Second-line ART for HIV-infected patients failing first-line therapy

Background

Globally, it is estimated there were 33 million people living with HIV in 2007, the majority of who reside in Sub-Saharan Africa (**UNAIDS 2008**). Highly active antiretroviral therapy (ART) has markedly reduced the morbidity and mortality of patients with HIV/AIDS (**Palella 1998; Holtgrave 2005**). The World Health Organization (WHO)'s current standard initial treatment options include two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) (**Gilks 2006**). Significant public and private resources have been devoted over the last 5 years to rapid scale-up efforts in middle and low-income countries, where a large proportion of HIV infected population resides (**Bendavid 2009**). A small proportion of patients on ART are on second-line therapy, an estimated 4% of adults on ART and 1% of children (**Renaud Thery 2007**). There is increasing recognition of the importance, if not urgency, in prioritizing effective and available second-line ART regimens in middle and low-income countries (**Sungkanuparph 2007; Gallant 2007; Boyd 2007**).

Role of Resistance and Options for Second-Line

Options for second-line therapy after failure on an NNRTI-containing regimen generally involve the switch from the first-line NNRTI to a protease inhibitor (PI) and alternate NRTIs. Similarly, following failure of a PI-containing regimen, a switch to a second-line NNRTI regimen and alternate NRTIs is recommended. Challenges in selecting second-line regimens in resource limited settings include cost and availability of drugs and limited access to viral load testing and genotypic resistance testing, which leads to late switches. Recent evaluations in low and middle-income countries of resistance patterns of patients failing first line show the majority of resistant viruses contain the M184V mutation, TAMS, and NNRTI mutations (see Appendix **Table 1. Resistance mutations at first-line failure** and **Gupta 2009**). In addition, the K65R mutation is present in a small portion of patients. There is evidence to suggest HIV subtype C may preferentially select for the K65R mutation (**Wainberg 2009**; **Coutsinos 2009; Wallis 2007**). These mutations limit the NRTI options for second-line therapy (See Appendix **Table 3**).

The current systematic review represents a collaborative effort between UCSF, CDC and WHO to address questions regarding the optimum second-line regimen in patients failing first-line therapy in anticipation of updating the Adult and Adolescent Guidelines for Antiretroviral Therapy (**WHO 2006**).

Guiding assumptions and existing WHO recommendations

- 2 NRTI + NNRTI as first-line, fixed-dose combinations preferred.
- 2 NRTI (at least one new) + a PI boosted with ritonavir is the preferred second line ART
- One thymidine-analogue NRTI (i.e., d4T or AZT), combined with 3TC, is the preferred first-line option for NRTI component in resource-limited settings.
- Emtricitabine (FTC) is an acceptable alternative to lamivudine (3TC), based on similar pharmacological, clinical and resistance patterns profiles.

OBJECTIVES

To assess the optimum second-line ART regimen in children ≥5 years old and adults living with HIV failing first-line therapy in low-and middle-income countries.

Methods
Standard Cochrane review methodology was used.

Types of studies
Randomised controlled trials.
Given the insufficient number of clinical trials, we evaluated relevant observational studies (cohort and case-control) meeting criteria for interest.
Systematic reviews and meta-analyses addressing interventions of interest were reviewed in detail.

Types of participants
Children ≥5 years and adults living with HIV failing first-line therapy

Types of interventions

Interventions and comparison (Age ≥5)

Intervention for second-line*	**Comparator for second-line****
After failing first-line NNRTI containing regimen: Lopinavir/ritonavir (LPV/r) + 2 NRTI regimen	all other boosted PI regimens (and non-boosted PI regimens for patients intolerant of ritonavir)
After failing first-line thymidine analogue and 3TC- containing regimen: NRTI backbone maintaining 3TC (tenofovir disoproxil fumarate [TDF] + 3TC or didanosine [ddI] + 3TC)	NRTI backbone not maintaining 3TC (TDF + ABC or ddI + ABC)
After failing 1st-line with abacavir (ABC): ZDV + 3TC in NRTI backbone	TDF + 3TC or ddI + 3TC in NRTI backbone
After failing first-line with TDF-containing regimen (limited to adults since TDF not approved in children): Zidovudine (AZT) + 3TC in NRTI backbone	ddI + 3TC in NRTI backbone
After failing first-line 3TC-containing regimen: 3 drug regimen	4 drug regimen maintaining 3TC (for eg, AZT + TDF + 3TC + LPV/r)

Specific questions of interest related to these comparisons were:
- What is the difference among boosted PIs in second line?
- Should lamivudine be maintained in second-line therapy?
- Should ddI be preferred in second-line therapy?
- Is adding fewer than three new active drugs effective?

Additional targeted reviews
Two review questions emerged during the review process prompting targeted reviews. The first was a comparison of boosted PIs in treatment-naïve patients as an indirect way to evaluate performance of selected boosted PIs among PI-naïve (and NNRTI experienced) patients. Boosted LPV was compared to boosted atazanavir (ATV), fosamprenavir (FPV) or darunavir (DRV) in randomised controlled trials. The working group selected these boosted PIs based on preference for heat stable, ritonavir-boosted, fixed dose combination protease inhibitors. See Appendix **Figure 1. Search strategy for boosted PIs**.

The second question was a review of PI monotherapy studies as an indirect way to evaluate PI use in second-line therapy among patients who may have recycled NRTIs or inactive NRTIs due to resistance.

The methods for these reviews mirrored the primary search and review process although there was only one coder involved.

Types of outcome measures
Critical outcomes
1) Mortality
2) Severe adverse events: Grade 3 and 4 clinical events as described in DAIDS (2004).
3) Disease progression (AIDS and non-AIDS related illnesses)
4) Adherence/Retention/Tolerability
Important Outcomes
5) Viral load response: reported as proportion of patients with viral load <50 copies/ml at study end. If authors used another threshold, such as 400 copies/ml, the lowest value reported was used for analysis.
6) CD4 recovery: reported as geometric mean or median increase from baseline.
7) Development of drug resistance: reported as a dichotomous outcome as identified by study authors.

Adverse events. Severe adverse events were classified according to grade 1 to 4 of the Adverse Event Toxicity Scale **(Division of AIDS 2004)** and reported as the proportion of participants that experienced grade 3 and 4 clinical and laboratory adverse events. Using this scale, grade 1 and 2 denote mild to moderate symptoms, grade 3 denotes serious symptoms and grade 4 denotes life-threatening events requiring significant clinical intervention.

Clinical response to ART. We assessed clinical response by the proportion of participants that progressed either to CDC-defined AIDS (that is stage III to stage IV disease) or who developed a second opportunistic infection or malignancy.

Adherence, tolerance, retention. We defined this variable to be the proportion of study participants that reached the end of the study on their initially assigned regimen. This category, therefore, includes participants whose regimens were altered because of toxicity, those lost to follow-up, those whose regimens were changed because of clinical or virologic failure and those who withdrew from the study for other reasons.

Virologic response to ART. Virologic response was reported as the proportion of participants that reached a pre-defined concentration of HIV-1 RNA, typically <400

copies/mL or <500 copies/mL, or who suppressed viral replication to non-detectable levels, typically <50 copies/mL. For purposes of meta-analysis we used the lower value.

Immunologic response to ART. We defined immunologic response to ART as the mean change in the concentration of CD4 lymphocytes from baseline, as expressed in cells/μL. When studies presented median, instead of mean, we used the median values as reported.

Drug Resistance: Acquisition of major genotypic resistance mutations as reported by authors. Minor mutations were not reported.

Search Methods

Scope of search
With the assistance of the HIV/AIDS Review Group Trials Search Coordinator, we formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press or in progress). Full details of the Cochrane HIV/AIDS Review Group methods and the journals hand-searched are published in *The Cochrane Library* in the section on Collaborative Review Groups (http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/HIV/frame.html). We combined the randomised controlled trial (RCT) strategy developed by the Cochrane Collaboration and detailed in the **Cochrane Reviewers' Handbook (Higgins 2008)** in combination with terms specific to antiretroviral therapy.

Limits. The searches were performed without limits to language or setting. The searches excluded studies conducted in pregnant or lactating women and infants <1 year of age. The searches were limited to human studies published from 1995 (start of the triple-drug combination antiretroviral therapy era) to the present.

Electronic searches

We searched the following electronic databases:

Journal and trial databases

- MEDLINE
- EMBASE
- CENTRAL (Cochrane Central Register of Controlled Trials)
- LILACS (Latin American and Caribbean Health Sciences Literature)
- Cochrane HIV/AIDS Group Trials Register
- Web of Science

Conference databases

- Aegis
- AIDSearch: AIDSearch covers abstracts from a number of relevant international conferences including the International AIDS Conference, the International AIDS Society (IAS) Conferences on HIV Pathogenesis, Treatment, and Prevention, the Conference on Retroviruses and Opportunistic Infections (CROI), the British HIV

Association Conference and the International Congress on Drug Therapy in HIV infection.
- NLM Gateway (for HIV/AIDS conference abstracts before 2005)

We also hand searched conference proceedings from the CROI, International AIDS Conferences and IAS Conferences on HIV Pathogenesis, Treatment, and Prevention from 2005 to 2009.

Ongoing trials. We searched the following prospective trials registers:

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

Other resources

Researchers and relevant organizations. We contacted individual researchers working in the field, such as the AIDS Clinical Trials Group, and policymakers based in inter-governmental organizations including the Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO to identify trials either completed or ongoing.

Reference lists. We checked the reference lists of all studies identified by the above methods and examine the bibliographies of any systematic reviews, meta-analyses, or current guidelines we identify during the search process.

Search Terms
Standard HIV/AIDS Cochrane Collaborative Group search terms were be used. Major subject heading terms included: highly active antiretroviral therapy, antiretroviral agents, treatment failure, adherence, resistance, salvage therapy, HIV protease inhibitors and individual drug names.

Search Strategy, second-line

Search	Most Recent Queries	Time	Result
#22	Search (#18 AND #19) NOT (animals [mh] NOT human [mh]) Limits: Publication Date from 1995/01/01 to 2009/07/15	13:32:19	617
#21	Search (#18 AND #19) NOT (animals [mh] NOT human [mh])	13:26:51	624
#20	Search #18 AND #19	13:24:02	626
#19	Search (zidovudine OR lamivudine OR stavudine or didanosine OR emtricitabine OR nevirapine OR efavirenz OR tenofovir OR abacavir OR atazanavir OR lopinavir/ritonavir OR darunavir OR fosamprenavir OR indinavir OR saquinavir OR ritonavir OR nelfinavir OR tipranavir OR Trizivir OR Combivir OR Kaletra OR Truvada OR Duovir OR Viraday OR Triomune OR Odivir)	13:20:10	23441
#18	Search #3 AND #16 AND #17	10:07:57	1473
#17	Search TREATMENT FAILURE	10:07:35	153495
#16	Search #10 OR #11 OR #12 OR #15	10:06:53	347813
#15	Search MEDICATION ADHERENCE OR ADHERENCE	10:05:56	53496
#12	Search (SECOND-LINE THERAPY) OR (SECOND-LINE	10:03:31	6787

	TREATMENT) OR (SECOND-LINE ANTIRETROVIRAL THERAPY) OR (SECOND-LINE ANTIRETROVIRAL TREATMENT)		
#11	Search SALVAGE THERAPY	10:01:29	14918
#10	Search (DRUG RESISTANCE) OR (DRUG RESISTANCE, VIRAL) OR (ANTIVIRAL DRUG RESISTANCE) OR (ANTIVIRAL DRUG RESISTANCES)	10:01:15	277283
#3	Search #1 AND #2	09:50:43	66143
#2	Search Antiretroviral Therapy, Highly Active[MeSH] OR Anti-Retroviral Agents[MeSH] OR Antiviral Agents[MeSH:NoExp] OR ((anti) AND (hiv[tw])) OR antiretroviral*[tw] OR ((anti) AND (retroviral*[tw])) OR HAART[tw] OR ((anti) AND (acquired immunodeficiency[tw])) OR ((anti) AND (acquired immunedeficiency[tw])) OR ((anti) AND (acquired immuno-deficiency[tw])) OR ((anti) AND (acquired immune-deficiency[tw])) OR ((anti) AND (acquired immun*) AND (deficiency[tw]))	09:49:48	99298
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MH]	09:49:32	253117

For the subsequent questions that emerged over the period of the review, targeted searches (with limits to RCTs) were performed to address comparisons among boosted PIs in ART-naive patients. Databases and conferences were searched with the terms atazanavir, lopinavir, ritonavir, fosamprenavir, darunavir and protease inhibitor (**see** Appendix **Search strategy for boosted PIs**). For the monotherapy review, both search results were searched for the terms, “monotherapy” and “PI monotherapy.” Searches were limited to randomized controlled trials.

Inclusion Criteria:

- Intervention trial. Given the in insufficient number if trials, cohort, case control, and case series study designs were included (targeted reviews on boosted PIs and PI monotherapy limited to RCTs).
- Evaluates second-line ART in patients failing first-line, including any three-drug second-line regimens or four-drug regimens that contain lamivudine
- Includes a clear definition of failure based on clinical, immunologic and/or virologic criteria and rationale for switching to second-line (for example, WHO 2006 Guidelines, see appendix)
- Failure of a WHO recommended first-line, including three-drug regimens of two NRTIs + NNRTI OR failure of PI + two NRTIs OR failure of triple NRTI regimen

- Provides sufficient regimen-specific information about first and second-line drugs to compare regimens and outcomes of interest

Exclusion Criteria

- Studies evaluating ART in patients failing more than one regimen
- Letter, editorial, non-systematic review, case report, cross-sectional study
- Studies evaluating substituting rather than switching ART (as described in WHO 2006, substituting is for toxicities and usually involves single drug changes while switch is due to clinical, immunologic or virologic failure and involves changing entire regimen).
- Studies evaluating failure of first-line single-drug regimens or four-drug regimens
- Studies evaluating second-line four-drug regimens that do not contain 3TC
- Studies evaluating non-boosted PIs in adults (except in the setting of intolerance of ritonavir), double PI regimens, new therapies including integrase inhibitors, chemokine receptor antagonists or fusion inhibitors.

Search Outcomes

EH and LC independently conducted the selection of potentially relevant studies by scanning the titles, abstracts, and descriptor terms of all downloaded material from the electronic searches. Irrelevant reports were discarded, and the full article was obtained for all potentially relevant or uncertain reports. EH and LC independently applied the inclusion criteria. JH acted as arbiter where there was disagreement. Studies were reviewed for relevance, based on study design, types of participants, exposures and outcomes measures. Finally where resolution was not possible because further information was required, the study was allocated to the list of those awaiting assessment. Attempts to contact authors to provide further clarification of data are ongoing.

For the subsequent review questions, EH screened titles and extracted data.

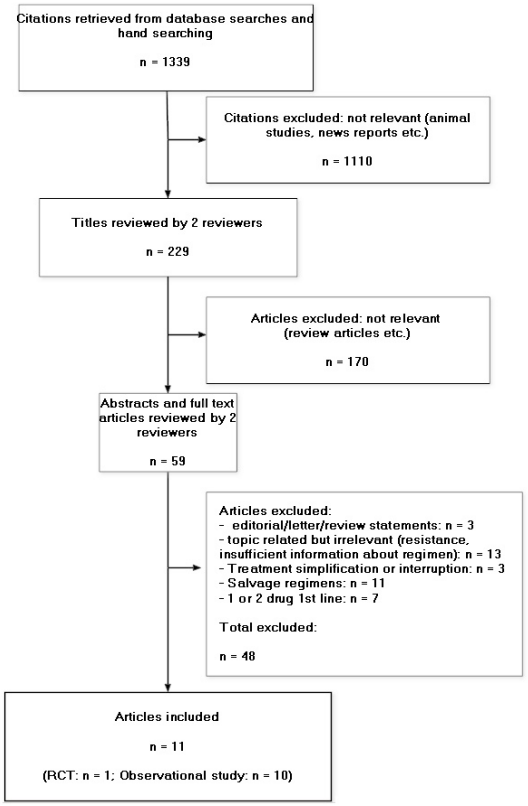
Search Yield

Primary Search

Searches were conducted on July 12, 2009 and produced 1330 titles after duplicates were removed. After initial screening, 208 titles and abstracts were reviewed independently by two reviewers (LC and EH) for inclusion and exclusion criteria. Fifty-nine abstracts or full articles were reviewed by two authors. One RCT, seven observational studies and three abstracts were identified. See **Figure 1. Flow chart, primary search results**.

There were five ongoing trials identified (see Appendix **Table 2. Ongoing trials**).

Figure 1 (primary search results)

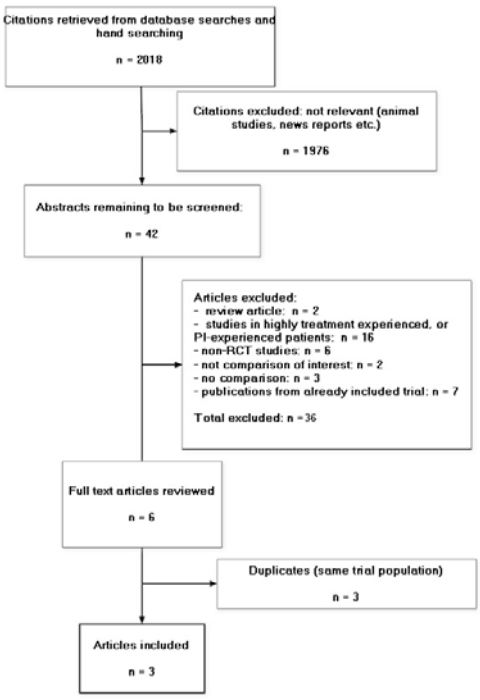


Targeted searches

The boosted PI search took place on September 5, 2009. Two thousand nineteen titles from databases were searched as well as titles from IAS (2007-2009) and CROI (1997-2009). Forty-two abstracts were reviewed in full. Three RCTs were identified with multiple associated publications (see **Figure 2. Flow chart, boosted PI studies**). The publication with the longest time period with complete reporting was included (**Mills 2009; Eron 2006; Molina 2008**).

Nineteen articles were reviewed from the monotherapy searches resulting in the identification of four published trials and five abstracts or posters that were included (see **Table 9 PI monotherapy studies**). Some studies had multiple publications; in these instances, the longest follow up information was included.

Figure 2 (boosted PI)



Data extraction and management

After initial search and article screening, two reviewers independently double-coded and entered onto a detailed and standardized data extraction form information from selected studies. Extracted information included:

Study details: citation, start and end dates, location, study design and details
Participant details: study population eligibility (inclusion and exclusion) criteria, ages, population size, attrition rate, details of HIV diagnosis and disease and any clinical, immunologic or virologic staging or lab information, first-line drug regimen details including drug name, dose and duration
Interventions details: second-line drug names, doses, duration, ancillary testing and monitoring, any other information on adherence or resistance
Outcome details: mortality, clinical disease progression (AIDS and non-AIDS events), treatment response (CD4 recovery and viral load response), adherence, resistance, and adverse events

Data analysis and presentation of findings

We used Review Manager 5 provided by the Cochrane Collaboration for statistical analysis and **GradePro (GradePro 2008)** software to produce Summary of Findings and Evidence Profile tables.

When interventions and study populations were sufficiently similar across different studies, we statistically pooled the outcomes and examined the differences between the two models using both fixed and random-effects models, with final results presented using random-effects models. We summarised dichotomous outcomes for effect in terms of risk ratio (RR), risk difference (RD) and number needed to treat (NNT) with their 95% confidence intervals. We summarized continuous outcomes with a weighted mean

difference (WMD) and 95% confidence interval. We evaluated observational studies, non-randomised trials and randomised clinical trials separately.

We summarized the quality of evidence for each outcome for which data were available in GRADE Summary of Findings and GRADE Evidence Profile Tables (**Guyatt 2008**).

Subgroup analysis and investigation of heterogeneity

We examined heterogeneity among trials using the chi-square statistic with a significance level of 0.10 and the I-squared statistic. We interpreted an I-squared estimate greater than 50% as indicating moderate or high levels of heterogeneity and investigated its causes by sensitivity analysis. If heterogeneity persisted, we presented results separately and reported reasons for the observed heterogeneity.

Sub-group analysis was planned for different ages although this was not performed due to lack of data. Heterogeneity was explored using further sub-group analyses by trial quality, setting (middle- or low- versus high-income country) or other sub-groups judged relevant.

Publication bias. We assessed the potential for publication bias using funnel plots. We minimised the potential for publication bias by our comprehensive search strategy that included evaluating published and unpublished literature.

Assessment of risk of bias for individual randomised studies. Application of GRADE **(Guyatt 2008)** and Cochrane Collaboration tools for risk of bias for each individual study was applied and presented in summary tables. The GRADE and Cochrane approach assesses risk of bias in individual studies across six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential biases (see Table 3).

Assessment of risk of bias for individual observational studies. We assessed observational studies for risk of bias using the above criteria in **Table 4** and also the Newcastle-Ottawa Quality Assessment Scale (NOS) shown in **Tables 5 and 6 (Wells 2009).** The NOS is a validated scale from 0 to 9 that uses a 'star rating system' and assesses quality of cohort and case-control studies in three main areas: selection of study groups, comparability of study groups and ascertainment of exposure or outcome.

Table 4. The Cochrane Collaboration's tool for assessing risk of bias in controlled trials.

Domain	Description	Review authors' judgment
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total Randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Table 5. Newcastle-Ottawa quality assessment scale for cohort studies.

Note: A study can be awarded a maximum of one star (★) for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ★
   b) somewhat representative of the average _____ in the community ★
   c) selected group of users, eg nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ★
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) secure record (eg surgical records) ★
   b) structured interview ★
   c) written self report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes ★
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ★
   b) study controls for any additional factor ★ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ★
   b) record linkage ★
   c) self report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ★
   b) no
3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ★
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) □
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Table 6. Newcastle-Ottawa quality assessment scale for case-control studies.

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ★
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ★
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ★
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ★
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ★
   b) study controls for any additional factor ★ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ★
   b) structured interview where blind to case/control status ★
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ★
   b) no

3) Non-Response rate
   a) same rate for both groups ★
   b) non respondents described
   c) rate different and no designation

Table 7. GRADE approach to assessing the quality of evidence across studies.

Quality of Evidence (summary score)	Study Design	Downgrading Factors	Upgrading Factors
High (4) = Further research is very unlikely to change our confidence in the estimate of effect.	Randomised trials or valid accuracy studies for diagnostic tests begin with a score of High (4)	**Study limitations:** -1 Serious -2 Very serious **Consistency:** -1 Serious -2 Very serious **Directness:** -1 Serious -2 Very serious **Precision:** -1 Serious -2 Very serious **Publication Bias** -1 Serious -2 Very serious	**Large effect** +1 Large +2 Very Large **Plausible confounding would change the effect** +1 **Dose-response gradient** +1 if present
Moderate (3) = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.			
Low (2) = 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.	Observational studies or indirect accuracy studies for diagnostic tests begin with a score of Low (2).		
Very low (1) = Any estimate of effect is very uncertain.			

Note: *We specifically considered whether evidence directly addressed low- and middle-income country settings in assessing quality of evidence. If the question being addressed only has evidence from high-resource settings, the quality of evidence will be downgraded by -1 for lack of directness.*

Assessment of quality of evidence across studies

The quality of evidence across a body of evidence was assessed with the GRADE approach (see **Table 7**), defining the quality of evidence for each outcome as, "the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest" **(Higgins 2008).** The quality rating across studies has four levels: high, moderate, low or very low. RCTs are categorized as high quality but can be downgraded; similarly, other types of controlled trials and observational studies are categorized as low quality but can be upgraded. Factors that decrease the quality of evidence include limitations in design, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, or high probability of publication bias. Factors that can increase the quality level of a body of evidence include a large magnitude of effect, if all plausible confounding would reduce a demonstrated effect and if there is a dose-response gradient.

DESCRIPTION OF THE STUDIES

One clinical trial (**Fox 2006**) and seven observational studies (**Abgrall 2007; Barreiro 2003; Mocroft 2001; Sproat 2005; Vray 2003; Pujades Rodriguez 2008; Cozzi-Lepri 2002**) and three abstracts (**Murphy 2008; Gomo 2008; Hull 2009**) met inclusion criteria and were extracted. The observational studies addressed a wide range of second-line questions and were too heterogeneous for pooled estimates. A narrative review was performed for these observational studies. Four additional studies were identified of boosted PI interventions in populations in which salvage regimens and second-line regimens are mixed (**Dragsted 2003; Dragsted 2005; Phillips 2001; de Mendoza 2006**). These studies were read in full detail, although they were not double-coded or put in GRADE tables.

Five ongoing trials addressing second-line therapies in low or middle-income countries were identified (see **Table 2**). **Table 8** contains a list of all the studies identified in this review.

Table 8. List of included studies

RCTs	Observational studies	PI monotherapy RCTs	Boosted PI comparison RCTs	Ongoing trials
Fox 2006 (COLATE)	**Abgrall 2007** **Barreiro 2003** **Cozzi Lepri 2002** **Gomo 2008** **Hull 2009** **Pujades Rodriguez 2008** **Mocroft 2001** **Murphy 2008** **Sproat 2005** **Vray 2003**	**Arribas 2005** (OK) **Arribas 2009a** (OK04) **Arribas 2009b** (MONET) **Cameron 2008** **Delfraissy 2008** (MONARK) **Gutmann 2008** (MOST) **Katlama 2009** (MONOI-ANRS) **Nunes 2007** (KalMo) **Waters 2008/Singh 2007** **PIVOT (**On going study)	**Eron 2006** (KLEAN) **Molina 2008** (CASTLE) **Mills 2009** (ARTEMIS)	**2LADY** **Second-line** **627055** **SARA** **EARNEST**

Randomised Controlled Trials

One randomised trial (**Fox 2006**) evaluated maintaining lamivudine compared to not maintaining lamivudine in 136 treatment-experienced patients in Europe (COLATE trial). Experienced patients were divided into strata A, those who were starting their second regimen after failure, and Strata B, those who were starting a regimen after more than one prior regimen. Outcomes for the open-label, randomised trial were average area under the curve minus baseline (AAUCMB) reduction in $\log_{10}$ HIV RNA after 48 weeks, mean reduction in HIV RNA, median increase from baseline in CD4 T-cell counts,

clinical non-fatal adverse events, baseline resistance patterns and evolutionary distances in a subpopulation that had sequences performed.

Observational Studies

Pujades-Rodriguez 2009 is a descriptive study that evaluated 370 of 48,338 treatment naive patients who began second-line therapy after initial NNRTI-based first line regimen in Medecins Sans Frontieres (MSF) centres in 26 resource-limited countries. This observational study evaluated the probability of remaining alive and in care at 12 and 24 months, and factors associated with outcomes on second line regimens.

Murphy 2008 evaluated second-line LPV/r based therapy in 184 patients who needed second-line regimens in Durban, South Africa. Seventy-two percent switched due to immunologic and or virologic failure (the rest due to adverse drug effect or other on NNRTI first-line). The main outcome of the retrospective cohort study was virologic suppression at 6 months, with evaluation of subgroups including those with ddI in nucleoside backbone or not, 1 prior regimen or >1 prior regimen, indication for second-line. Adverse events were also documented.

Sproat 2005 compared virologic response of 586 patients in the UK from 1998-2000 who were switched to a regimen containing ddI or non-ddI regimens in the presence or absence of the M184V mutation. Outcomes were factors related to virologic and immunologic success by multivariate analysis.

Hull 2009 is a small study of 117 patients with virologic failure and documented M184V mutation without other NRTI or PI mutations, who were analysed for virologic response on lamivudine-containing or sparing regimens along with boosted PIs and another NRTI.

Gomo 2009 is an analysis of 91 patients from the DART trial who switched to second-line therapy and were evaluated for changes in lipid profiles. All patients had LPV/r-based second-line therapy (regimens included LPV/r +NNRTI or LPV/r + NNRTI + ddI or LPV/r +TDF + ddI/3TC/AZT) after triple nucleoside first-line therapy (in 91%).

Five observational studies evaluated second-line therapies after first line PI failure (**Barreiro 2003**; **Cozzi-Lepri 2002**; **Abgrall 2007**; **Mocroft 2001**; **Vray 2003**). All but **Mocroft 2001** evaluate NVP compared to EFV after PI failure. Mocroft 2001 evaluates second-line PI regimens in patients with PI experience. These studies were retained for reference but given their limited contribution to the main study question and low quality evidence, were not emphasized in the current review.

<u>Randomised Controlled Trials of Monotherapy with boosted PIs</u>

Nine randomised, open-label clinical trials addressed the issue of monotherapy with boosted PIs (see Table). A recent systematic review (**Bierman 2009**) and a Cochrane protocol on the topic (**Jaoko 2009**) were reviewed in detail, and the authors contacted, to supplement the searches that were performed.

There were four published manuscripts (**Cameron 2008; Delfraissy 2008; Arribas 2005 and Arribas 2009a**) and five abstracts or posters (**Nunes 2007; Waters 2008; Arribas 2009b; Katlama 2009; Gutmann 2009**) identified. For trials with outcomes published for multiple time points, the longest time point assessed with complete information by

outcome was included. The most common comparison was boosted lopinavir compared to combination ART (cART) that included boosted lopinavir and two NRTIs (**Arribas 2005; Arribas 2009a; Nunes 2007; Waters 2008; Delfraissy 2008**). Cameron 2008 compared efavirenz-based cART to lopinavir/ritonavir monotherapy. Two abstracts compared boosted darunavir monotherapy to cART with Darunavir (**Arribas 2009b**; **Katlama 2009**). The MONARK trial (**Delfraissy 2008**) and the **Cameron 2008** paper included ART-naive patients, while all other studies enrolled patients with suppressed viral load for a minimum of six months (Katlama 2009 required 18 months). None of the trials took place in low or middle-income countries. **Table 9** contains a description of included monotherapy trials.

Table 9. Monotherapy studies

Trial name/ Author	Design	Participants	Intervention	Outcomes
OK04 Arribas 2009a Pulido 2008a	Randomised, open-label, non-inferiority, multicentre trial	205 adults in Spain with HIV RNA <50 copies/ml for at least 6 months on LPV/r + 2 NRTI (or TDF + NRTI) for 4 weeks, no prior history of failure on PI	LPV/r 400/100 mg BID or Continue LPV/r 400/100 mg BID plus 2NRTI (or TDF + NRTI)	Proportion of patients without therapeutic failure at 48 weeks (failure= 2 measures HIV RNA >500 separated by 2 weeks); change of randomized therapy; treatment discontinuation; LTFU; failure to reach virologic response for those on monotherapy reinduced; proportion with viral suppression (<50 copies/ml) at 48 and 96 weeks; time to loss of virologic response; change in CD4; development of resistance
OK Arribas 2005 Pulido 2008b	Randomised, open-label, multicentre study	42 adults with HIV RNA <50 copies/ml for at least 6 months, no history of PI failure, were receiving LPV/r plus 2NRTI for >4 weeks in Spain	LPV/r 400/100 mg BID or Continue LPV/r 400/100 mg BID and 2 NRTI or TDF +NRTI	1. Proportion of patients with HIV RNA < 500 copies/ml at 48 weeks. 2. Secondary endpoints <50 copies/ml at 48 weeks, 3. TLOVR, 4. CD4 changes, 5. development of resistance

				6. lab changes, AE
MONARK Delfraissy 2008 Ghosen 2009 (descriptive); Spire 2008 (secondary outcomes); Delaguerre 2009 (resistance testing); Flandre 2009 (prognostic factors)	Randomised open label, multi centre trial	138 adults in Europe with CD4>100, ART naïve, >18, HIV-RNA <100,000 copies/ml	LPV/r 400/100 mg BID or LPV/r 400/100 mg BID and ZDV/3TC 300/150 mg BID	Proportion of patients with HIV RNA <400 copies/ml at 24 weeks and <50 at 48 weeks, occurrence of resistance mutations, correlation with early response and LPV concentration
KalMo Nunes 2006, Nunes 2007	Randomised, open-label	Adults with VL <80 copies/ml on HAART x 6 months, without prior failure., CD4 > 200 cells/ul and CD4 nadir >100 cells/ul.	switch to LPV/r monotherapy or Continue ART	VL < 80 copies/ml at 48, 96 weeks Virologic failure (HIV RNA >500 copies /ml)
UK study Waters 2008 (48 weeks) Singh 2007 poster (24 weeks)	Randomised, open-label, single center study	54 adults with CD4>200 and HIV <50 copies/ml x 6 months on HAART, fewer than 5 PI mutations	LPV/r 400/100 mg BID or Continue cART	Rates of maintenance of VL <50 copies/ml and change in CD4 24, 48 weeks
M03-613 study Cameron 2008	Randomised, open label study	155 ART naïve adults with HIV-1 RNA >1000 copies./ml, absence of resistance to study drugs	LPV/r 400/100 mg BID plus 3TC/AZT 150/300 mg BID then simplify week 24-48 to monotherapy or EFV 600 mg QD plus 3TC/AZT BID	Proportion of patients by ITT-E with HIV RNA < 50 copies/ml at 96 weeks, lab changes and limb fat changes
MONET Arribas 2009 IAS	Randomized, open-label, multicentre study in	256 patients with HIV RNA < 50 copies/ml for at least 24 weeks	switch to DRV/r 800/100 mg QD monotherapy or switch to DRV/r	Proportion with VL <50 copies/ml by ITT at week 48

	Europe, Russia and Israel		800/100 mg QD plus 2 NRTI	
MONOI-ANRS 136 Katlama 2009 IAS	Randomised, open-label	225 adults on cART with HIV RNA <400 copies/ml for at least 18 months	8 week induction with DRV/r 600/100 mg BID plus 2 NRTI then monotherapy or Continue DRV/r plus 2 NRTI	Proportion with failure (2 consecutive measures >400 copies/ml), treatment modification or discontinuation at week 48
MOST Gutmann CROI 2009	Randomised, open-label, multi centre study in Switzerl and	60 adults with HIV-RNA < 50 copies/ml for at least 6 months and no prior treatment failure	LPV/r monotherapy or continue triple ART	Treatment failure in CSF and genital compartment at 48 weeks

CSF, cerebrospinal fluid; ITT, intention to treat; VL, viral load

The **OK04 Study** is a randomised, open-label, non-inferiority trial of lopinavir/ritonavir monotherapy compared with lopinavir/ritonavir plus two nucleosides in 205 suppressed patients followed for the primary endpoint of proportion of patients without therapeutic failure (defined as confirmed HIV RNA greater than 500 copies/ml) or loss to follow up or change from randomised therapy. Other outcomes evaluated are time to loss of virological response (TLOVR), development of HIV resistance, changes in CD4 count, treatment related adverse events and changes in laboratory values. Outcomes have been published for 48 weeks (**Pulido 2008**) and 96 weeks (**Arribas 2009a**).

Cameron 2008 studied 155 ART-naive patients with HIV >1000 copies/ml randomised 2:1 to LPV/r twice daily or efavirenz (EFV) once daily. All patients received combination 3TC/AZT (150mg/300mg) twice daily. Patients on LPV/r plus 3TC/AZT simplified to monotherapy with LPV/r during weeks 24-48 if 3 consecutive HIV-1 RNA measurements were <50 copies/ml. The primary endpoint was the proportion of patients with HIV-1 RNA <50 copies/ml at week 96. Other endpoints included time to loss of virologic response (TLOVR), laboratory changes, resistance and adverse events.

The **MONARK trial** (**Delfraissy 2008**) is a randomised, open-label, multicentre study in which 138 patients naive to ART were randomised to lopinavir/ritonavir 400mg/100mg BID monotherapy or LPV/r 400mg/100mg BID plus zidovudine/lamivudine (300mg/150mg) twice daily. Primary endpoints were the proportion with plasma HIV-RNA below 400 copies/ml at 24 weeks and below 50 copies/ml at 48 weeks. Secondary outcomes included acquisition of resistance in patients with suboptimal response, correlation of early response and trough LPV/r concentrations.

The **KalMo** study reports 48 week (**Nunes 2006**) and 96 week (Nunes 2007) outcomes from a randomised, open-label trial of 60 adults in Brazil on cART with viral suppression (VL < 80 copies/ml for at least 6 months) who were randomised to maintain current regimen or to switch to LPV/r 400/100 mg BID. The primary study endpoint was viral suppression (<80 copies/ml) at 48 weeks.

Waters 2008 describes a randomised, open-label, single centre trial of 54 adults with viral suppression (VL < 50 copies/ml for at least 6 months) with fewer than 5 PI mutations who were randomised to continue their HAART or switch to LPV/r monotherapy. Rates of maintenance of viral suppression and changes in CD4 count were assessed at 24 (**Singh 2007**) and 48 weeks (**Waters 2008**).

The **OK study** (**Arribas 2005**) was a pilot, open-label, randomised study of 42 patients with viral suppression who were receiving LPV/r (400mg/100mg BID) plus two NRTIs and no history of PI failure who were randomised to stop the NRTIs or not. The primary outcome was the proportion of patients with HIV-RNA <500 copies/ml at 48 weeks. Other secondary endpoints included proportion with <50 copies/ml at 48 weeks, TLOVR, development of HIV resistance, changes in CD4 count, adverse events and changes in laboratory values.

Gutmann 2009 evaluated 60 Swiss patients who had viral suppression for at least 6 months (<50 copies/ml) and no prior treatment failure who were randomised to continue triple drug ART or switch to monotherapy with lopinavir/ritonavir. The primary endpoint was treatment failure (1 log increase in HIV RNA from baseline) in CSF and/or genital tract. There was a predefined stopping rule for this trial of 20% failure (6 patients) in the monotherapy arm.

Arribas 2009b presented 48 week outcomes from the open-label, randomised, non-inferiority MONET trial in which 256 patient with HIV RNA <50 copies/ml for at least 24 weeks were randomised to DRV/r 800mg/100 mg once daily or DRV/r plus two NRTIs. Outcomes are reported at 48 weeks for efficacy (viral load <50 copies/ml).

Katlama 2009 is another randomised, open-label, non-inferiority trial in which 225 adults patients on ART and HIV-RNA <400 copies/ml for at least 18 months were randomised to continue a triple drug regimen of DRV/r 600/100 mg BID with two NRTIs or switch to DRV/r monotherapy. The primary endpoint was the proportion with virologic failure (defined at 2 consecutive HIV RNA levels above 400 copies/ml) or modification or discontinuation of study drug.

One ongoing large, randomised, open-label trial in the UK, Ireland and Italy of 400 participants with viral suppression who will be randomised to ritonavir-boosted PI monotherapy or to continue triple ART was identified (**PIVOT**: Protease Inhibitor Monotherapy Versus Ongoing Triple-therapy in the long-term management of HIV infection, ISRCTN 04857074). This is a five-year study looking at safety, efficacy and resistance outcomes.

<u>Rondomised Controlled Trials of Boosted PIs</u>

LPV/r and ATV/r

The **CASTLE trial** was an open-label, randomised trial that randomised 833 ART naive patients to ATV/r 300mg/100mg once daily or LPV/r 400 mg/100 mg twice daily. The main outcome was proportion of patients with viral load <50 copies/ml at 48 weeks; development of resistance, adverse events and rates of virologic failure were also reported (**Molina 2008a**). A 96-week analysis by disease severity (**Uy 2009**), safety and efficacy at 96 weeks (**Molina 2008b**) and renal outcomes (**McGrath 2009**) are also reported in conference abstracts.

LPV/r versus DRV/r
The **ARTEMIS trial** was an open-label, non-inferiority trial with 689 ART-naive patients randomised to once daily DRV/r or LPV/r (once daily or twice daily). The primary outcome was virologic reponse; other outcomes included adverse events and median CD4 at 48 weeks (**Ortiz 2008**) and 96 weeks (**Mills 2009; Baraldi 2009**). This was an industry-funded study performed in 26 centres.

LPV/r and FPV/r
The **KLEAN trial** was an open-label, randomised, multi center, non-inferiority trial in 878 patients comparing boosted FPV (700mg/100 mg) given BID to boosted LPV (400 mg/100mg) given BID, both in combination with Abacavir(ABC)/3TC 600mg/300mg given once daily. Primary endpoints were proportion with HIV-1 RNA under 400 copies/ml and those discontinuing study drug for any reason at 48 weeks (**Eron 2006**). Other outcomes assessed were changes in CD4, development of resistance, adherence assessed by pill counts, adverse events and changes in lipid profiles. There is a follow up study up to 144 weeks of patients who had VL <400 copies/ml at 48 weeks and agreed to continue (**Pulido 2009**). The follow up results are discussed but not represented in the GRADE table due to the selection bias of this follow up population.

ATV/r and DRV/r
No studies were identified.

Risk of bias in included studies
See **Figures 3-5, Risk of Bias** (second-line, boosted PI comparison and PI monotherapy) for included studies and See **Table 12** for NOS Rating of observational studies.

Allocation
The trial addressing 3TC use in second-line therapy (**Fox 2006**) had adequate sequence generation, and allocation concealment. On PI monotherapy trials and boosted PI trials where information was available from the manuscript or through communication with the study author, all trials had adequate sequence generation. Some trials had insufficient reporting to make a judgement (**Gutmann 2009; Katlama 2009; Nunes 2007; Singh 2007**).

Blinding
Fox was not a blinded trial. All boosted monotherapy trials and the three trials comparing boosted protease inhibitors were all open-label.

Incomplete outcome data
For **Fox 2006**, outcome reporting for the primary efficacy data was complete. Most of the PI monotherapy trials reported follow up of randomised patients, as did the boosted PI trials; in addition all studies performed analyses by intention-to-treat.

Selective reporting
There does not appear to be selective reporting from **Fox 2006**. Many of the PI monotherapy abstracts do not offer sufficient information to give a 'yes' or 'no' judgment.

Other potential sources of bias
All boosted PI trials were industry sponsored. Many of the PI monotherapy trials were supported by industry, as well.

EFFECTS OF INTERVENTIONS

Maintaining lamivudine in second-line NRTI backbone
The COLATE trial (**Fox 2006**) found no significant difference in average area under the curve minus baseline of reduction in $\log_{10}$ HIV RNA copies/ml in patients who maintained 3TC in their second-line regimen compared to those who did not. The mean number of antiretroviral drugs other than 3TC received was 3.5 (3.2-3.8) for the On3TC arm and 3.4 (3.1-3.7) in the Off3TC arm. The results did not differ by experience with ART; in Strata A (those experiencing failure on their first 3TC-containing regimen) for the On3TC group, the results was 1 $\log_{10}$ reduction in HIV RNA (0.7-1.4) and in the Off3TC group it was 1.4 (1-1.8) while for Strata B (those experiencing failure on a second or later 3TC-containing regimen), it was 1.6 (1.3-1.9) in the On3TC group compared to 1.5 (1.3-1.8) in the Off 3TC group (p=0.75). In addition, there was no significant difference in mean reduction in $\log_{10}$ HIV RNA; for those on their second regimen, the mean reduction from baseline was 1.2 (0.9-1.5) and for those with more ART experience, the reductions was 1.6 (1.4-1.8, p=0.02). There were also insignificant differences in time to virological failure, CD4 count, time to viral suppression between those maintaining 3TC and those not maintaining 3TC (data not shown). See **GRADE Table 1**.

A recent small observational study **(Hull 2009)** also suggests similar virologic response among patients with M184V mutation and no PI mutations or other NRTI mutations who subsequently took 3TC or FTC plus NRTI plus a boosted PI compared to those on an 3TC or FTC sparing regimen or those on 3TC or FTC plus NRTI plus boosted PI plus other active agents.

Failure after first-line with ABC-containing regimens
There were no studies included.

Failure after first-line TDF-containing regimens
There were no studies included.

Use of ddI in second-line
Murphy 2008 reports no difference in viral suppression at 6 months among 76 patients with a ddI NRTI backbone on LPV/r based second-line compared to 79 without a ddI backbone in South Africa.

Sproat 2005 reports that in those patients taking ddI-containing regimens, there was no significant difference in the median change in VL or AAUCMB, or percentage of patients achieving undetectable VL, whether or not M184V mutation was present at baseline or not (p>0.05 except at week 12, p=0.035). In patients with M184V mutation at baseline, those on ddI-containing HAART had significantly better virologic outcome as measured

by AAUCMB than those not on ddI-containing HAART (p=0.007). No significant difference was shown, however, for the proportion attaining undetectable viral load.

Second-line with three active new drugs versus less than three active new drugs
Pujades Rodriguez 2008 did not report a difference in one compared to two new NRTI drugs in a second-line regimen on incidence of death or lost to follow up in patients evaluated in multiple MSF centres. In another observational study (**Mocroft 2001**) at multiple sites across Europe (and Israel), there was a significant association between the number of new NRTIs and virologic response (RH for two new NRTIs 1.99, 95% CI 1.45-2.73).

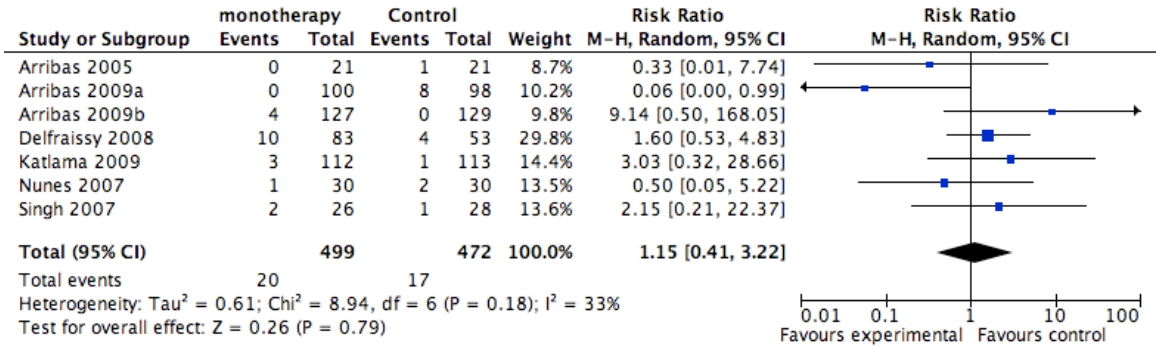
Cozzi Lepri 2002 found that among the 429 treatment-experienced patients, the incidence of confirmed failure (2 consecutive VL >500 copies/ml) was 0.38 events/person-year, which was slightly higher than in naive patients (0.33 events/person-year). In multivariate proportional hazards model, factors associated with virologic failure were higher viral load (adjusted relative hazard [aRH] 1.40 95% CI 1.17-1.67 for $\log_{10}$ HIV RNA copies higher), duration of prior antiretroviral treatment (aRH 1.03 95%CI 1.01-1.06) and number of previous NRTIs (aRH 1.48, 95% CI 1.13-1.94).

Monotherapy with boosted PIs
Nine randomised clinical trials including a total of 1,196 patients addressed the issue of monotherapy with boosted PIs compared to triple ART. Two trials compared darunavir combination therapy to darunavir monotherapy in suppressed patients while all others evaluated lopinavir/ritonavir monotherapy compared to combination ART.

Of the critical outcomes, there were no statistically significant differences between arms. Only 2 studies provided information on mortality (all causes of death reported as unrelated to study drugs); the other studies are presumed to not have had any deaths during study period. None of the studies reported on clinical disease progression.

The pooled Mantel Haenszel random effects relative risk estimate (RR_{MHRE}) for severe adverse events was 1.15 (0.41, 3.22) without evidence of statistical heterogeneity. There was some variability in reporting of adverse events. In general, the denominator used for this outcome was the number randomised who received at least one dose of study drug (intention to treat, exposed [ITT-E]). If Grade 3 or 4 events were not reported by arm, we used "discontinuations due to adverse events" (**Arribas 2009a**; **Nunes 2007; Arribas 2009b per communication with author**) or the author's assignment of "severe adverse events" (**Delfraissy 2008**; **Katlama 2009**). **Cameron 2008** reports three subjects did not complete study due to adverse events but not from which arm.

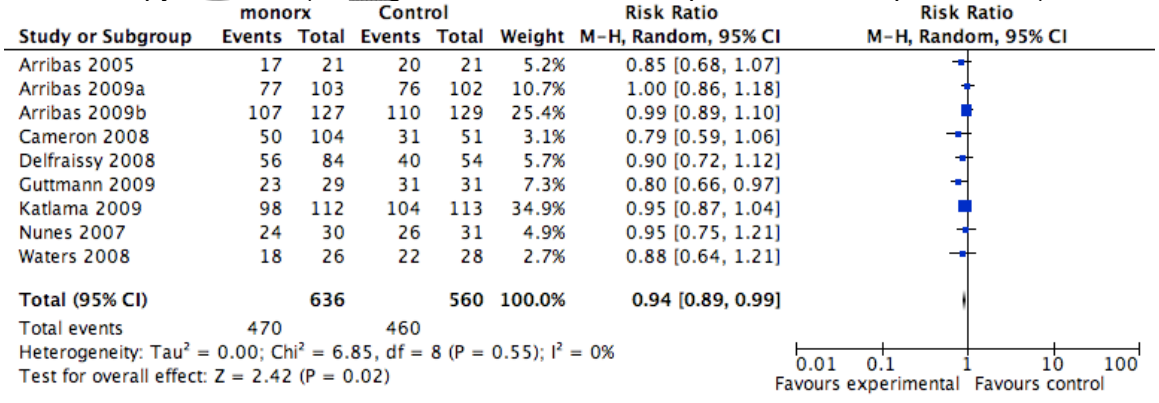
Forest Plot: Outcome Severe adverse events, PI monotherapy vs. cART



For non-Grade 3 or 4 adverse events, some trials found significant differences between arms. **Cameron 2008**, for instance, reports the proportion of patients with lipoatrophy at week 96 was significantly lower in the LPV/r group (5% and 35%, respectively, p<.001) compared to the combination therapy arm (with EFV and two NRTIs).

By ITT analysis, where missing data and re-intensification equals failure, the pooled RR_{MHRE} for virologic response (proportion with viral load <50 copies/ml at study end) was 0.94 (95% CI 0.89-0.99) in those on monotherapy compared to combination ART. There was no evidence of heterogeneity (p=0.55) and Higgins I^2 statistic = 0%. Two studies used thresholds other than <50 copies/ml (**Nunes 2007** used <80 copies/ml and **Gutmann 2009** used <400 copies/ml). Of note, the **Gutmann 2009** trial was stopped early due to virologic failures in the monotherapy arm. The failures in the monotherapy group were associated with low CD4 nadir (all failures had a CD4 <200 cells/μl; p<0.01 for association of failure and CD4 nadir <200 compared to >200 cells/μl). Similarly, in a post-hoc analysis of OK04 and OK trial data, **Pulido 2009** reports that low CD4 nadir <100 cells/μl in addition to poor adherence and lower baseline haemoglobin were associated with loss of virological suppression.

Forest Plot. Outcome virologic response (VL <50 copies/ml) by ITT analysis, PI monotherapy vs cART (*disregard label under forest plot, 'favours experimental')

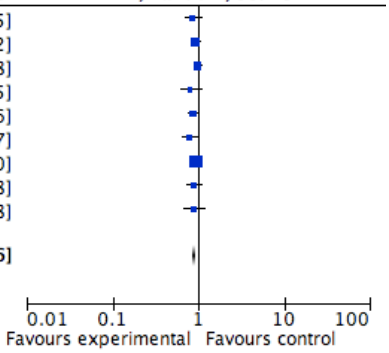


In a follow up analysis among those on-treatment (where denominator is those randomised and dosed with discontinuations or losses to follow-up censored), the pooled RR_{MHRE} was 0.92 (95% CI 0.88-0.96), without evidence of statistical heterogeneity.

Forest Plot: Outcome of virologic response (VL <50 copies/ml) PI monotherapy vs. ART with on-treatment analysis

Study or Subgroup	monorx Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Arribas 2005	17	20	20	20	4.4%	0.85 [0.70, 1.05]
Arribas 2009a	67	77	72	76	15.1%	0.92 [0.83, 1.02]
Arribas 2009b	107	124	110	125	16.6%	0.98 [0.89, 1.08]
Cameron 2008	50	88	31	44	2.7%	0.81 [0.62, 1.05]
Delfraissy 2008	56	67	40	41	12.0%	0.86 [0.76, 0.96]
Guttmann 2009	23	29	31	31	4.8%	0.80 [0.66, 0.97]
Katlama 2009	97	103	102	103	37.4%	0.95 [0.90, 1.00]
Nunes 2007	24	29	26	28	4.7%	0.89 [0.73, 1.08]
Singh 2007	18	24	22	26	2.3%	0.89 [0.67, 1.18]
Total (95% CI)		**561**		**494**	**100.0%**	**0.92 [0.88, 0.96]**
Total events	459		454			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.32$, df = 8 (P = 0.32); $I^2 = 14\%$
Test for overall effect: Z = 3.82 (P = 0.0001)



One important finding to note is that three studies found a higher proportion of patients with intermittent viraemia (>50 and <400 or 500 copies/ml) in the monotherapy arm compared to the ART arm (**Delfraisy 2008**; **Cameron 2008**; **Arribas 2009**). Up to 12% of patients required reintensification in the monotherapy arm (12% in Arribas 2009a, 23% on monotherapy in Cameron 2008, ~5% in Cameron 2008, 14% (3/21) in Arribas 2005).

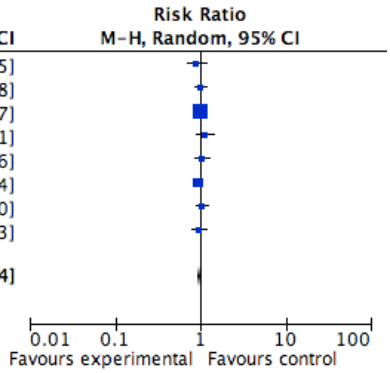
The outcome immunologic response could not be pooled due to variability in reporting (mean change vs. median change from baseline and no standard error). However, most studies reported no statistically significant differences in change of CD4 from baseline between arms (**Cameron 2008; Delfraissy 2008; Arribas 2005; Nunes 2007; Arribas 2009a**). Two studies reported that CD4 levels "remained stable" (**Waters 2008**; **Arribas 2009b**). Two studies did not report this outcome (**Katlama 2009**; **Gutmann 2009**).

The pooled estimate for the proportion who remained on their randomised study treatment was not different between arms RR_{MHRE}=0.99 (0.95, 1.04). **Gutmann 2009** is not included in this estimate as the trial stopped early and the numbers for this outcome were not accessible.

Forest plot: Outcome of retention PI monotherapy vs ART

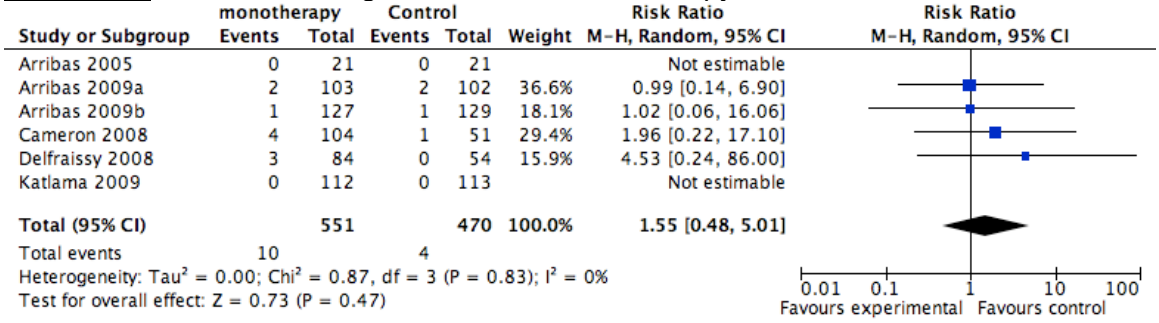
Study or Subgroup	Montherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Arribas 2005	17	21	19	21	3.0%	0.89 [0.70, 1.15]
Arribas 2009a	77	103	76	102	7.4%	1.00 [0.86, 1.18]
Arribas 2009b	118	127	120	129	41.5%	1.00 [0.93, 1.07]
Cameron 2008	78	104	34	51	3.8%	1.13 [0.90, 1.41]
Delfraissy 2008	67	84	41	54	5.5%	1.05 [0.87, 1.26]
Katlama 2009	98	112	104	113	24.0%	0.95 [0.87, 1.04]
Nunes 2007	28	30	28	31	8.4%	1.03 [0.89, 1.20]
Singh 2007	23	26	26	28	6.3%	0.95 [0.80, 1.13]
Total (95% CI)		**607**		**529**	**100.0%**	**0.99 [0.95, 1.04]**
Total events	506		448			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.93$, df = 7 (P = 0.79); $I^2 = 0\%$
Test for overall effect: Z = 0.40 (P = 0.69)



The acquisition of major PI mutations was relatively rare in most trials.

Forest plot: Outcome of drug resistance PI monotherapy vs. ART



The **GRADE Table 2** shows outcomes and quality of evidence for the boosted PI monotherapy trials. The overall quality of evidence was down-graded due to indirectness. For severe adverse events, the quality was down-graded for open-label trials and for some outcomes with <300 events, the quality was downgraded for imprecision. Of note, six of nine trials were industry sponsored (and three did not clearly state whether industry supported the work).

Boosted PI comparison

Observational Studies

Pujades Rodriguez 2008 did not report a significant difference between LPV and nelfinavir (NFV) second-line regimens, nor between boosted and unboosted PI regimens in second-line after failure on first-line NNRTI-containing regimens.

Two observational studies studied LPV/r-based second line regimens in Africa (South Africa and Uganda/Zimbabwe) without comparison to another boosted PI and reported lipid values. **Gomo 2008** found significant lipid changes (mean change from start of LPV/r second-line regimens) for total cholesterol, triglycerides HDL and LDL at 48 weeks (p<.001), although the elevations are reported as modest. **Murphy 2008** reported that 25% of patients had hypercholesterolemia at 6 months (defined as >215 mg/dl) and 26% had hypertriglyceridemia (>200 mg/dl); there is no baseline comparison rate reported.

Randomised Controlled Trials in ART naïve patients

No trials of boosted PI comparisons in patients failing an NNRTI first-line regimen were identified. Three RCTs comparing the boosted PIs of interest in ART-naive patients were included. All studies were funded by industry and included participants from multiple sites, none in low or middle-income countries.

LPV/r and ATV/r

There were no significant differences in the primary virologic outcomes from the **CASTLE study** at 48 weeks. At week 48, 78% and 76% had undetectable viral load from the boosted ATV and LPV arms, respectively. There were six deaths in each group. Serious adverse events were not different between groups, although more patients in the LPV/r group reported Grade 2-4 nausea and diarrhoea compared with the ATV/r group (11% in LPV/r group reporting diarrhea and 2% in ATV/r group). Laboratory values differed between groups for some outcomes. Sixteen patients in the ATV/r group had Grade 4 increases in total bilirubin compared to none in the LPV/r group. Mean percentage changes from baseline in fasting cholesterol, non-HDL cholesterol and triglycerides at week 48 were higher in the LPV/r group than the ATV/r group (p<0.0001).

Acquisition of resistance mutations to PIs was similar in both arms. A separate analysis of creatinine clearance also showed similar function in both groups at 48 weeks (**McGrath 2009**). In the subgroup of patients with baseline CD4 count <50 cells/μl, 96-week treatment-related Grade 2-4 adverse events were significantly lower in the ATV/r arm compared to the LPV/r arm (25% vs. 43%) (**Uy 2009 IAS**). Higher response rates (VL <50 copies/ml at 96 weeks by ITT where non-completion equals failure) were seen in the ATV/r for baseline VL <100,000 copies/ml and 100,000-500,000 copies/ml (75% vs. 68% and 76% vs 68%, respectively).

LPV/r versus DRV/r

The **ARTEMIS trial** randomised 343 patients to DRV/r and 346 to LPV/r. Forty-eight and 96 week outcomes by ITT are similar in showing non-inferiority of boosted darunavir. At week 48, 84% and 78% had viral load < 50 copies/ml in DRV/r and LPV/r arms, respectively. At week 96, 79% and 71% had confirmed VL <50 copies/ml. In patients with higher baseline VL and lower CD4, response rates were higher for DRV/r than LPV/r (76% versus 63%, respectively, in patients with baseline VL >100,000 copies/ml, p=0.023 and for patients with baseline CD4 < 200 cells/ul 79% versus 65%, p=0.009). Inpatients with HIV-1 RNA < 100,000 copies/ml or CD4 at least 200 at baseline, response rates were not significantly different between arms. The median change from baseline between groups was not significant (171 cells/μl in LPV/r and 188 cells/μl in DRV/r, p=0.57). Adverse events varied between groups, with more diarrhoea reported in LPV/r arm compared to DRV/r arm (11% vs. 4%, p<0.001). Laboratory analysis revealed higher total cholesterol (median percentage increase from baseline to week 96 23% vs. 15%) and triglycerides (median percentage increase from baseline to week 96 50% vs. 12%) in the LPV/r arm compared to DRV/r (p<0.01 and p<0.001, respectively). At 48 weeks, Grade 3 or 4 events were 64/343 in DRV/r arm compared to 75/346 in LPV/r arm. At 96 weeks, "any serious AE" is reported as 34/343 in DRV/r and 55/346 in LPV/r group. At week 96, DRV/r arm had fewer virologic failures (12 vs. 17%, p=0.0437). In analysis of patients for resistance mutations, those who had VL >50 copies/ml and baseline and endpoint genotypes available, there were no major protease mutations in either arm. Four of 31 failures in DRV/r arm had minor IAS-USA protease inhibitor associated mutations and 7/46 did in LPV/r arm.

LPV/r and FPV/r

The **KLEAN study** evaluated outcomes at 48 weeks and reported non-inferiority of FPV/r compared with LPV/r in combination with ABC/3TC at 48 weeks. Using the population randomised who received a dose of study drug (ITT-E), where non-responders (rebound >400 copies, failure to reach <400 copies/ml or discontinuation) are failures, 73% and 71% had VL <400 copies/ml at week 48. For the criterion of <50 copies/ml, 66% (285/434) and 65% (288/444) met the endpoint. There were five deaths, four in the FPV/r arm and none were thought related to study drug. Median CD4 count increases were similar across arms (176 cells/μl, interquartile range [IQR] 106-281 in FPV/r group and 191 cells/μl (IQR 124-287) in the LPV/r group). Adverse events leading to premature discontinuation occurred in 12% and 10% in the FPV/r and LPV/r groups, respectively. The median percentage adherence was reported as similar between arms.

The **GRADE Tables 3-5** show outcomes from the three boosted PI trials. The quality of evidence is downgraded due to concerns about precision (low number of events) for some outcomes and some study limitations. The patient population is also noted to be indirect, with access to viral load monitoring, resistance testing and regimen alteration.

Excluded studies on boosted PIs

There are multiple trials comparing boosted PIs in highly treatment-experienced patients or in patients failing first-line PI regimens and started on second-line PI regimens that were outside the scope of this review (see **Table 10** in **Appendix)**. Two RCTs of boosted PI comparisons were identified with mixed populations of ART-experienced and ART-naïve patients; the ART-experienced patients were predominantly PI-experienced (**Dragsted 2003; Dragsted 2005**). One additional analysis of different boosted PIs in experienced patients was identified (**de Mendoza 2006**).

The MaxCmin1 Trial (**Dragsted 2003**) was a randomised, multi centre open-label trial comparing indinavir (IDV)/r (800/100 mg) twice daily plus two NRTIs to saquinavir (SQV)/r (1000/100 mg) twice daily plus two NRTIs in 306 patients and was powered to show equivalence between arms (80% chance that 95% CI for the difference in virological failure would exclude a difference >15% in either direction). Most patients (61%) were PI-experienced and 25% were ART-naive. At 48 weeks, 27% of patients in the IDV/r and 25% in the SQV/r arm had virological failure. When switching counted as failure, this difference increased to 49% and 34% between IDV/r and SQV/r, respectively (p=.009). There was no difference in the time to virologic failure between study arms (p=0.76). The authors conclude that IDV/r and SQV/r have comparable virologic effects and there were more treatment limiting adverse events in the IDV/r arm.

In the MaxCmin2 trial (**Dragsted 2005**), the same research group studied lopinavir/ritonavir (400/100 mg) twice daily plus two NRTIs to SQV/r (1000/100 mg) twice daily plus two NRTIs in 324 randomized patients, 29% of whom had prior exposure to NNRTIs and 52% of whom had prior PI exposure. At 48 weeks, 25% of the LPV/r had virologic failure (where discontinuation = failure) compared to 39% in the SQV/r arm (p=.005). Discontinuations occurred in 14% compared to 30% in the LPV/r and SQV/r arms, respectively, and the primary reason for discontinuation was non-fatal adverse events.

In **de Mendoza 2006**, a retrospective analysis of 389 patients in Spain who had prior PI failure and were given a subsequent boosted PI regimen were evaluated for virologic response and adverse events. The highest rates of virologic response (VL <50 copies/ml) by ITT analysis occurred in those patients on ATV/r, Tipranavir/ritonavir (TPV/r) and LPV/r (72.4%, 68.2% and 54.3% response, respectively). Discontinuations due to adverse events was highest in the IDV/r group (22.8%) compared to all others (p=.03). In multivariate analysis, the number of PI mutations at baseline was associated with lower virologic response at week 24 (OR= 0.77, 95% CI 0.68-.87; p<.001).

NVP vs EFV for second-line after failure on PI-containing regimen

The four studies evaluating NNRTI use after PI experience (**Abgrall 2007; Barreiro 2003; Cozzi Lepri 2002; Vray 2003)** all showed associations between EFV over NVP and virologic response. All studies except **Vray 2003** (which had experienced patients only) had mixed populations of ART-experienced or naïve patients; we used results for experienced patients only.

Cost-effectiveness and descriptive studies

Chimbete 2009 reports first-line failure rate of 7-8% per annum (most patients on triple NRTI first-line regimens) and good immunological response on LPV/r/AZT/3TC second-line regimen in patients in the DART trial in Uganda and Zimbabwe. **Ferradini 2007**

found similar immunological response in patients on LPV/r-based second-line regimens in Cambodia. **Pujari 2008** also found good response on boosted PI-based second-line regimens (10% virologic failure rate at 6 months) in Western India after first-line NNRTI failure, although reported a high rate of toxicities (with a report of intra-PI switch being highest for IDV/r). Similarly, **Murphy 2008** reported overall virologic suppression (<50 copies/ml) at 6 months to be 82% in patients in South Africa on LPV/r-based second-line after failure on NNRTI first-line therapy. One report from the UK (**Aderogba 2004)** reported a second-line PI/r failure rate of 59% after first-line NNRTI regimen in adults in London.

In **Feedberg 2007**, a cost-effectiveness study in India found an incremental cost of USD $1880/year of life saved (YLS) for offering two regimen options compared to first-line alone, with modeling based on first-line regimen of stavudine (d4T)/3TC/NVP and second-line PI/r-based regimen. The model in Freedberg's model was sensitive to cost of the second-line drugs.

In **Walensky 2007**, a cost-effectiveness model simulating clinical care in Cote d'Ivoire consistently favored initial NNRTI-based regimen followed by PI-based regimen over starting with a PI-based regimen. Results were consistent, even in the setting of NNRTI resistance (up to 76%). Boosted PI regimen costs and their efficacy as second-line drugs were the most influential factors in the model.

Third line therapies

Recent studies in resource-limited settings suggest there will be an ongoing need for expanded ART options in third-line therapy. The proportion of patients on second-line ART in resource-limited settings is estimated between ~1-5% (**Renaud Thery 2007**; **Egger 2009**; **Pujades Rodriguez 2008**). Estimates of failure on first-line NNRTI-based regimens range between 18-32% (**Ramadhani 2007; Keiser 2008**; A. Calmy, personal communication regarding confidential unpublished data; **Bartlett 2009**). There is evidence to suggest that a higher proportion of patients meet criteria for virologic failure yet are not switched to second-line therapy, and this switch rate may be influenced by availability of routine viral load monitoring and urban versus rural location, among other factors (A. Calmy, personal communication regarding confidential, unpublished data; **Egger 2009**; **Davies 2009**). Recent unpublished data suggests failure rates of second-line therapy of 18.8% (A. Calmy, personal communication regarding confidential unpublished data). As access to monitoring improves and scale up of initial ART continues, demand for second-line and third-line regimens will increase.

There are studies of newer agents in second-line regimens including etravirine in resource limiting settings (**Sungkanuparph 2008**), suggesting newer options for PI-intolerant patients, or potentially for highly treatment-experienced patents. **Table 11** contains selected trials of etravirine (ETR), raltegravir (RAL) or boosted darunavir (DRV/r) in treatment-experienced patients. In addition to the clinical trials listed in Table 4, there is recent observational data that supports the success of DRV/r or RAL in three-class ART experienced patients; virological success (VL <50 copies/ml) at 24 weeks was greater for those treated with DRV/r, RAL or both compared to nonprotease inhibitor strategy (OR for DRV/r 4.24 95% CI 1.28-14.06 and for RAL OR 3.1 95% CI 1.12-8.62) (**McKinnell 2009**). Recent reviews have also been published summarized trials of DRV and ETR (**McKeage 2009**; **Schiller 2009**).

Table 11. Trials of etravirine or raltegravir in treatment-experienced patients

Comparison	Trial name	Publications	Follow up	Outcomes/Notes
ETR + BR vs. placebo + BR Background regimen (BR) = DRV/r + 2 NRTI +/- enfuvirtide	DUET 1, 2	Mills 2009 poster	96 weeks	* DUET 1 & 2 found greater efficacy with ETR compared to placebo in those on background regimen.
DRV/r + RAL + ETR (+ clinician choice)	TRIO	Fagard 2009 IAS	48 weeks	* SINGLE ARM study of highly experienced patients with HIV RNA >1000 copies/ml; 86% virologic success (<50 copies/ml) at week 48, and 15/103 patients had Grade 3-4 AE.
RAL vs. enfuvirtide	EASIER	DeCastro 2009	24 weeks	* Among highly experienced patients on enfuvirtide regimen with viral suppression, those randomized to switch to RAL had similar efficacy outcomes at 24 weeks; AE uncommon.
RAL + optimized background therapy (OBT) vs. placebo + OBT	BENCHMARK-1, 2	Steigbigel 2008	48 weeks	* In highly treatment experienced patients with failure, viral suppression <50 copies/ml in 62.1% in RAL + OBT arm compared to 32.9% (p<.001) in placebo + OBT arm

SUMMARY

Second line findings

Failure rates on second-line therapy are estimated to be ~15%. In general, response on therapy with second-line regimens including boosted PIs has been encouraging. The need for third-line options should be anticipated.

Second line NRTIs

The current review aimed to address a number of questions related to use of NRTIs in second-line therapy. Despite a comprehensive search, very few studies were identified of relevance. One trial suggests no difference in virological outcomes among those maintaining 3TC on second-line regimens compared to those who do not (low quality of evidence). Observational data support this finding.

Boosted PI comparisons

Single trials evaluating comparison of LPV/r to DRV/r, ATV/r or FPV/r in ART-naïve patients showed non-inferiority of all three PIs when compared to LPV/r (low to moderate quality evidence).

Boosted PI monotherapy

There is moderate quality evidence that patients PI monotherapy have lower virologic response than patients on combination ART. There were no other significant differences in critical or important outcomes (very low to moderate quality evidence), although non-critical outcomes such as Grade 2 adverse events and lipoatrophy were not captured in the GRADE table. Further, there is evidence from individual trial reports of higher rate of viral rebound <500 copies/ml in patients on monotherapy compared to combination ART. Accessibility of monitoring and reintensification with NRTIs was an important aspect of most trials.

Implications for research

Urgent trials are needed to guide second and third-line therapy in low and middle-income countries. Ongoing trials identified in this review will contribute substantially to the next generation of recommendations for second-line ART.

Acknowledgements

We gratefully acknowledge the contributions of Nancy Santesso and Holger Schunemann for their consultation and technical expertise with GRADEPro and Grade Tables presented in this review. We would also like to thank Tara Horvath for her assistance with searches.

INCLUDED STUDIES

Abgrall 2007

Methods	Cohort analysis of second-line after PI failure
Participants	1440 patients in French Hospital Database who switched from PI to NVP, EFV or ABC-containing regimen with V> >500 copies/ml.
Interventions	557 (39%) switched to EFV-containing regimen, 637 (44%) switched to NVP-containing regimen and 246 (17%) to ABC-containing regimen.
Outcomes	Kaplan Meier 12 month probability of virologic suppression was 73.6% (95% CI 69.5%-77.7%) for EFV-cART; 53.9% (95% CI 49.4%-58.3%) for NVP-cART and 66.1% (95% CI 59.4%-72.8% for ABC-cART), p<.01.
Notes	

Barreiro 2003

Methods	retrospective analysis of factors associated with virologic

	outcomes in patients with protease inhibitor experience on subsequent NNRTI therapy
Participants	162 patients in Spain with prior PI exposure, two-thirds who had detectable VL at switch.
Interventions	NVP or EFV
Outcomes	Virologic response (<50 copies/ml) higher in those on EFV vs NVP (38% compared to 22%, p<.05). More side effects in EFV vs. NVP arm (31% vs. 18%, respectively; AE leading to discontinuation similar in both groups (16% and 17%).
Notes	

Cozzi-Lepri 2002

Methods	Cohort of ART naive and ART-experienced patients at multiple centers in Italy (I.Co.N.A. study) on NVP or EFV
Participants	694 NNRTI naive patients starting NVP or EFV. 429 patients were pre-treated and 265 were ART naive.
Interventions	289 pretreated patients started NVP + 2NRTIs and 140 pre-treated patients started EFV + 2 NRTIs.
Outcomes	factors associated with virologic failure. Among pre-treated patients, those on NVP had RH 2.42 (95% CI 1.43-4.07, p=.0009) for virologic failure compared to EFV.
Notes	

Gomo 2008

Methods	Analysis of DART patients initiating second-line therapy and lipid profiles at baseline (2nd line initiation) and at 48 week follow up
Participants	66 included patients in Uganda and Zimbabwe in DART trial
Interventions	2nd line of LPV/r +NNRTI (41%) or ddI + LPV/r + NNRTI (50%) or LPV/r + TDF + ddI/3TC/AZT (9%) with baseline and 48 week fasting lipids
Outcomes	mean change in LDL, HDL and vLDL and triglycerides mmol/L at 48 weeks
Notes	lipid elevations in LPV/r arms

Hull 2009

Methods	Retrospective cohort
Participants	117 patients with documented M184V mutation and no PI-mutations or other NRTI mutations followed at British Columbia

	HIV Drug Treatment Center 2000-2006
Interventions	Regimen A: 3TC or FTC + NRTI + bPI Regimen B: 3TC or FTC + NRTI + bPI + additional active agent(s) Regimen C: 2 NRTIs + bPI +/- additional active agents (sparing 3TC or FTC)
Outcomes	Significant factors related to time to HIV-1 RNA suppression by multivariate analysis included history of IF+DU and adherence to subsequent regimen. Type of failed regimen and type of subsequent regimen were not significantly associated with virologic outcome.
Notes	ICAAC 2009 abstract

Mocroft 2001

Methods	observational study of virologic and immunologic outcomes of patients on second-line
Participants	981 patients in EuroSida cohort with HIV RNA >1000 copies/ml after minimum of 16 weeks on first-line PI regimen.
Interventions	Dual PI as second-line in 45%. Of those on single PI, IDV and Nelfinavir most common.
Outcomes	factors associated with virologic response on second-line (use of PI in first line, use of NRTIs in first line, viral load, CD4
Notes	those who added two new nucleosides had RH for VL <500 copies/ml 1.99 (95% CI 1.45-2.73, p<0.0001)

Murphy 2008

Methods	retrospective cohort
Participants	184 patients requiring second-line regimen in Durban, South Africa. First line for majority D4T/3TC/EFZ.
Interventions	LPV/r based second line
Outcomes	primary outcome virologic suppression at 6 months with evaluation of subgroups based on: 1) NRTI backbone (ddi containing vs not) 2) 1 prior regimen or >1 prior regimen 3) indication fro second line (failure vs adverse drug effect/other). No difference by NRTI backbone (82% suppressed in both ddi-containing (n=76) and non ddI containing (n=79), p=0.90. 78% of those with 1 prior regimen experience (n=91) and 88% of those with >1 prior regimen (n=64) had virological suppression at 6 months (p=0.08). 79% of 112 who were on 2nd line after failure compared to 91% of

	43 who were on 2nd line for adverse effect/other had virologic suppression at 6 months (p=0.2).
Notes	abstract, not much information and no apparent adjusting in analysis.

Pujades-Rodriguez 2008

Methods	Descriptive analysis using individual patient data from 62 MSF-supported HIV centers in 26 countries between 2001 and 2006.
Participants	370 (0.8%) out of 48,338 patients on second-line after NNRTI first-line; >15 years of age.
Interventions	51% on LPV based second line, 43% on NFV based second line; 56% on boosted PI. ZDV-ddI (34%) and ABC-ddI (22%) most common backbone in 2nd line.
Outcomes	370 switched to 2nd line; median f/u 8 months on 2nd line. 28 deaths and 18 LTFU Probability of remaining alive and in care at 12 and 24 months= 0.86 (95% CI 0.81-0.90) and 0.77 (95% CI 0.69-0.83), which did not differ by number of NRTI drugs changed. Numbers were slightly higher (NS) for LPV vs NFV-based therapy.
Notes	

Sproat 2005

Methods	Retrospective analysis among patients on second-line ddI or non-ddI containing regimens and association with M184V mutation on virological outcome
Participants	586 patients who had failure followed in UK cohort from 1998-2000, 281 who switched to ddI containing ART of whom 105 had M184V mutation and 305 who switched to non-ddI of whom 65 had M184V mutation
Interventions	ddI or non ddI subsequent cART
Outcomes	virologic response: percentage of patients attaining undetectable VL (<400 copies/ml) was similar in those on ddI, irrespective of presence of M184V. In patients with M184V at baseline, virologic outcome of AAUCMB was better in those on ddI containing cART compared to non-ddI containing ART (p=.007), but no significant difference by proportion attaining undetectable VL. For those on ddI-containing HAART, greater median fold-change in phenotypic resistance to ddI was recorded in presence of M184V (2.2 vs. 1.2, p<.001).

Notes	Limited to no information about previous regimen(s)

Vray 2003

Methods	Analysis of factors associated with virological response among patients on therapy after PI failure.
Participants	541 patients who failed PI regimen with HIV RNA >1000copies/ml and participated in the Narval Trial comparing phenotyping, genotyping to standard of care for choice of subsequent ART.
Interventions	Multivariate analysis with model including drug concentrations, prescription of drugs at baseline and second-line, mutations, qualitative variables and outcome of virologic success (HIV-1 RNA < 200 copies/ml).
Outcomes	Factors associated with virological response by multivariate analysis: 1) EFV prescription to NNRTI naive patients (OR 4.37, 95% CI 2.76-6.90) 2) randomization to genotypic resistance testing arm 3) lamivudine prescription at baseline (OR 1.69, 95% CI 1.01-2.83) 4) baseline prescription of ABC to ABC-naive patients.
Notes	

PI Monotherapy studies

Arribas 2005

Methods	open-label, randomised pilot study
Participants	42 patients in Spain with HIV-1 RNA <50 copies/ml for 6 months and >4 weeks on LPV/r +2NRTI (or TDF + NRTI)
Interventions	Continue triple ART (n=21) or simplify to LPV/r (n=21)
Outcomes	Proportion of patients with HIV-1 RNA < 500 copies/ml and <50 copies/ml at 48 weeks Change in CD4 count Adherence Proportion with loss of viral suppression and resistance tests
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Computer generated randomization
Allocation concealment?	Yes	central allocation
Blinding? (Investigators)	No	open-label study
Blinding? (Patients)	No	
Incomplete outcome data addressed?	Yes	
Free of selective reporting?	Yes	All outcomes reported upon from those

		described in methods
Free of other bias?	Unclear	Unrestricted grant from Abbott laboratories

Arribas 2009a

Methods	open-label, randomised non-inferiority trial OK04 study
Participants	198 patients without history virologic failure on LPV/r plus 2 NRTI and HIV RNA < 50 copies/ml x 6 months
Interventions	LPV/r monotherapy compared to LPV/r + ZDV/3TC bid
Outcomes	Percent of patients without therapeutic failure (defined as HIV RNA > 500 copies/ml at week 48), proportion of patients with VL >50 copies/ml at week 96, development of resistance, change in CD4 count, and comparisons of adverse events, adherence, and incidence of abnormal lab values.
Notes	Pulido 2008 is 48 week outcome publication

Risk of bias table

Item	**Judgement**	**Description**
Adequate sequence generation?	Yes	Yes, computer generated (per Pulido 2008 methods)
Allocation concealment?	Unclear	n/r, presumed yes.
Blinding? (Investigators)	No	open-label study
Blinding? (Patients)	No	open-label study
Incomplete outcome data addressed?	Yes	~75% on treatment at 96 weeks; losses accounted for.
Free of selective reporting?	Yes	appears so from study information
Free of other bias?	Unclear	funded by Abbott laboratories

Arribas 2009b

Methods	randomised, open-label, multicentre, non-inferiority trial
Participants	256 patients with VL < 50 copies/ml for at least 24 weeks (NNRTI based 43% and PI based 57%), median age 43 years and median CD4 575 cells/ul
Interventions	randomised to switched to DRV/r (800/100 mg) daily (n=127) or DRV/r daily plus 2 NRTI (n=129)
Outcomes	treatment failure at 48 weeks, safety, discontinuations
Notes	abstract from IAS

Risk of bias table

Item	**Judgement**	**Description**
Adequate sequence generation?	Yes	computer-generated per email with author
Allocation concealment?	Yes	central telephone allocation
Blinding? (Investigators)	No	open-label
Blinding? (Patients)	No	open-label
Incomplete outcome data addressed?	Yes	appears so from information provided, ITT analysis
Free of selective reporting?	Unclear	insufficient data to judge from abstract
Free of other bias?	Unclear	sponsored by industry

Cameron 2008

Methods	randomised, open-label trial

Participants	155 adults (mean age 38, 79% male, 65% White) ART naive
Interventions	LPV/r + 3TC/ZDV for 24 weeks then simplified to LPV/r if HIV <50 copies/ml on 3 consecutive measures (n=92) compared to EFZ + 3TC/ZDV
Outcomes	at 96 weeks: proportion of patients with HIV RNA < 50 copies/ml by ITT. For monotherapy patients, Kaplan meier estimates of time to loss of virologic response since monotherapy initiation were calculated and compared to a subset of EFZ group. Changes in lab parameters and lipoatrophy also compared between groups.
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	computer generated per written communication with author
Allocation concealment?	Yes	central phone allocation per written communication with author
Blinding? (Investigators)	No	open-label study
Blinding? (Patients)	No	open-label study
Incomplete outcome data addressed?	Yes	for primary outcome. 75 and 69% competed to 96 weeks. ITT analysis and sensitivity analysis for virologic response by varying definitions of failure.
Free of selective reporting?	Unclear	insufficient information to provide judgement. Primary and secondary outcomes reported as described. No mortality outcomes
Free of other bias?	Unclear	no adherence measures. Supported by Abott.

Delfraissy 2008

Methods	randomised, open-label clinical trial in Europe MONARK trial (outcomes at 48 weeks)
Participants	136 treatment naive adult patients with HIV-RNA < 100,000 copies/ml and CD4>100 cells/ul
Interventions	LPV/r monotherapy or LPV/r + ZDV/3TC
Outcomes	proportion of patients with HIV RNA <400 at 24 weeks and < 50 and <400 at 48 weeks, occurrence of resistance mutations in those with suboptimal response.
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	computer generated per email from author
Allocation concealment?	Yes	central telephone allocation per email from author
Blinding? (Investigators)	No	no, open label
Blinding? (Patients)	No	no, open-label

Incomplete outcome addressed?	Yes	per flow chart
Free of selective reporting?	Yes	for outcomes listed in methods
Free of other bias?	Unclear	study sponsored by Abbott Laboratories

Guttmann 2009

Methods	randomised open label multi center trial in Switzerland
Participants	60 adult patients with HIV RNA <50 copies/ml for at least 6 months and no previous treatment failure
Interventions	continue triple ART or LPV/r monotherapy
Outcomes	Primary endpoint was treatment failure in CSF and genital compartments at 48 weeks. Premature study termination was planned if 20% of patients in monotherapy arm failed.
Notes	Trial stopped early for failure in Monotherapy arm

Risk of bias table

Item	**Judgement**	**Description**
Adequate sequence generation?	Unclear	insufficient information in poster; attempted to contact author
Allocation concealment?	Unclear	insufficient information to judge
Blinding? (Investigators)	No	open-label
Blinding? (Patients)	No	open-label
Incomplete outcome data addressed?	Yes	from tables
Free of selective reporting?	Yes	based on info in poster and a priori definitions and endpoints
Free of other bias?	Yes	appears so, no disclosures offered. Emailed author 9-20

Katlama 2009

Methods	randomised, open label, non-inferiority trial
Participants	225 patients on cART with VL <400 copies/ml for at least 18 months
Interventions	randomised to DRV/r (600/100 mg) BID monotherapy (n=112) or DRV/r plus 2 NRTI (n=113)
Outcomes	virologic failure at 48 weeks (2 consecutive HIV RNA levels >400 copies/ml) or modification/discontinuation
Notes	IAS abstract

Risk of bias table

Item	**Judgement**	**Description**
Adequate sequence generation?	Unclear	insufficient information for Yes or No judgement, attempt to contact author
Allocation concealment?	Unclear	insufficient information to judge
Blinding? (Investigators)	No	open-label
Blinding? (Patients)	No	open-label
Incomplete outcome data addressed?	Yes	yes based on limited information provided; ITT analysis
Free of selective reporting?	Unclear	insufficient information to judge

Free of other bias?	Unclear	unclear if industry supported

Nunes 2007

Methods	open-label, randomized trial
Participants	60 patients with suppressed VL for 6 months
Interventions	Randomized to LPV/r monotherapy or to continue current triple HAART regimen.
Outcomes	Percent of patients with VL <80 copies/ml, CD4 count, lipid levels
Notes	poster

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	info not provided other than 1:1 randomization
Allocation concealment?	Unclear	insufficient information to judge; no contact for author
Blinding? (Investigators)	No	open label
Blinding? (Patients)	No	open-label
Incomplete outcome data addressed?	Unclear	yes although N=30 in each arm and no explanation about loss to f/u or drop out. Analysis by ITT.
Free of selective reporting?	Unclear	all outcomes reported upon but insufficient information to provide Yes or No judgement
Free of other bias?	Unclear	partially supported by Abbott labs

Singh 2007

Methods	randomised open label 48 week trial, report at 24 weeks
Participants	52 patients with HIV infection and VL < 50 copies/ml x 6 months and CD4>200 with <5 PI mutations randomised to LPV/r monotherapy or continuation of combination ART
Interventions	LPV/r 400/100 mg monotherapy or continuation of regimen
Outcomes	rate of maintained viral suppression (19/26 in monotherapy group compared to 23/28 in continuation group, p=0.64). Change in CD4: -40 (95% CI -100 to 21) cells/ml in monotherapy group compared to +42 (-14 to 97) in continuation group (p NS)
Notes	Waters 2008 is 48 week results

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	not reported (poster)
Allocation concealment?	Unclear	not reported
Blinding? (Investigators)	No	open-label
Blinding? (Patients)	No	open-label
Incomplete outcome data addressed?	Yes	Analysis by ITT. 2 patients lost from each group at 24 week analysis
Free of selective reporting?	Unclear	insufficient information to judge
Free of other bias?	Unclear	insufficient information to judge

Boosted PI Studies

Eron 2006

Methods	randomised, open label, multicentre, non-inferiority trial (KLEAN trial)
Participants	878 ART naive adults in Europe, US, Canada
Interventions	1. FPV/r 700/100 mg BID plus ABC/3TC 600/300 mg QD (n=434) 2. LPV/r 400/100mg BID plus ABC/3TC 600/300 mg QD (n=444)
Outcomes	Proportion on patients at week 48 with VL <400 copies in the ITT-E population and proportion who discontinued randomised treatment due to adverse events. Secondary endpoints included proportion with HIV-1 RNA <50 copies/ml, changes in CD4 counts, development of resistance, adherence based on pills counts, adverse events and fasting lipid measures.
Notes	Pulido 2009 is follow up study

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	computer generated
Allocation concealment?	Yes	centralised interactive phone response
Blinding? (Investigators)	No	open-label
Blinding? (Patients)	No	open-label
Incomplete outcome data addressed?	Yes	flow of results and explanations of LTFU. 77% and 78% completed study t0 48 weeks
Free of selective reporting?	Unclear	presumed so although protocol not available
Free of other bias?	Unclear	industry funded by makers of FPV

Molina 2008

Methods	open-label, non-inferiority, randomised clinical trial (CASTLE trial)
Participants	883 ART naive, adult patients at multiple sites
Interventions	1. Atazanavir/ritonavir (300/100) mg once daily (n=440) or 2. Lopinavir/ritonavir (400/100) twice daily in combination with fixed dose tenofovir/emtricitabine (300/200 mg) once daily (n=443).
Outcomes	Proportion of patients by ITT with viral load <50 copies/ml at week 48, mean increase in CD4, severe adverse events, resistance profiles in those not with virological failure, retention adherence, adverse events
Notes	Molina 2008 is 48 week outcomes

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomisation was done with a computer-generated centralised randomisation schedule and was stratified by HIV RNA level at enrolment (<100 000 or ≥100 000 copies per mL) and geographic region (Africa, Asia, Europe, North America, South America).
Allocation concealment?	Yes	per email form author centralised phone allocation

Blinding? (Investigators)	No	open-label
Blinding? (Patients)	No	open-label
Incomplete outcome data addressed?	Yes	all outcomes accounted for; >80% on study drug at week 48 in both arms
Free of selective reporting?	Yes	All outcomes reported on from methods
Free of other bias?	Unclear	Bristol Meyers Squibb sponsor and involved in all aspects

Ortiz 2008

Methods	open-label, randomised, non-inferiority trial (ARTEMIS trial)
Participants	ART-naive adults at 26 centres
Interventions	1. 343 randomised to DRV/r 800/100 mg once daily 2. 346 randomised to LPV/r 800/200 mg daily (given either once or divided twice daily). All patients received a fixed background regimen of TDF 300 mg and FTC 200 mg qd. Randomisation stratified by baseline VL < or > 100,000 copies/ml and CD4 > or < 200 cells/ul.
Outcomes	Time to loss of virologic response, HIV-1 RNA copies/ml <50, median change from baseline in CD4 , safety outcomes (adverse events), adherence and retention, virologic failures and resistance at 48 weeks (Ortiz 2008) and 96 weeks (Mills 2009)
Notes	Mills 2009 96-week outcomes used; Ortiz referred to for methods.

Risk of bias table

Item	Judgement	Description
Adequate sequence?	Yes	centralized predefined list with interactive voice response to ensure 1:1 randomization within strata
Allocation concealment?	Yes	not described, presumed yes due to central randomization and interactive telephone system.
Blinding? (Investigators)	No	open-label study
Blinding? (Patients)	No	open-label study
Incomplete outcome data addressed?	Yes	>80% still in study at follow up point; losses accounted for and explained.
Free of selective reporting?	Unclear	Unclear although all study outcomes delineated in methods reported on. Analysis by intention to treat.
Free of other bias?	Unclear	Industry funded by makers of Darunavir (Tibotec)

Included Studies

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Llibre JM, Perez-Alvarez N. Hill A, Moyle G. Relative antiviral efficacy of ritonavir-boosted darunavir and ritonavir-boosted tipranavir vs. control protease inhibitor in the POWER and RESIST trials. HIV Med 2007; 8: 259-264. Methodological accuracy in cross-trial comparisons of antiretroviral regimens in multitreated patients. HIV medicine 2007;8(8):568-70; author reply 571-2. [PubMed: 17944691]

Mallolas 2009
Mallolas J, Podzamczer D, Milinkovic A, Domingo P, Clotet B, Ribera E, et al. Efficacy and safety of switching from boosted lopinavir to boosted atazanavir in patients with virological suppression receiving a LPV/r-containing HAART: the ATAZIP study. Journal of acquired immune deficiency syndromes (1999) 2009;51(1):29-36. [PubMed: 19390327]

McKeage 2009
McKeage K, Perry CM, Keam SJ. Darunavir: a review of its use in the management of HIV infection in adults. Drugs 2009;69(4):477-503. [PubMed: 19323590]

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Pozniak A, Opravil M, Beatty G, Hill A, de Bethune MP, Lefebvre E. Effect of baseline viral susceptibility on response to darunavir/ritonavir versus control protease inhibitors in treatment-experienced HIV type 1-infected patients: POWER 1 and 2. AIDS research and human retroviruses 2008;24(10):1275-80. [PubMed: 18844462]

Rachlis 2007
Rachlis A, Clotet B, Baxter J, Murphy R, Lefebvre E. Safety, tolerability, and efficacy of darunavir (TMC114) with low-dose ritonavir in treatment-experienced, hepatitis B or C co-infected patients in POWER 1 and 3. HIV clinical trials 2007;8(4):213-20. [PubMed: 17720661]

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Smith 2008
Smith KY, Weinberg WG, Dejesus E, Fischl MA, Liao Q, Ross LL, et al. Fosamprenavir or atazanavir once daily boosted with ritonavir 100 mg, plus tenofovir/emtricitabine, for

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Soriano 2008
Soriano V, Garcia-Gasco P, Vispo E, Ruiz-Sancho A, Blanco F, Martin-Carbonero L, et al. Efficacy and safety of replacing lopinavir with atazanavir in HIV-infected patients with undetectable plasma viraemia: final results of the SLOAT trial. The Journal of antimicrobial chemotherapy 2008;61(1):200-5. [PubMed: 17999977]

Steigbigel 2008
Steigbigel RT, Cooper DA, Kumar PN, Eron JE, Schechter M, Markowitz M, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. The New England journal of medicine 2008;359(4):339-54. [PubMed: 18650512]

APPENDIX

Search strategy, boosted PI comparisons

Publication Date from 2000/01/01 to 2009/09/05
PubMed: HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) AND randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR controll* [tw] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] AND (HIV Protease InhibitOR s[Mesh] OR lopinavir OR ritonavir OR lopinavir/ritonavir OR Kaletra OR LPV/r OR fosamprenavir OR Lexiva OR Telzir OR FPV OR FPV/r OR Darunavir OR Prezista OR DRV OR DRV/r OR TMC 114 OR TMC114 OR Atazanavir ATV OR ATV/r OR Reyataz) AND (Human NOT Animal)
WEB OF SCIENCE:(TS=HIV OR TS=HIV/AIDS OR TS=AIDS) AND (TS=protease inhibitor OR TS=lopinavir OR TS=ritonavir OR TS=lopinavir/ritonavir OR TS=Kaletra OR TS=LPV/r OR TS=fosamprenavir OR TS=Lexiva OR TS=Telzir OR TS=FPV OR TS=FPV/r OR TS=Darunavir OR TS=Prezista OR TS=DRV OR TS=DRV/r OR TS=TMC 114 OR TS=TMC114 OR TS=Atazanavir ATV OR TS=ATV/r OR TS=Reyataz) AND Document Type=(Article OR Meeting Abstract OR Meeting Summary OR Meeting-Abstract OR Proceedings Paper) Timespan=2000-2009. Databases=SCI-EXPANDED.
COCHRANE “CENTRAL”: HIV protease inhibitors[MeSH]

Table 2. Ongoing Second-line trials

Trial ID	Location	population	intervention and comparator	Outcomes	end date
NCT 00928187 (2LADY)	Burkina Faso, Cameroon, Senegal	450 adults with first-line failure on NNRTI and 2 NRTIs	Second-line with: FTC/TDF+LPV/r or ABC+ddI+LPV/r or FTC/TDF + DRV/r	HIV RNA <50 copies/ml (48 weeks) and clinical outcomes	2012
NCT 00931463 (SECOND-LINE)	48 sites (global)	550 adults with failure on NNRTI + 2 NRTIs	Second-line with: LPV/r +2 NRTIs or LPV/r + RAL	HIV RNA <200 copies/ml (48 weeks) and safety, other endpoints	2012
NCT 00627055	Thailand	200 adults on NNRTI + 2NRTI and HIV RNA>1000 copies/mL	Second-line with: LPV/r monotherapy or LPV/r + TDF/FTC or TDF/3TC	efficacy and safety at 48 weeks	2011
ISRCTN 13968779 (SARA)	Uganda and Zimbabwe	240 adults enrolled in DART trial who failed on first line and have had 24 weeks second-line	Second-line with: LPV/r monotherapy or LPV/r-based triple therapy	efficacy and safety	2009
NCT 00988039 (EARNEST)	Malawi, Uganda, Zimbabwe	1200 patients >12 years with failure on first line NNRTI + 2 NRTIs	Second-line with: LPV/r monotherapy or LPV/r + RAL or LPV/r + 2 NRTIs	clinical, virologic, immunologic control at 96 weeks	2013

Figure 3. Risk of bias: PI monotherapy trials

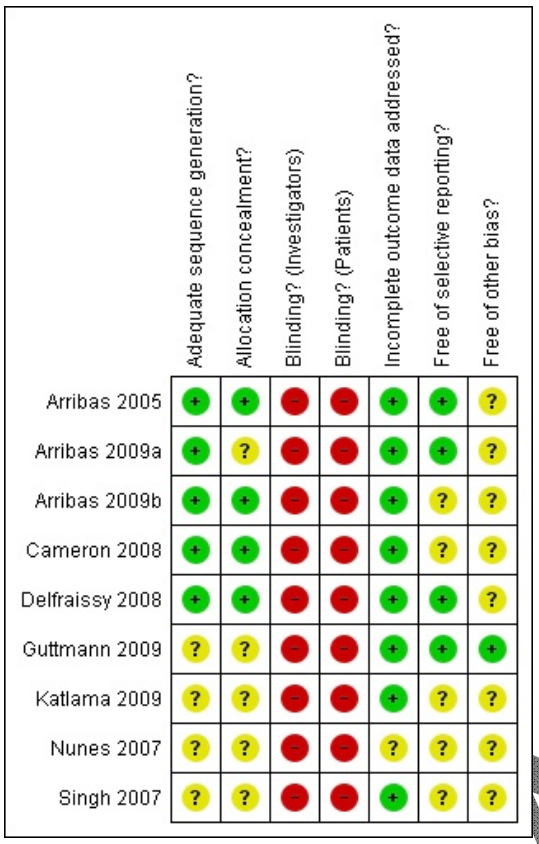

Figure 4. Risk of bias: lamivudine in second-line therapy

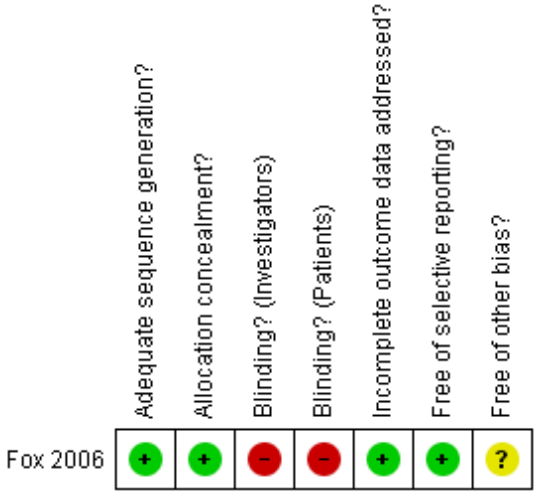

Figure 5. Risk of bias: boosted PI trials

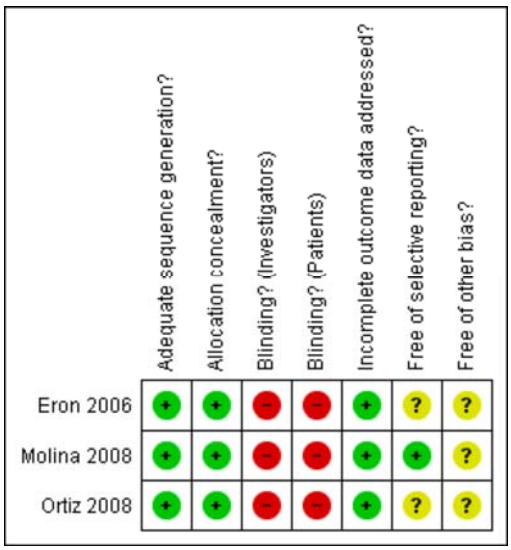
Adequate sequence generation?
Allocation concealment?
Blinding? (Investigators)
Blinding? (Patients)
Incomplete outcome data addressed?
Free of selective reporting?
Free of other bias?
Eron 2006
Molina 2008
Ortiz 2008

Table 1. Resistance patterns after first-Line failure
Adapted from Gupta 2009 and Hosseinipour 2009 IAS

Resistance profile at first-line failure	Cameroon (Kouanfack 2009)	Malawi (Hosseinipour 2009)	South Africa (Marconi 2008)	Thailand (Sungkanuparph 2007)	Haiti (Charles 2008)	Uganda, Zimbabwe (DART 2008)	Uganda (Kamya 2007)	India (Kumarasamy 2009)
Description (N), First line regimen, years	N=178 (24 mos) d4T/3TC or AZT/3TC and NVP or EFV 2006-2007	N=96 d4T/3TC/NVP 2006-2007	N=124 d4T/3TC + EFV or NVP 2005-2006	N=98 d4T/3TC/NVP 2003-2005	N=29, Ages 13-29 2003-2005	N=87, ABC /AZT/3TC arm 56 and NVP/AZT/3TC arm 31 ABC / NVP	N=7 2004-2005	N=138 d4T/3TC/NVP (46%); AZT/3TC/NVP (29%) 1996-2008
Any NNRTI	73%	93%	78.3%	92%	79%	7% / 71%	100%	65%
Any TAMS	18%		32%	37%	9%	55% / 29%		60%
>3 TAMS	8%	25%	13%	13%		14% / 6%		
M184V/I	71%	81%	64%	84%	72%	88% / 74%	100%	79%
K65R	0%	23%	2%	6%	*			5%

Table 3: Likely Mutation patterns on NRTI regimens based on relationship to time of loss of control of viral replication

NRTI Component	Early mutation patterns	Late mutation pattern	Implications for subsequent regimens
ZDV+3TC or d4T+3TC	M184V	M184V+ multiple TAMS	No active NRTIs
TDF+3TC	M184V+K65R	M184V+K65R	AZT will generally remain active

Source: Adapted from "Second-line therapy in MSF: description, clinical outcome and perspectives". Alexandra Calmy, Fernando Pascual, MSF Access Campaign AIDS Working Group, MSF. WHO Second-Line Meeting, 21-22 May, 2007.

WHO Prioritization Exercise Overview, 2007
Adapted from Slide from M. Vitoria

1st Line NRTI Choice	NRTI Component	PI Component
If AZT or d4T used in first line	ABC+ddI TDF+3TC (FTC)	ATV/r LPV/r
If TDF is used in 1st line	AZT+3TC	
If ABC is used in 1st line	AZT+3TC TDF+3TC (FTC)	

Table 10. Boosted PI trials in ART-experienced patients

Comparison	Trial name	Publications	Follow up	Outcomes/Notes
ATV/r v LPV/r	ATAZIP	Mallolas 2009	48 weeks	* In ATAZIP, a non-inferior, open-label RCT of patients suppressed on LPV/r showed similar efficacy and better lipid parameters in ATV/r arm compared to LPV/r arm at 48 weeks
	SLOAT	Soriano 2008	48 weeks	*In SLOAT trial comparing suppressed patients who switched to ATV or ATV/r compared to remaining on LPV/r, there was similar efficacy between arms and better lipid profiles in ATV arms.
	BMS 045	Johnson 2006, Johnson 2005	96 weeks	* In Johnson 2005, 2006, ATV/r was as effective as LPV/r in treatment-experienced patients with better lipid profile. LPV/r arm used more anti-diarrhoeal and lipid lowering agents
DRV/r v LPV/r	TITAN	Pozniak 2008 Madruga 2007	48 weeks	* DRV/r non-inferior to LVP/r in treatment experienced patients with similar safety profile
ATV/r v ATV	ARIES	Squires 2009	144	*Non-inferiority of ATV to

	SWAN	(IAS) Gatell 2007	48	ATV/r after induction *Significantly lower virologic rebound in those who switch while suppressed from control PI (+/- ritonavir) to ATV (+/- ritonavir), similar safety profile and better lipid profiles on ATV regimen
DRV/r vs. cPI	POWER 1, 2, 3	Clotet 2007 Pozniak 2008 Molina 2007 Hill A 2007 Garcia 2008	48 weeks	*POWER 1 & 2 found significantly greater clinical efficacy at 48 weeks with DRV/r compared to cPI
TPV/r vs. cPI	RESIST 1, 2	Hicks 2006	48 weeks	* RESIST 1 & 2 found 33.6% of highly PI-experienced patients had virologic response on TPV/r at 48 weeks compared to 15.3% on cPI each plus OBT (p<.0001). GI side effects and raised transaminase and lipids in TPV/r arm.

Table 12. NOS Rating for observational studies

Item	Pujades Rodriguez 2008	Hull 2009	Murphy 2008	Sproat 2005	Gomo 2008
Representativeness of Cohort	1	1	1	0	0
Selection of Non-exposed Cohort	1	1	1	1	1
Ascertainment of Cohort	1	1	1	1	1
Outcome of Interest Not Present at Start of Study	1	1	0	1	1
Comparability of Cohorts 1	1	1	0	1	1
Comparability of Cohorts 2	1	0	0	0	0
Assessment of Outcome	0	1	1	1	1
Long Enough Follow-up	0	0	1	0	1
Adequacy of Follow-up	1	0	1	0	0
TOTAL	7	6	6	5	6

GRADE Table 1.

Question: Should Lamivudine (3TC) be maintained in second-line antiretroviral regimens for patients failing first-line therapy?
Settings:
Bibliography: Fox Z, Dragsted U, Gerstoft J, et al. A randomized trial to evaluate continuation versus discontinuation of lamivudine in individuals failing a lamivudine-containing regimen: the COLATE trial. Antiviral Therapy 2006;11(6):761-770.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Maintaining 3TC in 2nd line	No 3TC in 2nd line (control)	Relative (95% CI)	Absolute		
Mortality - not measured[1]												
0	-	-	-	-	-				-	-		CRITICAL
Progression of Disease - not measured												
0	-	-	-	-	-				-	-		CRITICAL
Severe adverse events (follow-up 48 weeks)												
1	randomised trials	no serious limitations[3]	no serious inconsistency	serious[4]	serious[5]	none	-	-		Not estimable[2]	⊕⊕OO LOW	CRITICAL
Adherence/tolerability/retention - not reported												
0	-	-	-	-	-				-	-		CRITICAL
Virologic response (follow-up 48 weeks; measured as: mean reduction from baseline log_{10} copies/ml of HIV RNA; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[4]	serious[5]	none	28[6]	27	-	MD 0.4 lower (0.87 lower to 0.07 higher)	⊕⊕OO LOW	IMPORTANT
Proportion achieving VL <50 copies/ml (follow-up 48 weeks)												
1	randomised trials	no serious limitations[2]	no serious inconsistency	serious[4]	serious[5]	none	38/65 (58.5%)	30/66 (45.5%)	RR 1.29 (0.92 to 1.80)	132 more per 1000 (from 36 fewer to 364 more)	⊕⊕OO LOW	IMPORTANT
Immunologic response (follow-up 48 weeks; measured as: median increase in CD4 from baseline[7]; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[4]	serious[5]	none	65	66	-	median increase 11	⊕⊕OO LOW	IMPORTANT

[1] Table 1 reports 1 death in Off3TC arm among patients who initiated treatment but discontinued
[2] Numbers provided are non-fatal clinical adverse events per arm/total adverse events (among 49 participants). Further information not provided. No difference in adverse events between arms; 43/94 (45.7%) events in On3TC arm and 51/94 (54.3%) events in Off3TC arm (p=0.25).
[3] Open-label study; not downgraded for this. Partial funding from Industry in early phases of trial, also not downgraded for this (low risk of bias since study drug not favoured significantly by results).
[4] Clinician optimized regimen; patients not from resource limited setting (study population from 12 European countries).

[5] Few events or low number of patients
[6] Numbers represent Strata A, a priori sub-group of patients with only 1 prior 3TC containing regimen (n=55). Similar results for Strata B, those with more than 1 prior regimen (n=76). The mean reductions from baseline in HIV RNA in overall groups were 1.4 $\log_{10}$ copies/ml (95% CI 1.1-1.6) in On3TC group and 1.5 (95% CI 1.2-1.7) in Off3TC group.
[7] No SD or 95% CI available from study (IQR provided); unable to report mean difference between groups although median difference reported as not significant (+87 in On3TC compared to 76 in Off3TC group, p=0.41).

GRADE Table 2

Question: Should PI monotherapy be used for patients failing first line therapy?
Settings:
Bibliography: Arribas 2005; Arribas 2009a; Arribas 2009b; Cameron 2008; Delfraissy 2008; Guttmann 2009; Katlama 2009; Nunes 2007; Singh 2007 & Waters 2008.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PI monotherapy	cART	Relative (95% CI)	Absolute		
Mortality (follow up 96 weeks)												
2	randomised trials	no serious limitations[1]	no serious inconsistency	serious[2]	serious[3]	none[4]	3/207 (1.4%)	1/153 (0.7%)	RR 1.46 (0.22 to 9.8)	3 more per 1000 (from 5 fewer to 58 more)	⊕⊕OO LOW	CRITICAL
Clinical disease progression - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Serious adverse events (Grade 3 or 4 adverse event; follow up 1 study 24 weeks, 4 studies 48 weeks, 2 studies 96 weeks)[5]												
7	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20/499 (4%)	17/472 (3.6%)	RR 1.15 (0.41 to 3.22)	1 more per 1000 (from 28 fewer to 59 more)	⊕OOO VERY LOW	CRITICAL
Adherence/tolerability/retention (proportion on randomised treatment at study end; follow up 1 study 24 weeks, 4 studies at 48 weeks, 3 studies at 96 weeks)												
8	randomised trials	no serious limitations[1]	no serious inconsistency	serious[2]	no serious imprecision	none	506/607 (83.4%)	448/529 (84.7%)	RR 0.99 (0.95 to 1.04)	8 fewer per 1000 (from 42 fewer to 34 more)	⊕⊕⊕O MODERATE	CRITICAL
Virologic response (proportion with HIV RNA <50 copies/ml or lowest reported value; follow up 6 studies 48 weeks, 3 studies 96 weeks)												
9	randomised trials	no serious limitations[1]	no serious inconsistency	serious[2]	no serious imprecision	none	470/636 (73.9%)	460/560 (82.1%)	RR 0.94 (0.89 to 0.99)	49 fewer per 1000 (from 8 fewer to 90 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
immunological response (measured with: mean increase from baseline CD4; Better indicated by higher values; follow up 1 study 24 weeks, 2 studies 48 weeks, 2 studies 96 weeks)												
5	randomised trials	no serious limitations[1]	no serious inconsistency	serious[2]	no serious imprecision	none	338	256	-	not pooled[6]	⊕⊕⊕O MODERATE	IMPORTANT
Drug resistance (acquisition of major protease mutations; follow up 4 studies 96 weeks, 2 studies 96 weeks)												
6	randomised trials	no serious limitations[1]	no serious inconsistency	serious[2]	serious[3]	none	10/551 (1.8%)	4/470 (0.9%)	RR 1.55 (0.48 to 5.01)	5 more per 1000 (from 4 fewer to 34 more)	⊕⊕OO LOW	IMPORTANT

[1] Open-label studies, not down-graded for this except for severe adverse events, which may be more prone to bias in open-label trials. Six of 9 studies industry-sponsored and 3 with unclear reporting of sponsorship.
[2] All but 2 studies (Cameron 2008 and Delfraissy 2008) monotherapy studies enrolled patients with viral suppression and/or who were ART naive; indirect comparison to population who would use active PI in second-line after failure on first-line regimen.
[3] Low number of events (<300) and CI indicates potential for appreciable benefit and harm.
[4] Some concern for lack of clear mortality outcome reporting in the rest of the body of evidence since only 2 studies report deaths. Deaths reported in Cameron 2008 and Arribas 2009a were unrelated to study drugs; other studies presumed not to have any deaths (and mortality not primary endpoint in any of studies).

[5] ITT-E population used (randomized and dosed). Some variability in reporting; “serious adverse events” or “adverse events leading to discontinuation” used. Cameron 2008 not included as report is, “3 patients discontinued due to adverse events” but does not specify which arm.
[6] Estimate not pooled due to variability (median vs. mean) in reporting, or lack of raw numbers. All studies report non-significant differences between arms in immunologic changes.

GRADE Table 3

Question: Should Darunavir/ritonavir vs. Lopinavir/ritonavir be used for patients failing first line therapy?
Settings:
Bibliography: Mills AM, Nelson M, Jayaweera D, et al. Once daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96 week analysis. AIDS 2009;23:1679-1688.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Darunavir/ritonavir	Lopinavir/ritonavir	Relative (95% CI)	Absolute		
Mortality (follow-up 96 weeks)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious indirectness[3]	serious[2]	none	1/343 (0.3%)	5/346 (1.4%)	RR 0.2 (0.02 to 1.72)	12 fewer per 1000 (from 14 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
Severe adverse events (follow-up 96 weeks)[4]												
1	randomised trials	serious[1]	no serious inconsistency	serious indirectness[3]	no serious imprecision	none	34/343 (9.9%)	55/346 (15.9%)	RR 0.62 (0.42 to 0.93)	60 fewer per 1000 (from 11 fewer to 92 fewer)	⊕⊕OO LOW	CRITICAL
Clinical disease progression - not reported												
0	-	-	-	-	-				-	-		CRITICAL
Adherence/tolerability/retention (follow-up 96 weeks; reported as Retention, number still on randomised study drug[5])												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious indirectness[3]	no serious imprecision	none	284/343 (82.8%)	265/346 (76.6%)	RR 1.08 (1 to 1.17)	61 more per 1000 (from 0 more to 130 more)	⊕⊕⊕O MODERATE	IMPORTANT
Virologic response, proportion HIV-1 RNA <50 copies/ml (follow-up 96 weeks)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious indirectness[3]	no serious imprecision	none	271/343 (79%)	246/346 (71.1%)	RR 1.11 (1.02 to 1.21)	78 more per 1000 (from 14 more to 149 more)	⊕⊕⊕O MODERATE	IMPORTANT
Immunologic response (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious indirectness[3]	no serious imprecision	none	343	346	-	not estimable[6]	⊕⊕⊕O MODERATE	IMPORTANT
Drug resistance (follow-up 96 weeks), reported as acquired major PI mutation												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious indirectness[3]	serious[2]	none	0/343 (0%)	0/346 (0%)	-	not estimable[7]	⊕⊕OO LOW	IMPORTANT

[1] Open-label, industry sponsored study. Down-graded for being open-label study for outcome of severe adverse events but not others.
[2] Low number of events <300 and CI indicates potential for benefit and harm.
[3] Evaluation is in treatment naive patients is indirect measure of PI-naive patients who would use boosted PI in second line after failure of NNRTI based regimen.
[4] Reported as “Any serious AE.” For “Any AE leading to withdrawal,” there were19/343 in DRV/r arm and 35/346 in LPV/r arm.

[5] In post hoc analysis by self reported adherence, those adherent (>95% adherence) had similar VL response (<50 copies/ml) rates in both arms (82 and 78% in DRV/r and LPV/r, respectively). For those sub-optimally adherent (<95%), VL response 76% in DRV/r arm compared to 53% in LPV/r arm (p<0.0001).
[6] Median change from baseline in CD4 cell count was 188 cells/ul in LPV/r group and 171 cells/ul in DRV/r group .
[7] No major PI mutations were found among those with VL >50 copies/ml who had baseline and endpoint genotypes.

GRADE Table 4

Question: Should Atazanavir/ritonavir vs. Lopinavir/ritonavir be used for patients failing first line therapy?
Settings:
Bibliography: Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once daily atazanavir/ritonavir versus twice daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. Lancet 2008;372:646-55. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Atazanavir/ritonavir vs. Lopinavir/ritonavir in antiretroviral naïve HIV-1-infected patients: CASTLE 96 week Efficacy and Safety. 48th Annual ICAAC/IDSA Meeting, October 25-28, 2008, Washington DC. Abstract H-1250d.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Atazanavir/ritonavir	Lopinavir/ritonavir	Relative (95% CI)	Absolute		
Mortality (follow-up 48 weeks)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious indirectness[2]	serious[3]	none	6/440 (1.4%)	6/443 (1.4%)	RR 1.01 (0.33 to 3.1)	0 more per 1000 (from 9 fewer to 28 more)	⊕⊕OO LOW	CRITICAL
Severe adverse events (follow-up 96 weeks)[4]												
1	randomised trials	serious[1]	no serious inconsistency	serious indirectness[2]	serious[3]	none	63/441 (14.3%)	50/437 (11.4%)	RR 1.25 (0.88 to 1.77)	29 more per 1000 (from 14 fewer to 88 more)	⊕OOO VERY LOW	CRITICAL
Clinical disease progression - not reported												
0	-	-	-	-	-				-	-		CRITICAL
Adherence/Tolerability/Retention (follow-up 48 weeks; adherence questionnaire)												
1	randomised trials	serious[1]	no serious inconsistency	serious indirectness[2]	no serious imprecision	none	330/440 (75%)	316/443 (71.3%)	RR 1.05 (0.97 to 1.14)	36 more per 1000 (from 21 fewer to 100 more)	⊕⊕OO LOW	CRITICAL
Virologic response, proportion <50 copies (follow-up 96 weeks)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious indirectness[2]	no serious imprecision	none	308/440 (70%)	279/443 (63%)	RR 1.08 (0.99 to 1.18)[5]	54 more per 1000 (from 7 fewer to 121 more)	⊕⊕⊕O MODERATE	IMPORTANT
Immunologic response (follow-up mean 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious indirectness[2]	no serious imprecision	none	440	443	-	MD 21.2 lower (43.3 lower to 0.9 higher)[6]	⊕⊕⊕O MODERATE	IMPORTANT
Drug resistance (follow-up 96 weeks) reported as major PI mutation												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious indirectness[2]	serious[3]	none	1/440 (2.3%)	0/443 (1.8%)	RR 1.26 (0.5 to 3.16)	5 more per 1000 (from 9 fewer to 39 more)	⊕⊕OO LOW	IMPORTANT

[1] Open-label study, sponsored by industry. Not down-graded for being open-label unless outcome is "severe adverse events" or "adherence" where non-blinded treatment could bias outcome.
[2] Study evaluates ART-naive population, which is indirect population from PI-naive patients who would use PI in second line after failure on NNRTI based regimen.

[3] Low number of events, <300 and CI indicates potential for appreciable benefit and harm.
[4] Reported as, “Serious adverse events.” Of note, even subjects discontinued due to diarrhoea in LPV/r arm and 3 subjects discontinued due to jaundice/hyperbilirubinemia in ATV/r arm.
[5] ITT analysis where non-completer or rebound=failure (TLOVR). At 48 week outcomes, numbers for TLOVR and confirmed virologic response (CVR) were similar: for ATV/r 343/440 and LPV/r 338/443 (CVR) compared to ATV/r 343/440 and LPV/r 337/443 (TOLVR). CVR classifies rebounders who are re-suppressed as responders. TLOVR classifies response as 2 measurements < 50 copies/ml and maintained (without discontinuation or rebound).
[6] Mean increase from baseline of CD4 cell count similar between groups: 268 cells/ul in ATV/r versus 290 cells/ul in LPV/r group at 96 weeks.

GRADE Table 5

Question: Should Fosamprenavir/ritonavir vs. Lopinavir/ritonavir be used for patients failing first line therapy?
Settings:
Bibliography: Eron J, Yeni P, Gathe J et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. Lancet 2006;368:476-82.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Fosamprenavir/ritonavir	Lopinavir/ritonavir	Relative (95% CI)	Absolute		
Mortality (follow-up median 48 weeks)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious[2]	serious[3]	none	4/443 (0.9%)	1/444 (0.2%)	RR 4.01 (0.45 to 35.73)	7 more per 1000 (from 1 fewer to 78 more)	⊕⊕OO LOW	CRITICAL
Severe adverse events (follow-up median 48 weeks; adverse events leading to discontinuation)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	53/436 (12.2%)	43/443 (9.7%)	RR 1.25 (0.86 to 1.83)	24 more per 1000 (from 14 fewer to 81 more)	⊕OOO VERY LOW	CRITICAL
Clinical disease progression or death (follow-up median 48 weeks)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious[2]	serious[3]	none	11/443 (2.5%)	11/444 (2.5%)	RR 1 (0.44 to 2.29)	0 fewer per 1000 (from 14 fewer to 32 more)	⊕⊕OO LOW	CRITICAL
Adherence/tolerability/retention (follow-up median 48 weeks; adherence by pill counts reported as median percentage)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	427/443 (96.4%)	435/444 (98%)	RR 0.98 (0.96 to 1.01)	20 fewer per 1000 (from 39 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
Immunologic response (follow-up median 48 weeks; measured with: median increase in CD4 count from baseline; Better indicated by higher values)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious[2]	no serious imprecision	none	443	444	-	Not estimable[4]	⊕⊕⊕O MODERATE	IMPORTANT
Virologic response, proportion <50 copies/ml (follow-up median 48 weeks)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious[2]	no serious imprecision	none	285/443 (64.3%)	288/444 (64.9%)	RR 0.99 (0.9 to 1.09)	6 fewer per 1000 (from 65 fewer to 58 more)	⊕⊕⊕O MODERATE	IMPORTANT
Drug resistance (follow-up median 48 weeks), reported as acquired major PI mutations												
1	randomised trials	no serious limitations[1]	no serious inconsistency	serious[2]	serious[3]	none	0/443 (0%)	0/444 (0%)	-	Not estimable[5]	OOO⊕ LOW	IMPORTANT

[1] Open-label study; sponsored by industry. Not downgraded for this other than for severe adverse events and adherence, which may be subject to bias in open-label study.
[2] Evaluates comparison in ART-naive population, which is indirect to PI naive populations starting PI-based second-line after NNRTI first-line.

[3] Low number of events <300 and CI indicates potential for appreciable benefit and harm.
[4] Median increase in CD4 from baseline 176 cells/μl (IQR 106-281) in FPV/r group and 191 cells/μl (IQR 124-287) in LPV/r group
[5] No major PI associated mutations in either arm among the 35 patients who had protocol-defined failure and baseline and endpoint genotypes available.