Quadruple versus triple combination antiretroviral therapies for treatment naive people with HIV: systematic review and meta-analysis of randomised controlled trials

Qi Feng,[1] Aoshuang Zhou,[1] Huachun Zou,[2,3] Suzanne Ingle,[4] Margaret T May,[4] Weiping Cai,[5] Chien-Yu Cheng,[6,7] Zuyao Yang,[1] Jinling Tang[1,8]

ABSTRACT

OBJECTIVE
To evaluate the effects of four drug (quadruple) versus three drug (triple) combination antiretroviral therapies in treatment naive people with HIV, and explore the implications of existing trials for clinical practice and research.

DESIGN
Systematic review and meta-analysis of randomised controlled trials.

DATA SOURCES
PubMed, EMBASE, CENTRAL, Web of Science, and the Cumulative Index to Nursing and Allied Health Literature from March 2001 to December 2016 (updated search in PubMed and EMBASE up to June 2018); and reference lists of eligible studies and related reviews.

STUDY SELECTION
Randomised controlled trials comparing quadruple with triple combination antiretroviral therapies in treatment naive people with HIV and evaluating at least one effectiveness or safety outcome.

REVIEW METHODS
Outcomes of interest included undetectable HIV-1 RNA, CD4 T cell count, virological failure, new AIDS defining events, death, and severe adverse effects. Random effects meta-analyses were conducted.

RESULTS
Twelve trials (including 4251 people with HIV) were eligible. Quadruple and triple combination antiretroviral therapies had similar effects on all relevant effectiveness and safety outcomes, with no point estimates favouring quadruple therapy. With the triple therapy as the reference group, the risk ratio was 0.99 (95% confidence interval 0.93 to 1.05) for undetectable HIV-1 RNA, 1.00 (0.90 to 1.11) for virological failure, 1.17 (0.84 to 1.63) for new AIDS defining events, 1.23 (0.74 to 2.05) for death, and 1.09 (0.89 to 1.33) for severe adverse effects. The mean difference in CD4 T cell count increase between the two groups was −19.55 cells/µL (−43.02 to 3.92). In general, the results were similar, regardless of the specific regimens of combination antiretroviral therapies, and were robust in all subgroup and sensitivity analyses.

CONCLUSION
In this study, effects of quadruple combination antiretroviral therapy were not better than triple combination antiretroviral therapy in treatment naive people with HIV. This finding lends support to current guidelines recommending the triple regimen as first line treatment. Further trials on this topic should be conducted only when new research is justified by adequate systematic reviews of the existing evidence. However, this study cannot exclude the possibility that quadruple cART would be better than triple cART when new classes of antiretroviral drugs are made available.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised controlled trials comparing quadruple with triple combination antiretroviral therapies for treatment naive people with HIV have continued to be conducted over the past two decades

But during the same period, practice guidelines have also continued to recommend triple combination antiretroviral therapies as standard first line treatment, and have rarely mentioned quadruple therapies

WHAT THIS STUDY ADDS

This study clarified that the effects of quadruple therapies were not better than those of standard triple therapies

The finding lends support to current guidelines and suggests no need to update recommendations of triple therapy on first line treatment for people with HIV in general

As the chance that quadruple therapies turn out to be more favourable than triple ones is low, the idea of evidence based research deserves more emphasis in proposing further trials, which are generally expensive and pose potential harms to study participants

Introduction

HIV infection is responsible for a substantial disease burden. With an estimated 36.7 million people living with HIV/AIDS, 1.8 million new cases of HIV infection, and 1.0 million AIDS related deaths in 2016, the disease is one of the five leading causes of total years of life lost globally.[1 2] The use of antiretroviral therapy for people with HIV is effective in suppressing viral replication, decreasing viral load, reconstructing immune system, preventing progression to advanced stages and death, prolonging life expectancy, improving quality of life, and reducing risk of transmission to others.[3-9]

Antiretroviral drugs have six classes: C-C chemokine receptor type 5 (CCR5) antagonists, nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTIs), fusion inhibitors, protease inhibitors, and integrase strand transfer inhibitors.[10] Theoretically, they can be used as either monotherapy or combination treatments. In 2002, a systematic review by Jordan and colleagues[11] showed that triple therapy was more effective than double therapy, and that double therapy was more effective than monotherapy in first line treatment. Possibly as a result, an increased number of drugs was hypothesised

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to be associated with enhanced effectiveness of antiretroviral therapy. Trials comparing quadruple with triple combination antiretroviral therapies (cART) have been conducted in the past two decades.[12 13]

However, during the same period, practice guidelines[14-17] have consistently recommended triple cART as first line treatment for most treatment naive people with HIV, consisting of two NRTI drugs as the so-called backbone plus another drug (an NNRTI, integrase strand transfer inhibitor, protease inhibitor, or CCR5 antagonist). These guidelines have rarely mentioned quadruple cART, which has naturally led to the question of whether quadruple cART is more favourable than triple cART. If so, guidelines should be updated to reflect this finding. If not, whether and how further trials on this topic should be conducted would be important to know, so that limited resources can be allocated to areas where genuine uncertainties exist and used in a more efficient way. This question is especially relevant because of the idea of evidence based research, which advocates that no new studies should be conducted without an adequate systematic review of existing evidence justifying new research, and is increasingly accepted by the community of biomedical research.[18]

However, the above question could not be readily answered by individual trials because their findings were often inconsistent. For example, Gulick and collegaues[19] found that people with HIV receiving quadruple therapy seemed more likely to have undetectable HIV-1 RNA (sample size 765; odds ratio 1.38, 95% confidence interval 0.96 to 1.98) but a lower mean increase in CD4 T cell count (mean difference −8.00 cells/μL, −33.62 to 17.62) than those receiving triple cART. However, Orkin and colleagues[20] had the opposite results (sample size 53; 0.51, 0.15 to 1.96, for undetectable HIV-1 RNA; 21.00 cells/μL, −52.90 to 94.90, for increase in CD4 T cell count).

With most existing trials small in sample size, it remained uncertain whether the inconsistency between studies was caused by insufficient statistical power, true difference in the effects of different cART, or both. To dissect this issue, a comprehensive analysis of existing evidence was needed. Therefore, we conducted a systematic review and meta-analysis to compare the effects of quadruple with triple cART in treatment naive people with HIV and explore the implications of evidence from existing trials for clinical practice and research.

Methods
This systematic review was conducted in accordance with the recommendations of the Cochrane handbook for systematic reviews of interventions (version 5.1.0)[21] and reported following the PRISMA statement.[22]

Literature search
We conducted a search in PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, and the Cumulative Index to Nursing and Allied Health Literature via EBSCO from March 2001 to December 2016, and updated the search in PubMed and EMBASE up to June 2018. March 2001 was set as the starting point because Jordan and colleagues conducted a comprehensive literature search[11] in February 2001 and identified only one study comparing quadruple cART with triple cART,[23] which has been included in the present systematic review. Four groups of keywords (together with their synonyms and derivatives) were used in the literature search, including those for HIV/AIDS; randomised controlled trial; treatment and therapy; and abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zidovudine, NRTI, triple, and quadruple (supplement 1 shows the PubMed search strategy). We used the names of seven available NRTI drugs as keywords because the NRTI drugs are the so-called backbones in all cART. The reference list of included studies and relevant reviews were manually searched for additional studies.

Eligibility criteria and study selection
Randomised controlled trials that compared quadruple cART with triple cART for the first line treatment of people with HIV and evaluated at least one outcome of effectiveness or safety were considered eligible for the present systematic review. Measures of effectiveness included undetectable HIV-1 RNA (<50 copies/mL), CD4 T cell count, virological failure, new AIDS defining events, and all cause mortality, and the measure of safety was severe adverse effects (≥grade 3) as a composite outcome. We examined the composite outcome instead of specific adverse effects, because the composite was reported consistently by studies and thus combinable.

In determining the number of drugs, boosted protease inhibitor was counted as one drug, because the booster (ritonavir, cobicistat) is used in low doses to inhibit a particular liver enzyme that normally metabolises protease inhibitors and enhances the pharmacokinetic profile of other protease inhibitors rather than for its own antiretroviral activity.[24] We excluded studies with a follow-up length shorter than 48 weeks, which was not sufficient for observing clinically significant outcomes for a lifelong intervention. This timeframe had already been adopted by previous systematic reviews on HIV treatment.[25-27] If multiple publications from the same study were found, only the one with most complete information was included.

All records retrieved by literature search were assessed by two reviewers (QF and AZ) independently for inclusion. The titles and abstracts were first screened to examine their potential eligibility. Full texts of potentially eligible studies were then reviewed to determine their final eligibility. All disagreements were resolved by discussion or referring to a third reviewer (ZY).

Data extraction and quality assessment
A pre-designed form was used to extract study bibliographic information (eg, first author, publication year, study country), treatment information (eg, treatment duration, regimen), patient characteristics

(eg, sample size, age, proportion of male patients, baseline count of CD4 T cells, baseline viral load of HIV-1 RNA), main results (eg, risk ratio, mean difference), and information related to quality assessment from eligible studies. Two reviewers (QF and AZ) extracted data and assessed the methodological quality of included studies independently. All disagreements were resolved through discussion.

The Cochrane risk of bias tool was used for quality assessment.[28] This tool evaluated biases from seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and others. The risk of bias in each domain was judged as low, high, or unclear. The overall risk of bias in a study was classified as low if all domains had low risk, as high if one or more domains had high risk, or as unclear otherwise.[28] Because the study outcomes included both subjective (certain severe adverse effects such as pain, fatigue, and psychological symptoms require subjective assessments for grading) and objective (that is, other outcomes confirmed with standardised laboratory techniques or objective records) ones, the risk of bias in data on different types of outcomes was assessed separately according to Cochrane's guidelines.[28]

Data analysis

Triple cART was used as the reference group in meta-analysis. For continuous outcomes (that is, CD4 T cell count) in this systematic review, the mean change from baseline and standard deviation were extracted or calculated for each group in each study (supplement 2). We then calculated the difference in mean change between groups, and subsequently pooled them across the studies included in the meta-analysis. A difference in mean change greater than 0 favours quadruple therapy. For the other outcomes, which were binary, a risk ratio with 95% confidence interval was calculated on the basis of the number of people with HIV and number of events in each treatment group within each study, and then combined across studies to obtain an overall estimate. A risk ratio greater than 1 favours triple cART for all binary outcomes except for undetectable HIV-1 RNA.

The outcome data reported at the longest follow-up were used for primary analysis. This practice differed from previous reviews that used a uniform time frame of 48 weeks,[25 27] because we wanted to include as many eligible studies in the analysis as possible. The studies reporting data at 48 weeks were also combined in the present systematic review, but as a sensitivity analysis.

For those eligible trials that had more than one triple cART arm or quadruple cART arm within the same study, we first combined the arms with the same number of drugs (eg, combining multiple triple cART arms into one single triple cART arm) using the method recommended in the Cochrane handbook,[29] and then compared the merged arm with the comparative arm.

The random effects model was used for all meta-analyses. Statistical heterogeneity among the studies

was measured by the Cochrane Q test and I^2 statistic. A P value of 0.10 or less or an I^2 of 50% or more suggested substantial heterogeneity, in which case we used subgroup analyses and meta-regression, if appropriate, to analyse potential sources of heterogeneity.[30 31] The prespecified subgroup factors included CD4 T cell counts at baseline (<200 cells/μL or ≥200 cells/μL) and the class of the fourth drug in the quadruple cART arm. We conducted sensitivity analyses by removing the studies with high risk of bias, using the outcome data reported at 48 weeks only, or replacing the standard deviations of increase in CD4 T cell counts with those estimated by different methods. We planned to assess potential publication bias by funnel plots and Egger's test but actually did not do so, because the number of studies included in every meta-analysis was fewer than 10, in which case the funnel plots and Egger's test could yield misleading results and were not recommended.[32] All data analyses were performed with the meta package (version 4.9-2) in R software (version 3.4.3).

Patient and public involvement

No people with HIV were involved in the design or implementation of the study, measurement of the outcome, interpretation of results, or writing or editing of the manuscript. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

As shown in the figure 1, 13 710 records were retrieved from initial electronic search and one additional record from a later manual search. After screening titles, abstracts, and full texts, 12 studies including 4251 people with HIV were finally included in this systematic review.[12 19 20 33-41]

Study characteristics

Characteristics of 12 eligible studies are shown in table 1. Of 4251 patients who were randomised, 1693 were assigned to receive quadruple cART. One study[12] included one triple cART arm and two quadruple cART arms, one study[33] included two triple cART arms and one quadruple cART arm, one study[40] included three triple cART arms and one quadruple cART arm, while the other nine studies included two arms (that is, one triple cART arm and one quadruple cART arm). In 10 studies, the quadruple cART consisted of three drugs that were used in the triple cART arm plus a fourth drug, which was most frequently an NNRTI, followed by an NRTI, protease inhibitor, CCR5 antagonist, and fusion inhibitor. In another study,[35] the triple cART and quadruple cART had only two drugs in common, while the two cART groups in the remaining study[41] had no drugs in common. The median sample size was 214 (range 30-1216). The mean age was 37.1 years (range 32.9-43.5) and the median proportion of male individuals was 77.1% (range 58-100%). The follow-up length varied from 48 to 144 weeks (median 48). Four studies[19 33 38 41] recruited people

13 710
Records identified through database search
2646 PubMed
3796 Embase
2575 Cochrane Central Register of Controlled Trials
428 Cumulative Index to Nursing and Allied Health Literature
4265 Web of Science

6705
Duplicates

7005
Title and abstracts screened for eligibility

6965
Excluded
1823 Not randomised controlled trial
1076 Not treatment naive patients with HIV
3503 Not comparison of quadruple and triple cART
563 Did not evaluate interested outcomes

1
Reference identified through reference list search

41
Full texts screened for eligibility

29
Excluded
7 Not comparison of quadruple and triple cART
20 Did not evaluate interested outcomes
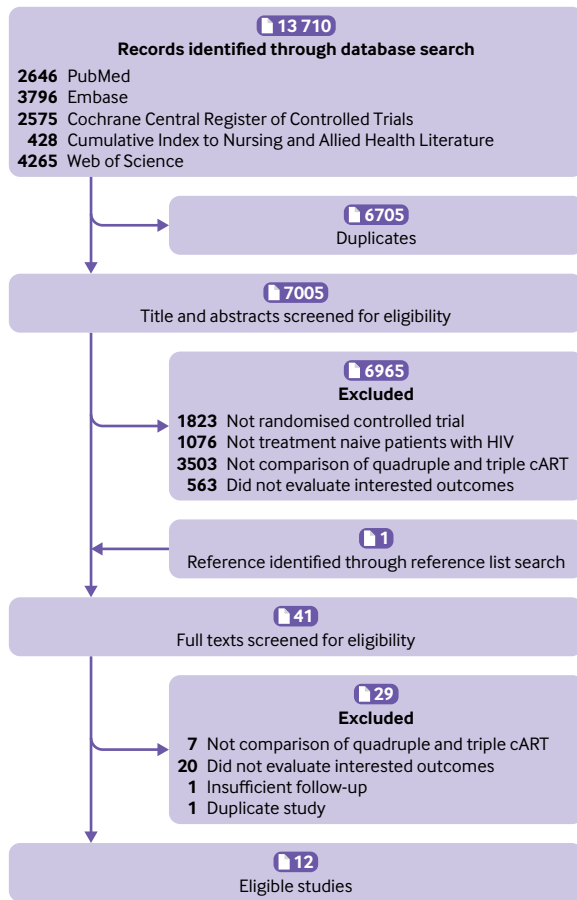1 Insufficient follow-up
1 Duplicate study

12
Eligible studies

Fig 1 | The flowchart of study selection

with HIV with a mean CD4 T cell count above 200 cells/µL at baseline.

All 12 studies reported on objective outcomes (table 2). Five studies[12 33-35 39] were at low risk of bias, one study[40] that reported data on undetectable HIV-1 RNA and virological failure was at high risk of bias due to incomplete outcome data, and six studies[19 20 36-38 41] were at unclear risk owing to insufficient reporting of randomisation and allocation concealment. Five studies reported on severe adverse events: one study[33] was at low risk of bias, two[12 40] were at high risk of bias because of no blinding of outcome assessment and incomplete outcome data, and another two[34 36] were at unclear risk of bias because of insufficient reporting of randomisation and blinding of outcome assessment.

Comparative effectiveness and safety of quadruple versus triple therapy

None of the quadruple therapies was significantly better than any of the triple therapies in any trial on any of the outcomes assessed (fig 2, fig 3, fig 4, fig 5, fig 6, fig 7). Meta-analyses showed that quadruple and triple cART had similar effects on all interested outcomes, with none of the point estimates favouring quadruple cART. Specifically, nine studies (n=3622 people with HIV) reported on undetectable HIV-1 RNA, and the overall risk ratio was 0.99 (95% confidence interval 0.93 to 1.05; heterogeneity test I^2=41%, P=0.10; fig 2). Five studies (n=1819) reported on change of CD4 T cell count; the overall mean difference was −19.55 cells/µL (−43.02 to 3.92; I^2=22%, P=0.27; fig 3). Five studies (n=2887) reported on virological failure; the pooled

Table 1 | Characteristics of included studies comparing quadruple with triple combination antiretroviral therapy as first line treatment for people with HIV

Study ID (country)	Sample size (quadruple/triple)	Age	Male patients (%)	Baseline CD4 count (cells/µL)	Baseline HIV viral load (log10/mL)	Follow-up (weeks)	Antiretroviral therapy Quadruple combination	Antiretroviral therapy Triple combination	Risk of bias Objective outcomes	Risk of bias Subjective outcomes
Fischl 2003[12] (US, Italy)	517 (349/168)	38.2	81.4	161.00	5.42	108	3TC+AZT+IDV+EFV; 3TC+AZT+IDV+NFV	3TC+AZT+IDV	Low	High
Kirk 2003[35] (Denmark)	233 (118/115)	37	75.5	137.50	5.00	48	2 NRTIs+NFV+NVP	2 NRTIs+SQV/r	Low	NA
van Leth 2004[40] (US, Australia, Europe, South Africa, Thailand)	1216 (209/1007)	34.1	63.4	190.00	4.70	48	d4T+3TC+NVP+EFV	d4T+3TC+EFV; d4T+3TC+NVP (once daily); d4T+3TC+NVP (twice daily)	High	High
Orkin 2005[20] (UK)	53 (27/26)	NA	NA	118.50	5.50	48	AZT+3TC+EFV+ABC	AZT+3TC+EFV	Unclear	NA
Portilla 2005[37] (Spain)	30 (15/15)	36.6	76.7	53.65	5.39	48	SQV+2 NRTIs+NFV	SQV+2 NRTIs	Unclear	NA
INITIO 2006[33] (Australia, Brazil, Canada, New Zealand, and 17 European countries)	764 (250/514)	38.6	79	223.33	4.93	144	ddl+d4T+EFV+NFV	ddl+d4T+EFV; ddl+d4T+NFV	Low	Low
Gulick 2006[19] (US)	765 (383/382)	38	81	215.00	4.77	144	AZT+3TC+EFV+ABC	AZT+3TC+EFV	Unclear	NA
Moyle 2006[36] (UK)	113 (57/56)	39.5	91.2	173.50	5.20	48	AZT+3TC+ABC+TDF	AZT+3TC+EFV	Unclear	Unclear
Joly 2013[34] (France)	194 (100/94)	43.5	77.8	32.00	5.40	48	FTC+TDF+LPV/r (or EFV)+ENF	FTC+TDF+LPV/r (or EFV)	Low	Unclear
Puertas 2014[38] (Spain)	30 (15/15)	32.9	100	424.50	4.95	48	RAL+TDF+FTC+MRV	RAL+TDF+FTC	Unclear	NA
Sierra-Madero 2014[39] (Mexico, South Africa)	276 (140/136)	37.1	64.5	34.00	5.35	48	EFV+TDF+FTC+MRV	EFV+TDF+FTC	Low	NA
Mora-Peris 2018[41] (UK)	60 (30/30)	33	58	441.00	4.67	48	ABC+3TC+DRV/r+MRV	TDF+FTC+ATV/r	Unclear	NA

3TC=lamivudine; ABC=abacavir; AZT=zidovudine; d4T=stavudine; ddl=didanosine; EFV=efavirenz; ENF=enfuvirtide; FTC=emtricitabine; IDV=indivavir; LPV=lopinavir; MRV=maraviroc; NFV=nelfinavir; NRTI=nucleoside reverse-transcriptase inhibitor; NVP=nevirapine; RAL=raltegravir; SQV=saquinavir; TDF=tenofovir disoproxil fumarate; DRV=darunavir; ATV=atazanavir; /r=boosted with ritonavir; NA=not available or not applicable.

Table 2 | Results of risk of bias assessment of included studies comparing quadruple with triple combination antiretroviral therapy as first line treatment for people with HIV

| Study (first author and year) | Random sequence generation | Allocation concealment | Blinding of participants and personnel | | Blinding of outcome assessment | | Incomplete outcome data | Selective reporting | Other bias | Overall risk of bias | |
			For subjective outcomes	For objective outcomes	For subjective outcomes	For objective outcomes				For subjective outcomes	For objective outcomes
Fischl 2003[12]	Low	Low	Low	Low	High	Low	Low	Low	Low	High	Low
Kirk 2003[35]	Low	Unclear	NA	Low	NA	Low	Low	Low	Low	NA	Low
van Leth 2004[40]	Unclear	Low	Low	Low	High	Low	High	Low	Low	High	High
Orkin 2005[20]	Unclear	Unclear	NA	Low	NA	Low	Unclear	Low	Low	NA	Unclear
Portilla 2005[37]	Unclear	Unclear	NA	Low	NA	Low	Unclear	Low	Low	NA	Unclear
INITIO 2006[33]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Gulick 2006[19]	Unclear	Unclear	NA	Low	NA	Low	Low	Low	Low	NA	Unclear
Moyle 2006[36]	Unclear	Low	Low	Low	Unclear	Low	Low	Low	Low	Unclear	Unclear
Joly 2013[34]	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Unclear	Low
Puertas 2014[38]	Unclear	Unclear	NA	Low	NA	Low	Low	Low	Low	NA	Unclear
Sierra-Madero 2014[39]	Low	Low	NA	Low	NA	Low	Low	Low	Low	NA	Low
Mora-Peris 2018[41]	Unclear	Unclear	NA	Low	NA	Low	Low	Low	Low	NA	Unclear

NA=study did not report subjective outcome (severe adverse effects).

risk ratio was 1.00 (0.90 to 1.11; I^2=23%, P=0.27; fig 4). Three studies (n=1338) reported on new AIDS defining events; the pooled risk ratio was 1.17 (0.84 to 1.63; I^2=0%, P=0.53; fig 5). Five studies (n=2379) reported on death; the pooled risk ratio was 1.23 (0.74 to 2.05; I^2=0%, P=0.99; fig 6). Five studies (n=2951) reported on severe adverse effects; the pooled risk ratio was 1.09 (0.89 to 1.33; I^2=48%, P=0.10; fig 7).

Subgroup and sensitivity analyses

The P value for Cochrane's Q test suggested presence of substantial heterogeneity in figure 2 and figure 7. Prespecified subgroup analyses showed that the results did not vary considerably according to baseline CD4 T cell count and the class of the fourth drug in the quadruple cART arm (supplement 3A-D). Because the number of studies included in the two meta-analyses was small, meta-regression was not performed. Sensitivity analyses that removed studies with potential bias showed consistent results with the primary meta-analyses (risk ratio 1.00 for undetectable HIV-1 RNA, 1.00 for virological failure, 0.98 for severe adverse effects, and 1.02 for AIDS defining events; supplement 3E, 3F, 3H, and 3I, respectively). Such sensitivity analyses were not performed for other outcomes because none of the studies reporting them was at a high risk of bias. Sensitivity analysis that pooled the outcome data reported at 48 weeks, which also showed consistent results, was performed for undetectable HIV-1 RNA and increase in CD4 T cell count only (supplement 3J and 3K) and not for other outcomes owing to lack of relevant data. When the standard deviations for increase in CD4 T cell count were replaced by those estimated by different methods, the results of figure 3 either remained similar (that is, quadruple and triple arms not statistically different) or favoured triple therapies (supplement 2). As explained in the methods section, potential publication bias was not assessed, because the number of studies was small (<10) in all of the above meta-analyses.
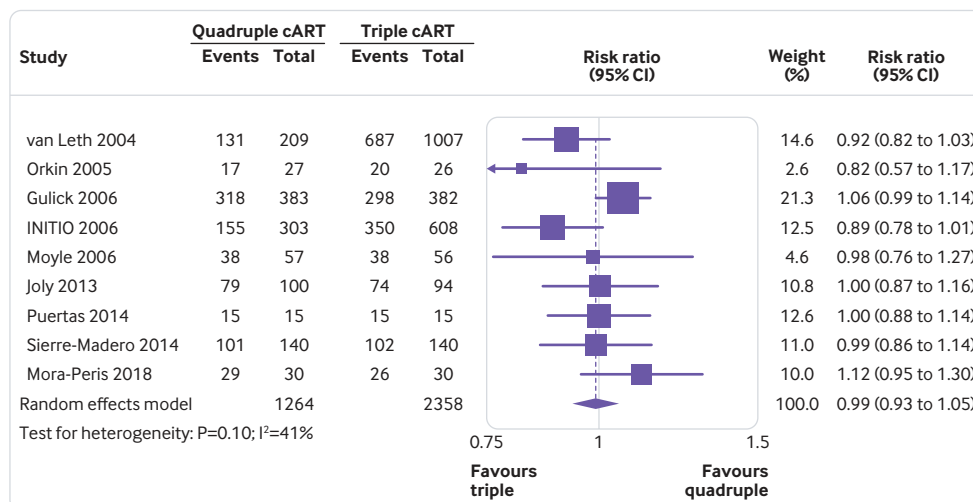
Fig 2 | Meta-analysis of comparative effects between quadruple and triple combination antiretroviral therapies (cART) as first line treatment for people with HIV, on undetectable HIV-1 RNA
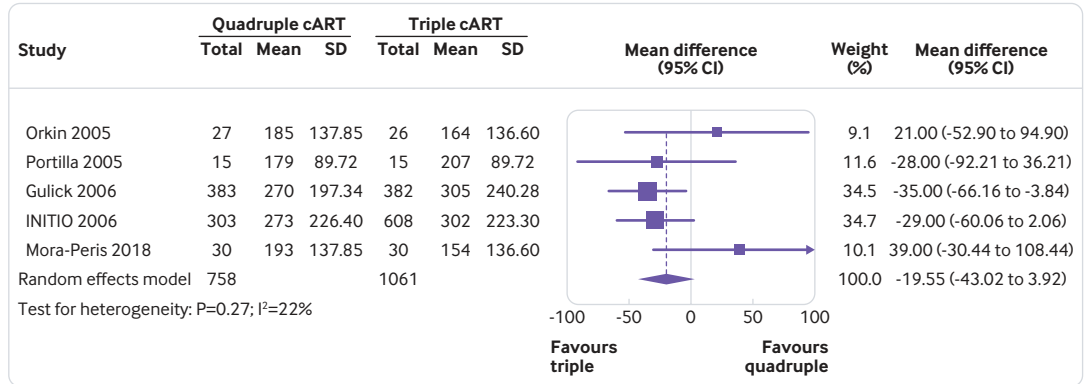
Fig 3 | Meta-analysis of comparative effects between quadruple and triple combination antiretroviral therapies (cART) as first line treatment for people with HIV, on increase in CD4 T cell count (cells/µL). SD=standard deviation

Discussion

Principal findings

This systematic review pooled data from 12 studies and showed that the effects of quadruple cART were not better than standard triple cART for first line treatment of people with HIV. Although marginally substantial heterogeneity was observed for two outcomes (undetectable HIV-1 RNA and severe adverse effects), prespecified subgroup and sensitivity analyses suggested that the primary results were robust across various scenarios. The study[13] that was excluded from this systematic review owing to insufficient follow-up time showed that the addition of a fourth drug did not lead to a greater increase in the CD4 T cell count at 36 weeks, which was consistent with our findings. The findings were also supported by mechanism studies conducted in animals.[42]

Strengths, weaknesses, and implications of the study

The systematic review by Jordan and colleagues[11] showed that escalating the number of antiretroviral drugs was an effective strategy to improve clinical outcomes. However, it did not evaluate quadruple cART because of the sparse data. The present systematic review is an important addition in this regard. Taking the results from the two systematic reviews together, we found that the effectiveness of cART increases as

the number of drugs escalates up to three, but does not continue increasing at four, while the risk of adverse effects seems to keep increasing as the number of drugs increases.

In the included studies, the triple therapies consisted of two NRTI drugs plus one NNRTI, protease inhibitor, or integrase strand transfer inhibitor as recommended, and the added fourth drug varied across studies, involving five classes of antiretroviral drugs. Although different drug combinations could influence the effects of quadruple or triple cART themselves, they would not necessarily lead to a big difference between the two types of regimen,[11 43] as shown by the subgroup analyses of this systematic review. In addition, the meta-analyses with no or very low heterogeneity (that is, fig 3, fig 4, fig 5, fig 6) showed that the effects of quadruple cART were not better than those of triple cART. Furthermore, adding a fourth drug to first line treatment not only increases financial and pill burden, which might lead to lower adherence to treatment and consequently drug resistance and treatment failure, but also limits drug options for second line treatments and beyond.[44 45] Thus, triple cART regimens could be seen as being superior to quadruple regimens. This finding lends support to current guidelines recommending triple therapy as first line treatment.[14-17]

The generalisability of the findings could be a concern, owing to the many potential drug

Fig 4 | Meta-analysis of comparative effects between quadruple and triple combination antiretroviral therapies (cART) as first line treatment for people with HIV, on virological failure

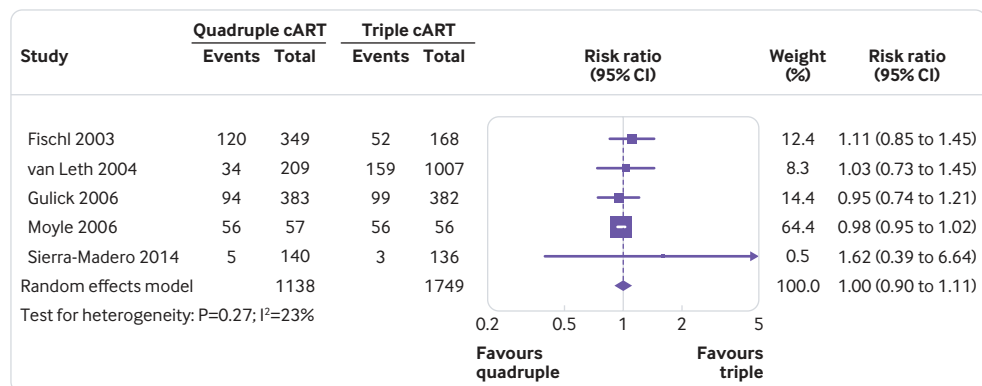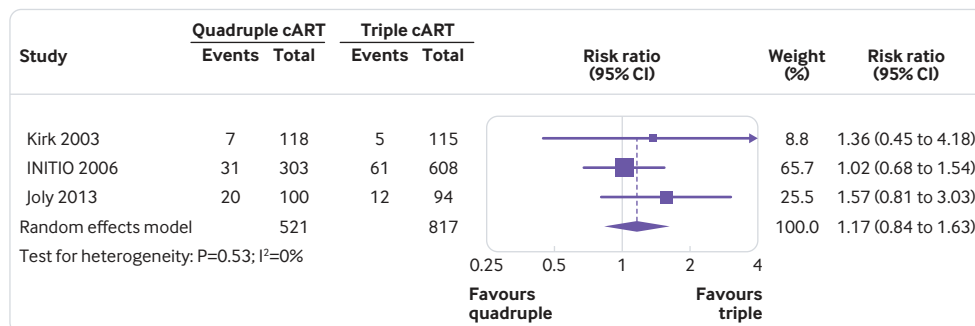| Study	Quadruple cART		Triple cART		Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
	Events	Total	Events	Total			
Kirk 2003	7	118	5	115		8.8	1.36 (0.45 to 4.18)
INITIO 2006	31	303	61	608		65.7	1.02 (0.68 to 1.54)
Joly 2013	20	100	12	94		25.5	1.57 (0.81 to 3.03)
Random effects model		521		817		100.0	1.17 (0.84 to 1.63)
Test for heterogeneity: P=0.53; I²=0%							

Fig 5 | Meta-analysis of comparative effects between quadruple and triple combination antiretroviral therapies (cART) as first line treatment for people with HIV, on new AIDS defining events

combinations for quadruple and triple cART, with only a few of these combinations evaluated in this systematic review. However, the tested cART regimens have been designed according to good evidence, beliefs, and scientific theories, so they are more likely to be better than other possible combinations. Given this assumption, it is unlikely that other combinations would be better than those tested in the trials. In fact, none of the tested quadruple therapies was statistically significantly better than any of the triple therapies in any trial on any of the outcomes assessed (fig 2, fig 3, fig 4, fig 5, fig 6, fig 7). This finding suggests strongly that these quadruple therapies be highly consistently not better than triple ones.

If the assumption does not hold that the tested cART regimens are better than any untested possible cART regimens, we would need new guiding rules that are better than current ones in designing combination therapies to increase the chance of success and improve cost effectiveness. Without a new guiding rule, there is only a faint possibility that more effective combinations have not been designed and tested so far. In addition, the cost of proving this belief would be huge, because of the large number of possible four drug and three drug combinations; the number of possible comparisons (pairs) between these combinations would be even larger. Given the currently available evidence shown in this study, further testing of new combinations might not be worthwhile.

Even if future studies comparing other drug combinations show a difference, quadruple cART regimens are more likely to be inferior to triple cART regimens, rather than the other way around, because none of the point estimates of effect from our meta-analyses favoured quadruple cART. This argument is especially tenable in view of the additional financial and pill burden and consequent issues associated with quadruple cART. Thus, the cost effectiveness of huge investment in such trials could be a concern. However, this systematic review cannot exclude the possibility that quadruple therapies would be better than triple ones when new classes of antiretroviral drugs are made available.

The above findings have important implications for future research. According to clinical trial registries, large trials to compare quadruple cART with triple cART are still being conducted, with primary interest in surrogate outcomes.[46] Some researchers have gone even further and compared quintuple cART regimens with triple cART regimens, which has unsurprisingly shown no difference in effects between the two regimens.[47 48] Thus, the idea of evidence based research deserves more emphasis in the proposal of further trials, which are generally expensive and pose potential harms to study participants. Network analysis could also be used to compare regimens across different trials in a principled and cost effective way.

This systematic review had a few limitations. Firstly, it was not pre-registered. However, the review was

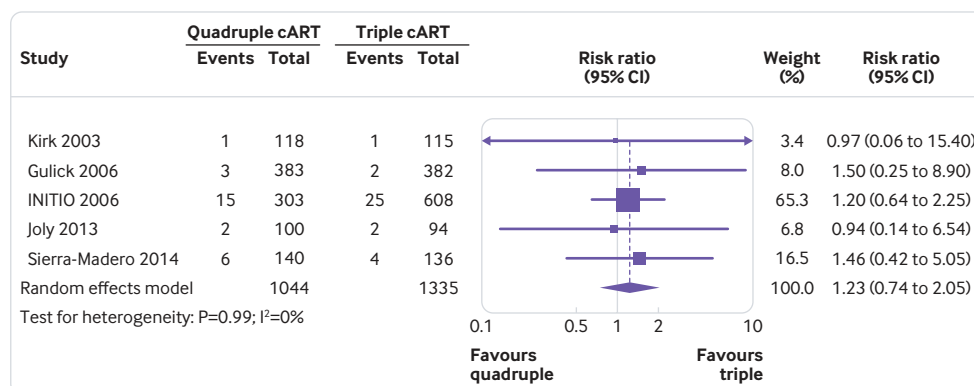| Study	Quadruple cART		Triple cART		Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
	Events	Total	Events	Total			
Kirk 2003	1	118	1	115		3.4	0.97 (0.06 to 15.40)
Gulick 2006	3	383	2	382		8.0	1.50 (0.25 to 8.90)
INITIO 2006	15	303	25	608		65.3	1.20 (0.64 to 2.25)
Joly 2013	2	100	2	94		6.8	0.94 (0.14 to 6.54)
Sierra-Madero 2014	6	140	4	136		16.5	1.46 (0.42 to 5.05)
Random effects model		1044		1335		100.0	1.23 (0.74 to 2.05)
Test for heterogeneity: P=0.99; I²=0%							

Fig 6 | Meta-analysis of comparative effects between quadruple and triple combination antiretroviral therapies (cART) as first line treatment for people with HIV, on death
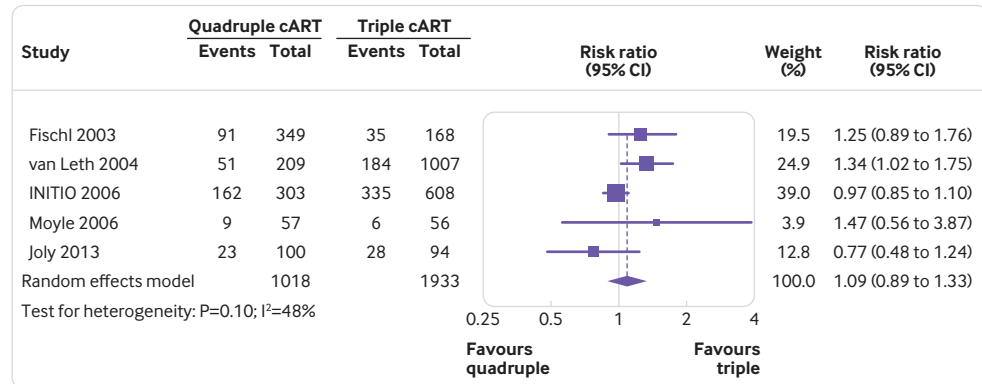
Study	Quadruple cART		Triple cART		Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
	Events	Total	Events	Total			
Fischl 2003	91	349	35	168		19.5	1.25 (0.89 to 1.76)
van Leth 2004	51	209	184	1007		24.9	1.34 (1.02 to 1.75)
INITIO 2006	162	303	335	608		39.0	0.97 (0.85 to 1.10)
Moyle 2006	9	57	6	56		3.9	1.47 (0.56 to 3.87)
Joly 2013	23	100	28	94		12.8	0.77 (0.48 to 1.24)
Random effects model		1018		1933		100.0	1.09 (0.89 to 1.33)
Test for heterogeneity: P=0.10; I²=48%							

Fig 7 | Meta-analysis of comparative effects between quadruple and triple combination antiretroviral therapies (cART) as first line treatment for people with HIV, on severe adverse effects

conducted and reported following the widely accepted guidelines to reduce manipulation and increase transparency. Furthermore, as all major clinical outcomes were studied and reported, the impact of potential incomplete reporting in this review (if any) on the main conclusions was reduced to minimum. Therefore, the validity of this systematic review is unlikely to have been influenced by the lack of pre-registration. Secondly, some of the included studies had potential bias because of no blinding of outcome assessment and incomplete outcome data, which might have undermined the reliability of the results. However, the effect estimates remained unchanged in sensitivity analyses that removed those studies, indicating that the potential bias in studies did not affect the results much. Finally, due to the small number of studies, funnel plots and Egger's test were not performed. Thus, we cannot rule out the possibility of publication bias.

Conclusion

In our review, the effects of quadruple cART were not better than triple cART in treatment naive people with HIV. This finding lends support to current guidelines recommending triple cART as first line treatment, especially considering the financial and pill burden and consequent issues introduced by a fourth drug. As the chance that quadruple cART turns out to be more favourable than triple cART is low, the idea of evidence based research deserves more emphasis in proposing further trials on this topic. However, this study does not exclude the possibility that quadruple cART would be better than triple ones when new classes of antiretroviral drugs are made available.

AUTHOR AFFILIATIONS
[1]Division of Epidemiology, Jockey Club School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China
[2]School of Public Health (Shenzhen), Sun Yat-Sen University, Shenzhen, China
[3]Kirby Institute, University of New South Wales, Sydney, Australia
[4]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[5]Department of Infectious Disease, Guangzhou Eighth People's Hospital, Guangzhou, China
[6]Division of Infectious Diseases, Department of Internal Medicine, Taoyuan General Hospital, Ministry of Health and Welfare, Taoyuan, Taiwan
[7]School of Public Health, National Yang-Ming University, Taipei, Taiwan
[8]Shenzhen Key Laboratory for Health Risk Analysis, Shenzhen Research Institute of the Chinese University of Hong Kong, Shenzhen, China

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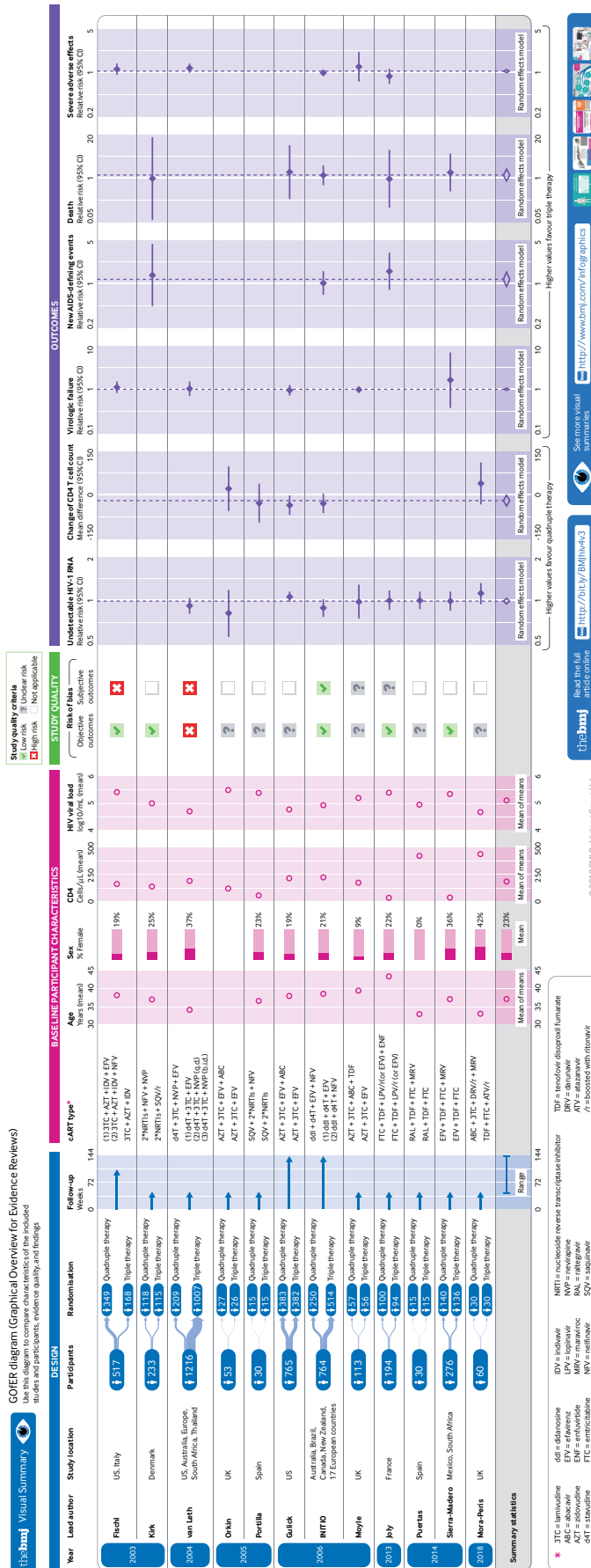
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Web appendix: Supplementary materials
Infographic: Visual summary of trial and participant characteristics

the bmj Visual Summary

GOfER diagram (Graphical Overview for Evidence Reviews)
Use this diagram to compare characteristics of the included studies and participants, evidence quality, and findings

DESIGN | **BASE LINE PARTICIPANT CHARACTERISTICS** | **STUDY QUALITY** | **OUTCOMES**

Study quality criteria
☑ Low risk ▨ Unclear risk ☐ Not applicable

Risk of bias: Objective outcomes / Subjective outcomes
☑ Low risk ❌ High risk

Year	Lead author	Study location	Randomisation	Participants	Follow-up Weeks	cART type*	Age Years (mean)	Sex % Female	CD4 Cells/μL (mean)	HIV viral load log10/mL (mean)
2003	Fischl	US, Italy	Quadruple therapy ↑349 / Triple therapy ↑168	↑517		(1) 3TC + AZT + IDV + EFV / (2) 3TC + AZT + IDV + NFV / 3TC + AZT + IDV		19%		
	Kirk	Denmark	Quadruple therapy ↑118 / Triple therapy ↑115	↑233		2*NRTIs + NFV + NVP / 2*NRTIs + SQV/r		25%		
2004	van Leth	US, Australia, Europe, South Africa, Thailand	Quadruple therapy ↑209 / Triple therapy ↑1007	↑1216		d4T + 3TC + NVP + EFV / (1) d4T + 3TC + EFV / (2) d4T + 3TC + NVP (qd) / (3) d4T + 3TC + NVP (bid)		37%		
2005	Orkin	UK	Quadruple therapy ↑27 / Triple therapy ↑26	↑53		AZT + 3TC + EFV + ABC / AZT + 3TC + EFV				
	Portilla	Spain	Quadruple therapy ↑15 / Triple therapy ↑15	↑30		SQV + 2*NRTIs + NFV / SQV + 2*NRTIs		23%		
2006	Gulick	US	Quadruple therapy ↑383 / Triple therapy ↑382	↑765		AZT + 3TC + EFV + ABC / AZT + 3TC + EFV		19%		
	INITIO	Australia, Brazil, Canada, New Zealand, 17 European countries	Quadruple therapy ↑250 / Triple therapy ↑514	↑764		(1) ddI + d4T + EFV + NFV / (2) ddI + d4T + NFV		21%		
2013	Moyle	UK	Quadruple therapy ↑57 / Triple therapy ↑56	↑113		AZT + 3TC + ABC + TDF / AZT + 3TC + EFV		9%		
	Joly	France	Quadruple therapy ↑100 / Triple therapy ↑94	↑194		FTC + TDF + LPV/r (or EFV) + ENF / FTC + TDF + LPV/r (or EFV)		22%		
2014	Puertas	Spain	Quadruple therapy ↑15 / Triple therapy ↑15	↑30		RAL + TDF + FTC + MRV / RAL + TDF + FTC		0%		
	Sierra-Madero	Mexico, South Africa	Quadruple therapy ↑140 / Triple therapy ↑136	↑276		EFV + TDF + FTC + MRV / EFV + TDF + FTC		36%		
2018	Mora-Peris	UK	Quadruple therapy ↑30 / Triple therapy ↑30	↑60		ABC + 3TC + DRV/r + MRV / TDF + FTC + ATV/r		42%		
	Summary statistics		Range				Mean of means	Mean	Mean of means	Mean of means

Follow-up scale: 0 72 144 (Weeks)
Age scale: 30 35 40 45 (Years)
CD4 scale: 0 250 500 (Cells/μL)
HIV viral load scale: 4 5 6 (log10/mL)

OUTCOMES

Undetectable HIV-1 RNA — Relative risk (95% CI): 0.5 / 1 / 2 — Random effects model — Higher values favour quadruple therapy
Change of CD4 T cell count — Mean difference (95% CI): -150 / 0 / 150 — Random effects model
Virologic failure — Relative risk (95% CI): 0.1 / 1 / 10 — Random effects model
New AIDS-defining events — Relative risk (95% CI): 0.2 / 1 / 5 — Random effects model — Higher values favour triple therapy
Death — Relative risk (95% CI): 0.05 / 1 / 20 — Random effects model
Severe adverse effects — Relative risk (95% CI): 0.2 / 1 / 5 — Random effects model

Abbreviations:
3TC = lamivudine
ABC = abacavir
AZT = zidovudine
d4T = stavudine
ddI = didanosine
EFV = efavirenz
ENF = enfuvirtide
FTC = emtricitabine
IDV = indinavir
LPV = lopinavir
MRV = maraviroc
NFV = nelfinavir
NRTI = nucleoside reverse transcriptase inhibitor
NVP = nevirapine
RAL = raltegravir
SQV = saquinavir
TDF = tenofovir disoproxil fumarate
DRV = darunavir
ATV = atazanavir
/r = boosted with ritonavir

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