NNRTI efavirenz (1 trial, 1147 participants: RR 1.93, 95% CI 1.46 to 2.55). Overall, there was no significant difference between the participants on NRTIs and those on either PI-based or NNRTI-based therapy (RR 1.14, 95% CI 0.56 to

2.32).

Whatever the definition of virological suppression considered, there was significant heterogeneity between the four studies (heterogeneity P<0.00001, I^2=93% for viral load<50copies/ml; heterogeneity P=0.0002, I^2=85% for viral load <400 copies/mL) with Kumar 2006, Kumar 2009 and Shapiro 2010 finding no significant differences between comparison groups and Gulick 2004 finding NRTIs to be inferior to efavirenz. For viral load of <50 copies/mL, the risk ratios were 1.15 (0.83 to 1.59) in the Kumar 2006 trial, 1.03 (0.85 to 1.25) in the Kumar 2009 trial, 0.73 (0.67 to 0.80) in the Gulick 2004 trial, 1.08 (0.99 to 1.17) in the Shapiro 2010 trial, and 0.97 (0.75 to 1.25) overall (Analysis 1.3). For viral load of <400 copies/mL, the risk ratios were 1.10 (0.65 to 1.84) in the Kumar 2006 trial, 0.96 (0.58 to 1.58) in the Kumar 2009 trial, 0.35 (0..26 to 0.49) in the Gulick 2004 trial, and 0.73 (0.39 to 1.36) overall (Analysis 1.2).

We found no significant differences between NRTIs and either PIs or NNRTIs on CD4+ cell counts (3 trials, 1687 participants: mean difference -0.01, 95% CI -0.11 to 0.09, I^2=0%: Analysis 1.4), the incidence of severe adverse events (4 trials; 2247 participants: RR 1.22, 95% CI 0.78 to 1.92, I^2=62%; Analysis 1.5) and hypersensitivity reactions (RR 4.04, 95% CI 0.41 to 40.02, I^2= 72%; Analysis 1.6). The Shapiro trial did not encounter a hypersensitivity reaction in any treatment group.

Gulick 2004 and Shapiro 2010 did not report on lipid levels. At week 96, Kumar 2006 found the least squares means increase in total cholesterol from baseline was significantly lower with NRTIs than with nelfinavir. Kumar 2006 also found that mean total cholesterol remained below 200mg/dL only in the NRTI group, and the proportion of patients with total cholesterol levels more than 200mg/dL after 96 weeks of treatment was significantly lower in the NRTI group. At 96 weeks, Kumar 2006 found no significant differences between the comparison groups in least squares means triglyceride levels and least squares means change from baseline in triglyceride levels. At 48 weeks, Kumar 2009 found the fasting lipids to be comparable in both the NRTI and atazanavir arms.

Using the GRADE approach (Balshem 2011), we rated the quality of the evidence on the relative effects of co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV infection as moderate outcome evaluated (Summary of findings for the main comparison).

DISCUSSION

The large Gulick 2004 trial found the co-formulated abacavir-lamivudine-zidovudine regimen to be virologically inferior to a regimen containing efavirenz and two or three nucleoside analogues after 32 weeks; Kumar 2006 and Kumar 2009 found the

triple nucleoside fixed-dose combination to be equivalent to nelfinavir- and atazanavir-based regimens in maintaining virological suppression over 96 weeks and 48 weeks, respectively; but Shapiro 2010 found viral suppression to be relatively superior in the co-formulated abacavir-lamivudine-zidovudine arm compared to the co-formulated lopinavir-ritonavir arm after six months of therapy. The significant heterogeneity of effects was largely due to differences in the control therapy used in the included trials (i.e. NNRTIs or PIs). Pooling the four trials, we did not find significant differences in virological suppression between initiating treatment with the triple nucleoside fixed-dose combination (NRTI) and therapy based on efavirenz (NNRTI), lopinavir-ritonavir (PI), nelfinavir (PI), or atazanavir (PI). In addition, the triple nucleoside fixed-dose combination regimen was well tolerated and had no deleterious effects on the lipid profile. Using the GRADE approach (Balshem 2011), we rated the overall quality of the evidence on the relative effects of the fixed-dose NRTI regimen for initiating HIV treatment as moderate. The main reason for downgrading the quality of the evidence was imprecision of the findings. The estimate of the treatment effect for each outcome has wide confidence intervals, which extend from the fixed-dose NRTI combination regimen being appreciably better to the regimen being appreciably worse than PI- or NNRTI-based regimens (Summary of findings for the main comparison).

The Shapiro 2010 trial examined the use of Trizivir® (NRTI) or Kaletra® (PI) as first-line therapy in HIV-infected pregnant women. Eventhough the rate of viral suppression after six months of follow-up (up till postpartum period) did not show any difference between the interventions, there was a significant increase in viral suppression to below 50 copies/ml with Trizivir® compared to Keletra® at delivery (81% and 69%, respectively). This difference was not observed when the viral set point was raised to 400 copies/ml (Shapiro 2010).

The Kumar 2006 study compared NRTI with a PI (nelfinavir) which is no longer a component of initial recommended regimen. The comparator nelfinavir has been shown to be inferior to current PI regimens both in tolerability and virological suppression and is no longer a preferred treatment option (Moore 2006). There is considerable heterogeneity amongst PIs as far as tolerability is concerned, with newer members of the class, such as atazanavir, very suitable for individuals with hyperlipidaemia (Kumar 2009). Ritonavir-boosted PIs are now routinely used to initiate therapy (Ananworanich 2008; Hammer 2008; Potard 2007). Ritonavir was not included in any of the comparator arms of either the Kumar or Gulick studies but was included in the Shapiro trial. However, ritonavir may not be appropriate for some HIV-infected patients, such as those with pre-existing hyperlipidaemia, metabolic syndrome, underlying severe depression, and intolerance of ritonavir. For the latter, it is important to have a treatment regimen that is both efficacious and safe (Kumar 2009).

Treatment of antiretroviral-naive HIV-infected patients requires regimens that have the potential to be used for a long period without the fear of mutations often associated with failing regimens. Treatment with co-formulated abacavir-lamivudine-zidovudine offers the opportunity for patients to switch over to other antiretroviral classes in case of treatment failure. Patients failing on co-formulated abacavir-lamivudine-zidovudine are unlikely to be associated with emergence of multi-NRTI resistance (Shaefer 2004). However, components of the fixed-dose combination regimen have been associated with certain side effects (Shaefer 2004). Zidovudine may cause anaemia in some patients, lamivudine is associated with gastrointestinal adverse events, while abacavir is commonly associated with hypersensitivity reactions. Recent studies have shown that abacavir is associated with fatal hypersensitivity reactions in patients with a rare human leukocyte antigen (HLA) allele, HLA-B*5701 (Mallal 2008; Hughes 2008; Saag 2008). This suggests the need for genetic screening in individuals receiving abacavir-based therapy to reduce the risk of hypersensitivity reactions associated with the drug, which are often characterized by two or more clinical signs or symptoms that can include fever, rash, gastrointestinal symptoms, respiratory symptoms, and constitutional symptoms. Shapiro and colleagues did not observe any abacavir-related hypersensitivity reactions in their trial conducted in Botswana as none of their participants tested positive for HLA-B*5701 (Shapiro 2010).

Our findings indicate that the triple nucleoside fixed-dose combination remains a viable option for initiating anti-retroviral therapy, especially in HIV-infected patients with pre-existing hyperlipidaemia; possibly preventing exacerbation of the condition and obviating the need for antihyperlipidaemic agents and their incumbent drug interactions. Like any other antiretroviral therapy, constant monitoring of patients receiving this combination drug is advised to detect any resistance or side effects that may be attributed to abacavir, zidovudine, or lamivudine.

Publication and language biases are potential threats to all systematic reviews. We did not restrict our search to any language or publication status (published or unpublished). We are therefore confident that we have identified all existing randomised controlled trials relevant to our question but cannot rule out the possibility that there are additional trials that are unpublished or published in sources not accessible to our search.

AUTHORS' CONCLUSIONS

Implications for practice

We found that co-formulated abacavir-lamivudine-zidovudine remains a viable option for initiating anti-retroviral therapy, especially in HIV-infected patients with pre-existing hyperlipidaemia and those who do not tolerate ritonavir. The varied geographical locations of the included trials augment the external validity of our findings. We are moderately confident in our estimate of

the treatment effects of the triple NRTI regimen as initial therapy for HIV infection. In the context of the GRADE approach, such moderate quality of evidence implies that the true effects of the regimen are likely to be close to the estimate of effects found in this review.

Implications for research

There is a need for antiretroviral treatment programmes to have robust monitoring systems capable of identifying patients most likely to develop severe adverse events, viral resistance, and mutations. Further research on co-formulated abacavir-lamivudine-zidovudine should be geared towards defining the subgroup of HIV patients for whom this regimen will be most beneficial.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gulick 2004

Methods	Sequence generation: Patients were randomly assigned with equal opportunity to the treatment arms. Treatment allocation was stratified by screening HIV-1 RNA levels (<100,000 copies/ml or >=100,000 copies/mL) Allocation concealment: Adequate (central remote randomisation) Blinding: Participants, providers, and assessors all blinded. Loss-to-follow-up: When the triple nucleoside arm was stopped, after a median of 32 weeks, 83 participants (7%) had discontinued the study for various reasons including withdrawal of consent (n=21) and loss to follow-up (n=21). Analysis: performed on an intention-to-treat basis and included all follow-up data
Participants	Antiretroviral-naive HIV-1-infected adults recruited from 33 units of The AIDs Clinical Trials Group (ACTG) in the US. Exclusion criteria: Immunomodulator investigational therapy or vaccines within previous 30 days, weight less than 40kg, pregnancy, or lactation. N=1147 Male 81%, mean age 38 (SD 9) years, whites 40%, blacks 36%, Hispanics 21%, mean HIV-1 RNA level 4.85 log(10) copies/mL [SD 0.70], mean CD4 cell count = 234 cells/mm^3 (SD187). No significant levels between treatment arms.
Interventions	Eligible subjects were randomly allocated to one of three regimens given orally at standard doses and intervals: Regimen A: zidovudine (ZDV)-lamivudine(3TC)-abacavir (ABC) [Trizivir]. Regimen B: ZDV-3TC [Combivir] + efavirenz Regimen C: ZDV-3TC-ABC + efavirenz. Participants took a total of seven pills per day (including placebos), divided into two doses. In the event of treatment-limiting toxic effects of study drugs, the identity of the implicated drug was allowed to be revealed and substitution of another drug in the same class was permitted. Stavudine could be substituted for ZDV, didanosine could be substituted for ABC, and nevirapine could be substituted for efavirenz.
Outcomes	1. Virologic failure i.e. two successive HIV-1 RNA values of 200 or more copies/ml at least 16 weeks after randomisation. 2. HIV-1 RNA level of less than 200 copies/ml and with a level below 50 copies/ml. 3. Change in CD4 cell count from base line 4. Adverse events
Notes	The study was reviewed annually for safety and efficacy by the data and safety monitoring board. The second annual review showed differences between the triple-nucleoside regimen and each of the efavirenz-containing regimens that met prespecified stopping guidelines, and the DSMB recommended stopping the triple-nucleoside portion of the study, continuing

Gulick 2004   (*Continued*)

double-blind follow-up of the other two groups, and analysing and presenting the results with the data for the triple-nucleoside group compared with the pooled data from the efavirenz groups. At the time of stopping the triple-nucleoside arm, the median duration of follow-up was 32 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned with equal opportunity to the treatment arms. Treatment allocation was stratified by screening HIV-1 RNA levels. Such an elaborate randomisation sequence is likely to have been computer-generated
Allocation concealment (selection bias)	Low risk	Central remote randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and providers blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors all blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	When the triple-nucleoside arm was stopped in the Gulick 2004 trial after a median of 32 weeks, 83 participants (7%) had discontinued the study for various reasons, including withdrawal of consent (2%) and loss to follow-up (2%)
Selective reporting (reporting bias)	Low risk	No

Kumar 2006

Methods	Sequence generation: Patients were "randomized 1:1:1" suggesting block randomisation, but no detail of method of generating the randomisation sequence was given. Allocation concealment: Not described. Blinding: Participants - No. Providers - No. Assessors - Unclear. Loss to follow-up: 26.4%(23/87) for Trizivir, 24.2% (22/91) in COM/NFV, and 14.5%(12/83) in d4T/3TC/NFV groups. Analysis: performed on an intention-to-treat basis.
Participants	Particpants recruited from 34 outpatient sites in USA, Puerto Rico, Guatemala, Dominican Republic & Panama. Inclusion criteria: Documented HIV infection; naive or limited experience with antiretroviral therapy; age >= 18 years; CD4+ count > 50 cells/microL; 1000 copies/ml < HIV-1 RNA < 200,000 copies/ml. Exclusion criteria: pregnancy, lactation, , no antihyperlipidaemic or antidiabetic medications. N=261 Male 50%, median age 34 (range 18-60) years , Whites 20.9%, Blacks 39.8%, Hispanics 37.0%, median HIV-1 RNA level 4.44 log(10) copies/ml [range2.23-5.77), median CD4 cell count = 339 cells/mm3 (range19-1269), median total cholesterol 163mg/dl (92-267), median triglycerides 107 mg/dl (range38-597) No significant levels between treatment arms.
Interventions	Patients meeting entry criteria were randomised 1:1:1 to: Regimen A: Trizivir twice daily. Regimen B: Combivir + nelfinavir 1250 twice daily. Regimen C: Stavudine 40 mg + 3TC 150 mg + nelfinavir 1250 mg twice daily. At enrolment participants were stratified into two groups based on their screening plasma HIV-1 RNA level: <1000-100,000 copies/mL or >100,000-200,000 copies/mL.
Outcomes	1. Change from baseline in LDL cholesterol. 2. Virologic failure i.e. two successive HIV-1 RNA values of 200 or more copies/ml at least 16 weeks after randomisation. 2. HIV-1 RNA level of less than 200 copies/ml and with a level below 50 copies/ml. 3. Change in CD4 cell count from base line 4. Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were "randomized 1:1:1" suggesting block randomisation, and presumable

Kumar 2006 *(Continued)*

		computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and providers not blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up: 26.4% for Trizivir, 24.2% in COM/NFV, and 14.5% in d4T/3TC/NFV groups
Selective reporting (reporting bias)	Low risk	No

Kumar 2009

Methods	Sequence generation: Patients were "randomized 1:1:1" suggesting block randomisation, but no detail of method of generating the randomisation sequence was given Allocation concealment: Adequate (central randomisation). Blinding: No blinding Loss to follow-up: 9% (12/138) in the ABC/3TC/ZDV and 10% (14/140) in the ATV + 3TC/ZDV groups Analysis: Performed on an intent-to-treat exposed basis
Participants	279 subjects recruited between May 2004 and March 2005 from 46 sites in USA and Mexico Inclusion Criteria: HIV-1 infection, 18 years or older, ART-naive, and plasma HIV-1 RNA >=5000 but <200,000c/ML and CD4+ cell count >= 100 cells/mm^3. Exclusion criteria: Patients were excluded if they had medical conditions or required medications that could compromise their safety or interfere with drug absorption, if they had protocol-specific abnormal laboratory values N=279 79% male and racially diverse (>50% non-white race or ethnicity), 82% had HIV-1 RNA <100,000c/mL at baseline
Interventions	Patients meeting inclusion criteria were randomized 1:1 to receive ABC/3TC/ZDV (Trizivir®) twice daily or ATV (once daily) + 3TC/ZDV (twice daily).
Outcomes	1. HIV-1 viral load 2. CD4+/CD8+ lymphocyte subsets 3. Clinical chemistry 4. Hematology 5. Serum lipid panels 6. Insulin 7. Hemoglobin

Kumar 2009 (*Continued*)

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were "randomized 1:1:1" suggesting block randomisation, and presumable computer-generated
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding: No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 9% in the ABC/3TC/ZDV and 10% in the ATV + 3TC/ZDV groups
Selective reporting (reporting bias)	Low risk	No

Shapiro 2010

Methods	Sequence generation: Computer-generated randomisation sequence Allocation concealment: Patients were randomised 1:1:1 to Trizivir, Kaletra or Combivir by block permutation according to clinical site. Randomisation was assigned by calling the Data Management Centre in Gaborone (Central randomisation) Blinding: Not described Loss to follow-up: 15/285 in Trizivir group, 13/275 in kaletra group, and 5/170 in observational group left the study but reasons not given Analysis: Not mentioned
Participants	560 pregnant women with HIV-1 infection were recruited between 2006 and 2008 in Botswana Inclusion criteria included confirmed HIV-1 infection, age at least 18yrs, 26 to 34 weeks of gestation, haemoglobin level of at least 8.0g/deciliter, absolute neutrophil count of at least 1000 cells per cubic millimeter, alanine aminotransferase and aspartate aminotransferase levels at most 2 times the upper limit of normal and women who preferred to exclusively feed their babies by formula were excluded

Shapiro 2010   (*Continued*)

Interventions	Patients meeting inclusion criteria were randomised 1:1 to receive ABC/3TC/ZDV (Trizivir®) twice daily or co-formulated lopinavir and ritonavir (Kaletra) twice daily + 3TC/ZDV (Combivir) twice daily
Outcomes	HIV viral load(viral suppression to <400 and <50 copies/ml) Mother-to-child transmission intrapartum and postpartum Adverse events
Notes	Study protocol available at: http://www.nejm.org/doi/suppl/10.1056/NEJMoa0907736/suppl_file/nejmoa0907736_protocol.pdf

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All randomisation assignments were made based upon computer-generated lists
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 5.2% in the Trizivir® and 5.1% in Keletra® arms left the study for reasons that are not stated.
Selective reporting (reporting bias)	Low risk	No

Characteristics of excluded studies   *[ordered by study ID]*

Study	Reason for exclusion
Ait-Khaled 2002	Abacavir, lamivudine, zidovudine not used as a fixed-dose combination
Cahn 2004	Abacavir, lamivudine, zidovudine not used as a fixed-dose combination
d'Ettorre 2009	Abstract and article not available and authors did not respond to article request
Feinberg 2003	Abacavir, lamivudine, zidovudine not used as a fixed-dose combination

(Continued)

Matheron 2003	Abacavir, lamivudine, zidovudine not used as a fixed-dose combination
Munderi 2010	Abacavir, lamivudine, zidovudine not used as a fixed-dose combination
Ndembi 2010	Abacavir, lamivudine, zidovudine not used as a fixed-dose combination
Shao 2009	Co-formulated abacavir-lamivudine-zidovudine not compared to PI or NNRTI regimens
Sprenger 2010	Co-formulated abacavir-lamivudine-zidovudine used as maintenance therapy
Staszewski 2001	Abacavir, lamivudine, zidovudine not used as a fixed-dose combination
Vibhagool 2004	Abacavir, lamivudine, zidovudine not used as a fixed-dose combination

DATA AND ANALYSES

Comparison 1. Fixed-dose NRTI versus PI or NNRTI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Virologic failure	3	1687	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.56, 2.31]
2 Virologic suppression (<400copies/ml)	4	2247	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.39, 1.36]
3 Virologic suppression (<50copies/ml)	4	2247	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.75, 1.25]
4 CD4 cell count	3	1687	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.11, 0.09]
5 Severe adverse events	4	2247	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.78, 1.92]
6 Hypersensitivity	4	2242	Risk Ratio (M-H, Random, 95% CI)	4.04 [0.41, 40.02]

WHAT'S NEW

Last assessed as up-to-date: 13 January 2013.

Date	Event	Description
29 January 2013	New search has been performed	Update of review.
29 January 2013	New citation required and conclusions have changed	One new trial found (Shapiro 2010) and included. Title and conclusions changed.

HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 3, 2009

Date	Event	Description
24 June 2008	New citation required and minor changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

MS led the preparation of the original review and the current update. MS, EJK, and CSW assessed the eligibility of identified studies and extracted data from included studies. SMA and JS arbitrated (in the original review) when MS, EJK and CSW could not reach a consensus. MS and CSW wrote the first draft of the review, and all authors commented on the review and approved the final version.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- University of Cape Town (MSS, CSW), South Africa.
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- South African Medical Research Council (CSW), South Africa.
- Liverpool School of Tropical Medicine (EJK), UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Acquired Immunodeficiency Syndrome [drug therapy]; Anti-HIV Agents [adverse effects; *therapeutic use]; Benzoxazines [therapeutic use]; Dideoxynucleosides [*therapeutic use]; Drug Combinations; HIV Infections [*drug therapy]; Lamivudine [adverse effects; *therapeutic use]; Nelfinavir [therapeutic use]; Oligopeptides [therapeutic use]; Pyridines [therapeutic use]; Randomized Controlled Trials as Topic; Zidovudine [adverse effects; *therapeutic use]

MeSH check words

Humans