Title: What ARV regimen to switch to in adults, pregnant women, adolescents and children living with HIV (once-daily PI regimens)?

Contents

1. PICO question

	What ARV regimen to switch (once-daily PI regimens)
P	1) Adults (including pregnant women), adolescents and children living with HIV (PI-naive), 2) Adults (including pregnant women), adolescents and children living with HIV (PI-experienced)
I	1) Use of second-line regimens containing boosted ATV, 2) use of second-line regimens containing boosted DRV
C	Use of second-line regimens containing LPV/r
O	Mortality, morbidity, severe adverse events, viral response, adherence, retention, switching rate, tolerability, CD4 response, TB incidence

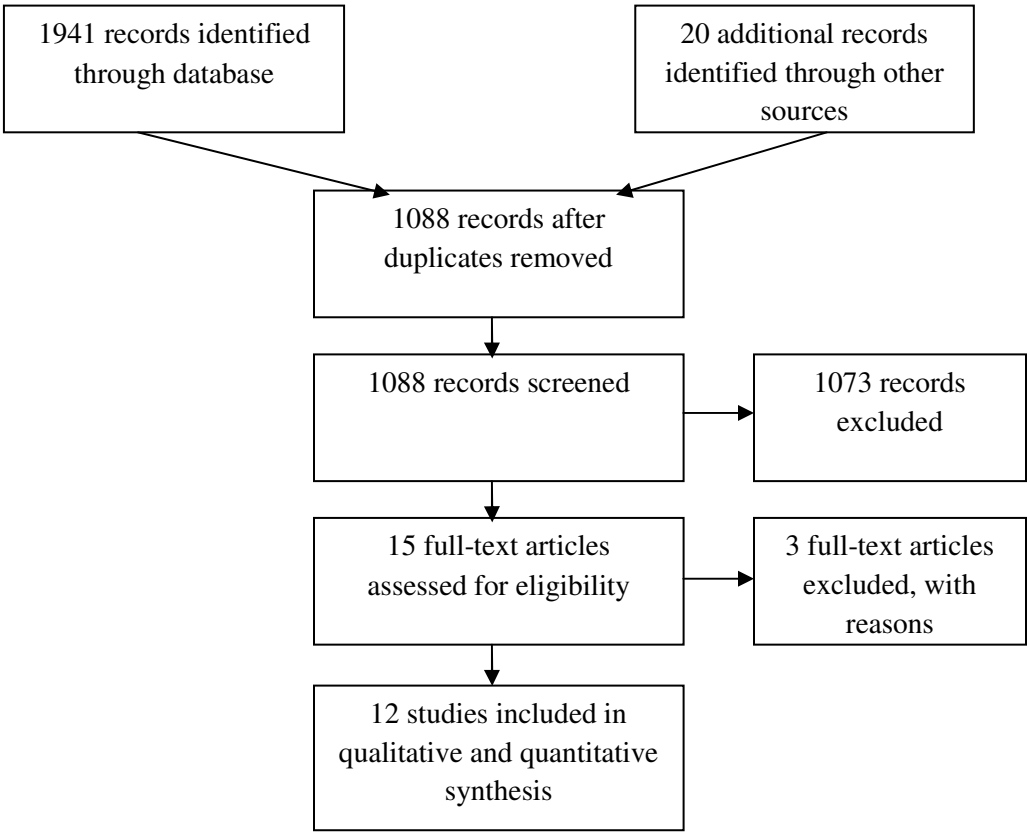
2. Search strategy

Search	Query
#5	**Search (((#1) AND #2) AND #3) AND #4**

This work was commissioned by the World Health Organization and carried out by The University of California, San Francisco (UCSF), Cochrane Review Group on HIV/AIDS

Search	Query
#4	Search "HIV Infections"[MeSH] OR HIV[MeSH] OR HIV[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR HIV infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immunedeficiency virus[tiab] OR ((human immun*) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab]))
#3	Search randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [MeSH] OR random allocation [MeSH] OR double-blind method [MeSH] OR single-blind method [MeSH] OR clinical trial [pt] OR clinical trials [MeSH] OR ("clinical trial" [tiab]) OR ((singl* [tiab] OR doubl* [tiab] OR trebl* [tiab] OR tripl* [tiab]) AND (mask* [tiab] OR blind* [tiab])) OR (placebos [MeSH] OR placebo* [tiab] OR random* [tiab] OR research design [mh:noexp] OR follow-up studies [MeSH] OR prospective studies [MeSH] OR control*[tiab] OR prospectiv* [tiab]) OR non-randomi*[tiab] OR before after study[tiab] OR time series[tiab] OR case control[tiab] OR prospective cohort[tiab] OR cohort*[tiab] OR cross-section*[tiab] OR prospective[tiab] OR retrospective[tiab] OR research design[mh:noexp] OR follow-up studies[MeSH] OR prospective studies[MeSH] OR longitud*[tiab] OR prospectiv*[tiab]) NOT (animals [MeSH] NOT human [MeSH])
#2	Search (Second-line[tiab] OR Second line[tiab] OR Second-line therapy[tiab] OR Second-line treatment[tiab] OR Second-line antiretroviral therapy[tiab] OR Second-line antiretroviral treatment[tiab] OR Salvage therapy[tiab] OR Treatment-experienced[tiab] OR Antiretroviralexperienced[tiab] OR ART-experienced[tiab] OR Experienced patients[tiab] OR "Treatment Failure"[Mesh])
#1	Search (Atazanavir[tiab] OR Lopinavir[tiab] OR Kaletra[tiab] OR Reyataz[tiab] OR Darunavir[tiab] OR Prezista[tiab] OR BMS-232632[tiab] OR TMC114[tiab] OR Aluvia[tiab] OR DRV[tiab] OR ATZ[tiab] OR ATV[tiab] OR LPV[tiab] OR DRV/r[tiab] OR ATZ/r[tiab] OR ATV/r[tiab] OR LPV/r[tiab] OR boosted[tiab] OR "HIV Protease Inhibitors"[Mesh])

3. Flow diagram of screening process



4. Evidence summaries

4.1. Atazanavir/ritonavir versus lopinavir/ritonavir (randomized controlled trials)

Outcome: mortality (96 weeks)

In one trial (BMS Study 045) with 96 weeks of follow-up, data did not exclude a potential superiority or inferiority of ATZ/r compared with LPV/r with respect to mortality (RR 0.2, 95% CI 0.01–4.23) among individuals taking ATZ/r compared with LPV/r. The quality of evidence was low and was downgraded for indirectness due to high-income setting, ART-experience history and NRTI backbone differences and for imprecision because of few events.

Outcome: viral response (96 weeks)

In one trial (BMS Study 045) with 96 weeks of follow-up, data did not exclude a potential superiority or inferiority of ATZ/r compared with LPV/r with respect to viral response (RR 0.91, 95% CI 0.64–1.29) among individuals taking ATZ/r compared with LPV/r. The quality of evidence was low and was downgraded for indirectness due to high-income setting and ART-experience history and NRTI backbone differences and for imprecision because of few events.

Outcome: severe adverse events (96 weeks)

In one trial (BMS Study 045) with 96 weeks of follow-up, data did not exclude a potential superiority or inferiority of ATZ/r compared with LPV/r with respect to severe adverse events (RR 1.26, 95% CI 0.63–2.51) among individuals taking ATZ/r compared with LPV/r. The quality of evidence was low and was downgraded for indirectness due to high-income setting and ART-experience history and NRTI backbone differences and for imprecision because of few events.

Outcome: immune response (96 weeks)

In one trial (BMS Study 045) with 96 weeks of follow-up, immune response did not differ significantly (median CD4 count increase of 160 cells/mm^3 versus 142 cells/mm^3, no 95% CI provided in paper) among individuals taking ATZ/r compared with LPV/r. The quality of evidence was low and was downgraded for indirectness due to high-income setting, ART-experience history and NRTI backbone differences.

Outcome: retention on treatment (96 weeks, on treatment and retained in study)

In one trial (BMS Study 045) with 96 weeks of follow-up, data did not exclude a potential superiority or inferiority of ATZ/r compared with LPV/r with respect to retention on treatment (RR 1.06, 95% CI 0.84–1.33) among individuals taking ATZ/r compared with LPV/r. The quality of evidence was low and was downgraded for indirectness due to high-income setting, ART-experience history and NRTI backbone differences.

4.2. Darunavir/ritonavir versus lopinavir/ritonavir and boosted PIs (randomized controlled trials)

Outcome: Mortality (48 and 96 weeks)

In two trials (POWER 1, 2 and TITAN) with 48 weeks of follow-up, data did not exclude a potential superiority or inferiority of DRV/r compared with LPV/r with respect to mortality (RR 1.62, 95% CI 0.23-11.22) among individuals taking DRV/r compared with LPV/r or other boosted PIs. In one trial (TITAN) with 96 weeks of follow-up mortality remained not significantly different (0.7% versus 1.3%). The quality of evidence was low and was downgraded for indirectness due to high-income setting, inclusion of boosted PIs other than LPV/r in some comparisons, use of twice-daily rather than once-daily dosing, and ART-experience history and NRTI backbone differences and for imprecision because of few events.

Outcome: Viral Response (96 weeks)

In two trials (POWER 1, 2 and TITAN) with 96 weeks of follow-up, a fixed effects meta-analysis found a significant difference favouring DRV/r compared with LPV/r with respect to viral response (RR 1.31, 95% CI 1.14–1.50). Viral response was analysed independently because of significant heterogeneity in one trial (POWER 1, 2) and was significantly better in the DRV/r arm (39% versus 9%, $P < 0.001$) compared with the boosted PI arm. In one trial (TITAN), if the viral definition of failure was relaxed to ≤400 copies/ml (pre-planned analysis), then the DRV/r arm was superior (67.5% versus 59.5%, $P = 0.04$). The quality of evidence was low and was downgraded for indirectness due to high-income setting, inclusion of boosted PIs other than LPV/r in some comparisons, use of twice-daily rather than once-daily dosing, ART-experience history and NRTI backbone differences and for imprecision because of few events.

Outcome: severe adverse events (48 and 96 weeks)

In two trials (POWER 1, 2 and TITAN) with 48 weeks of follow-up, data did not exclude a potential superiority or inferiority of DRV/r compared with LPV/r with respect to severe adverse events (RR 1.12, 95% CI 0.70–1.78) among individuals taking DRV/r compared with LPV/r or other boosted PIs. In one trial (TITAN) with 96 weeks of follow-up, severe adverse events remained not significantly different (13.8% versus 16.5%). The quality of evidence was low and was downgraded for indirectness due to high-income setting, inclusion of boosted PIs other than LPV/r in some comparisons, use of twice-daily rather than once-daily dosing, ART-experience history and NRTI backbone differences.

Outcome: immune response (96 weeks)

In two trials (POWER 1, 2 and TITAN) with 96 weeks of follow-up, immune response did not differ significantly in either trial among individuals taking DRV/r compared with LPV/r or other boosted PIs. The results could not be combined for meta-analysis. In one trial (POWER 1, 2), immune response was significantly better in the DRV/r arm (mean absolute increase in CD4 count, 133 cells/mm^3 versus 15 cells/mm^3, $P < 0.001$) compared with the boosted PI arm. In one trial (TITAN), there was no reported difference in immune response (median increase in CD4 count from baseline, 81 cells/mm^3 versus 93 cells/mm^3; the 95% CI could not be calculated because the data were not reported). The quality of evidence was low and was downgraded for indirectness due to high-income setting, inclusion of boosted PIs other than LPV/r in some comparisons, use of twice-daily rather than once-daily dosing, ART-experience history and NRTI backbone differences.

Outcome: retention on treatment (48 and 96 weeks, on treatment and retained in study)

In two trials (POWER 1, 2 and TITAN) with 48 weeks of follow-up, a fixed effects meta-analysis found a significant difference favouring DRV/r with LPV/r with respect to retention on treatment (RR 1.42, 95% CI 1.29–1.57). When analysed independently in one trial (POWER 1, 2), retention on treatment was significantly better in the DRV/r arm (78.6% versus 19.4%, $P < 0.001$) compared with the boosted PI arm. In one trial (TITAN) with 96 weeks of follow-up, retention on treatment was significantly better in the DRV/r arm (72.8% versus 63.0%, $P < 0.01$) compared with the LPV/r arm. The quality of evidence was low and was downgraded for indirectness due to high-income setting, inclusion of boosted PIs other than LPV/r in some comparisons, use of twice-daily rather than once-daily dosing, ART-experience history and NRTI backbone differences.

5. Quality of evidence

For ATZ/r versus LPV/r, the quality of evidence was deemed low, primarily for serious issues with indirectness. First, the patient population was from a high-income setting. Second, these patients were heavily treatment-experienced, including all patients having prior PI experience. Most patients in low- and middle-income countries being considered for switching due to treatment failure will have failed one previous non-PI-based regimen and are unlikely to have significant PI mutations. Third, NRTI background regimens were selected based on phenotypic sensitivity analysis, which is an unlikely scenario in low- and middle-income countries.

For DRV/r versus LPV/r, the quality of evidence was deemed low, primarily for serious issues with indirectness. For the first trial (POWER 1, 2), the patient population was from a high-income setting. Second, these patients were heavily treatment experienced, including with previous PIs. Most patients in low- and middle-income countries being considered for switching due to treatment failure will have failed

one previous non-PI-based regimen and are unlikely to have significant PI mutations. Third, only about one third of the comparison arm actually contained the primary boosted PI of interest, LPV/r, and the NRTI backbones (some with enfuviritide) are probably unrepresentative of typical WHO-recommended second-line regimen backbones. Fourth, the dosing of DRV/r in this study was 600 mg/100 mg twice daily rather than 800 mg/100 mg daily recommended for PI-naive patients.

For the other trial (TITAN), the patient population was from a high-income setting. Second, although all patients with previous LPV treatment were excluded, the treatment experience of this study population still consisted of 69% with some PI experience and 52% with ≥four NRTI experience, which contrasts with most patients in low- and middle-income countries, who fail a first two NRTI + one NNRTI regimen only. Third, while TITAN's comparison group all used LPV/r-based regimens, study patients also took an optimized background regimen consisting of ≥two NRTI ± NNRTI based in part on resistance testing data, an unlikely scenario in low- and middle-income countries. Fourth, the dosing of DRV/r in this study was also 600 mg/100 mg twice daily.

6. RCT subanalysis of PI-experienced only versus NNRTI-experienced only patients

ATZ/r versus LPV/r: BMS Study 045

Population ART experience. Treatment experience was defined as treatment having failed with two or more previous ARV regimen s that included one or more NRTIs, an NNRTI and PI with a baseline HIV RNA level >1000 copies/ml. All patients were therefore both NNRTI and PI-experienced. The proportion of patients with no PI mutations at baseline was low (see table below).

Baseline resistance in BMS Study 045

PI mutations	ATV/r (*n* = 120)	LPV/r (*n* = 123)
0	15%	10%
1–2	41%	43%
3–4	19%	21%
≥4	25%	26%

Results. Weeks 48 and 96: No difference reported in viral response comparing ATV/r versus LPV/r by the number of baseline PI mutations (no specific data provided comparing patients with 0 PI mutations versus >0). No difference in viral response comparing ATV/r versus LPV/r when phenotypic sensitivity testing revealed sensitivity to the treatment with PI (2.12 versus 2.09 $\log_{10}$ copies/ml declines respectively at week 48).

Interpretation. Few patients in this study might be considered NNRTI-experienced + functionally PI-naive (no PI resistance mutations): about 15% in the ATV/r arm and 10% in the LPV/r arm. While this study provides no detailed results, there did not appear to be any differences in viral efficacy comparing ATV/r versus LPV/r for this small subgroup. No participants from this study can be considered NNRTI-naive + PI-experienced.

DRV/r versus LPR/r: TITAN

Population ART experience. Treatment experience was defined as receiving ART for at least 12 weeks with a HIV RNA level >1000 copies/ml. Of the total patients, 31.4% were PI-naive and 23.7% were NNRTI-naive. These patients were evenly divided between arms. The study did not provide data on the overlap between these two groups. Baseline PI-resistance was low, with 98% fully susceptible to DRV

and 90% to LPV based on phenotype testing; 80% in the DRV arm and 84% in the LPV arm had no DRV resistance mutations.

Results. Week 96: LPV/r did better among PI-naive patients compared with DRV/r, but it was not statistically significant (68.8% versus 56.4% response, <50 copies/ml, $P = 0.08$). For PI-experienced patients, DRV/r did better than LPV/r (62.3% versus 49.0%, $P = 0.007$). Among patients with no baseline PI resistance mutations, LPV/r was numerically but not statistically significantly better than DRV/r (63.2% versus 56.3%, $P = 0.15$).

Interpretation. DRV outperformed LPV among PI-experienced patients (unclear NNRTI experience in these groups). Among PI-naive patients and among functionally naive (no PI resistance mutations) patients, LPV was numerically better than DRV, but none of these results were statistically significant (again, no specific data on what proportion of these patients were NNRTI-naive versus NNRTI-experienced were reported).

DRV/r versus LPR/r: POWER 1, 2

Population ART experience. Treatment experience was defined as having at least one primary PI mutation, HIV RNA level >1000 copies/ml, receiving a PI-containing regimen and previously using >one NRTI and ≥one NNRTI; thus, all patients were both PI and NNRTI experienced and had baseline PI resistance.

Results. Weeks 48 and 96: DRV/r had improved viral response (<50 copies/ml) compared with control PIs regardless of the number of baseline PI mutations.

Interpretation. No meaningful subgroup analyses were possible based on this study because there was no NNRTI-naive or functionally PI-naive subgroup (that is, no PI resistance) with which to make comparisons.

7. Summaries of studies not included in GRADE analysis: what ARV regimen to switch to in children

Brief summary of observational studies of children with no comparator arm or using obsolete regimens		
1	Bunupuradah T, Kosalaraksa P, Puthanakit T, Mengthaisong T, Wongsabut J, Lumbiganon P, Phanuphak P, Burger D, Pancharoen C, Ananworanich J. Monoboosted lopinavir/ritonavir as simplified second-line maintenance therapy in virologically suppressed	**Study design.** Single-arm observational study. **Population and setting.** 40 children living with HIV (interquartile range 10.5–13.2 years of age) from two clinical sites in Thailand (2007–2008). **Intervention.** Children with two consecutive HIV-RNA below 50 copies/ml at least three months apart while on double-boosted protease inhibitor (dPI) were switched to monoboosted lopinavir/r (mLPV/r). The previous dPI regimen was resumed within four weeks among children who experienced viral failure, defined as two HIV-RNA at least 500 or three HIV-RNA at least 50 copies/ml. **Results.** At 48 weeks, none had died or had HIV disease progression. 31 children were on mLPV/r and 29 (72.5%) had HIV-RNA less than 50 copies/ml. Nine resumed dPI due to mLPV/r failure, with four achieving undetectable HIV-RNA. Overall, 31 children (82.5%) had HIV-RNA suppression. The predicting factor for failing mlPV/r was baseline HIV-

Brief summary of observational studies of children with no comparator arm or using obsolete regimens		
	children. AIDS 2011; 25: 315-323.	RNA at least 50 copies/ml. No major protease mutations were found. **Conclusions.** The authors concluded that simplifying second-line treatment from dPI to mLPV/r enabled most children to sustain viral suppression at 48 weeks.
2	Charpentier C, Gody JC, Mbitikon O, Moussa S, Matta M, Pere H, Fournier J, Longo JDD, Belec L. Virological response and resistance profiles after 18 to 30 months of first- or second-/third-line antiretroviral treatment: a cross-sectional evaluation in HIV type 1–infected children living in the Central African Republic. AIDS Res Hum Retroviruses 2012; 28: 87-94.	**Study design.** Cross-sectional analysis from observational prospective cohort study. **Population and setting.** 15 children living with HIV 9–15 years old placed on second-line (n = 13) or third-line (n = 2) ART after a median of 18 months of ART from 1 site in Bangui, Central African Republic (2009). **Intervention.** 15 children receiving a second- or third-line regimen, an LPV-containing regimen was prescribed for seven (47%) and an indinavir-containing regimen for three children (20%). The five remaining children received a non-nucleoside reverse-transcriptase inhibitor (NNRTI)–based regimen. **Results.** In children under second- or third-line therapy, viral failure occurred in 47% and resistance (among the 10 tested) in 90%. **Conclusions.** The authors concluded that the distribution of antiretroviral drugs for children urgently needs to be improved in the Central African Republic, to increase adherence by treated children and to offer adequate HIV biological monitoring.
3	Delaugerre C et al. Predictive factors of viral success in HIV-1-infected children treated with lopinavir/ritonavir. J Acquir Immune Defic Syndr 2004; 37: 1269-1275.	**Study design.** Single-arm observational study. **Population and setting.** 69 (48 PI-experienced) children living with HIV with a mean age of 10.3 years who had received LPV/r for at least three months from one site in Paris, France (2000–2001). **Intervention.** All PI-naive children received LPV/r combined with two NRTIs. For PI-experienced children, LPV/r was associated with two NRTIs (n = 33) or two NRTIs plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI, n = 15). The mean dose of LPV/r was 10.2 ± 4.0 mg/kg administered twice per day. Twenty-two children received the oral solution, and 47 received the soft elastic capsule formulation. **Results.** After 18 months, 49% had plasma VL <50 copies/ml. During the follow-up, 25 (36%) children met the viral failure criteria, 4 of them after 9 months of treatment. The risk of viral failure, defined as two consecutive viral loads greater than 1000 copies/ml, was significantly higher when the children were previously treated with PIs and when the baseline LPV mutation score exceeded three mutations. In the pretreated children, the ratio of the plasma LPV maximal concentration to the baseline LPV score mutation was also associated with failure, independently of resistance score. Finally, in children for whom an LPV-containing regimen failed, accumulation of additional PI-associated resistance mutations was evidenced in viral isolates from children with previous PI treatment, even with viral replication levels less than 10 000 copies/ml. **Conclusions.** The authors concluded that, in pretreated children, LPV plasma levels should be optimized in an attempt to achieve sufficient drug concentrations to overcome the resistance level.

Brief summary of observational studies of children with no comparator arm or using obsolete regimens		
4	Larru B, Resino S, Bellon JM, de Jose MI, Fortuny C, Navarro ML, Gurbindo MD, Ramos JT, Soler Palacin P, Leon JA, Asensi M, Mellado MJ, Munoz-Fernandez MA. Long-term response to highly active antiretroviral therapy with lopinavir/ritonavir in pre-treated vertically HIV-infected children. J Antimicrob Chemother 2008; 61: 183-190.	**Study design.** Retrospective observational cohort study. **Population and setting.** 69 vertically infected children living with HIV (interquartile range 7.1–11.3 years) from four clinical sites in Spain (2000–2006). **Intervention.** Children receiving ARV regimen s containing LPV/r. **Results.** From the second to fourth year, the authors found an increase in %$CD4^+$ in all the children who had $CD4^+$ <25% and in those with baseline VL >100 000 copies/ml. They also found that %$CD4^+$ at baseline had a strong positive association with achieving $CD4^+$ >25% at 6, 12, 18, 24, 36 and 48 months of follow-up. The length of PI use had a negative association with reaching $CD4^+$ >25% at 24 and 48 months and achieving undetectable VL at 12 and 24 months. Four participants died during follow-up. **Conclusions.** The authors concluded that ongoing immune recovery among children on HAART with LPV/r after four years of follow-up and that LPV/r is safe and well tolerated among children living with HIV when given as part of a salvage regimen .
5	Puthanakit T, Jourdain G, Suntarattiwong P, Chokephaibulkit K, Siangphoe U, Suwanlerk T, Prasitsuebsai W, Sirisanthana V, Kosalaraksa P, Petdachai W, Hansudewechakul R, Waranawat N, Ananworanich J. High viral response rate after second-line boosted protease inhibitor–based antiretroviral therapy regimens in children from a resource limited setting. AIDS Res Ther 2012; 9: 20.	**Study design.** Retrospective chart review. **Population and setting.** 241 children living with HIV with a mean age of 9.1 years from eight clinical sites in Thailand (2002–2007). **Intervention.** PI-based ART after failing first-line NNRTI-based regimens. 104 children were switched to single-boosted PI and 137 children switched to double-boosted PI. **Results.** At week 48, 81% had HIV RNA <400 copies/ml (single boosted PI 83.1% versus double boosted PI 79.8%, p = 0.61) with a median CD4 rise of 9% (+7% versus + 10%, $P < 0.005$). However, only 63% had HIV RNA <50 copies/ml, with better viral suppression seen in single boosted PI (76.6% versus 51.4%, $P = 0.002$). **Conclusions.** The authors concluded that second-line PI therapy was effective for children for whom first-line NNRTI failed in a resource-limited setting. Double boosted PI were used in patients with extensive drug resistance due to limited treatment options.
6	Ramos JT, De Jose MI, Duenas J, Fortuny C, Gonzalez-Montero R, Mellado MJ, Mur A, Navarro M, Otero C, Pocheville I, Munoz-Fernandez MA, Cabrero. Safety and antiviral response at 12 months of	**Study design.** Observational cohort study (combining retrospective and prospective data). **Population and setting.** 45 children living with HIV (interquartile range 4.3–17.1 years) from 12 clinical sites in Spain (2001–2003). **Intervention.** Children experienced with the three classes of oral antiretroviral medicines among whom a LPV/r-containing regimen was started. **Results.** 42% of children achieved a plasma RNA of <400 copies/ml. Nonresponders had 7.0 ± 1.6 PI-associated mutations at baseline compared with 4.8 ± 1.7 in children achieving viral suppression

Brief summary of observational studies of children with no comparator arm or using obsolete regimens		
	lopinavir/ritonavir therapy in human immunodeficiency virus-1–infected children experienced with three classes of antiretrovirals. Pediatr Infect Dis J 2005; 24: 867-873.	($P < 0.06$). Adverse events were described in 18 children. **Conclusions.** The authors concluded that LPV/r is well tolerated when given as part of salvage regimen, although switching to pills is frequently required. The regimen has potent and durable antiretroviral activity in most heavily pretreated children, despite the presence of multiple mutations to all classes of oral antiretroviral medicines.
7	Resino S, Bellon JM, Ramos JT, Gonzalez-Rivera M, de Jose MI, Gonzalez MI, Gurbindo D, Mellado MJ, Cabrero E, Munoz-Fernandez MA. Positive virological outcome after lopinavir/ritonavir salvage therapy in protease inhibitor-experienced HIV-1-infected children: a prospective cohort study. J Antimicrob Chemother 2004; 54: 921-931.	**Study design.** Observational prospective cohort study. **Population and setting.** 67 children living with HIV with an age range from 1.4 to 17.1 years from 12 clinical sites in Spain (2000–2003). **Intervention.** LPV/r therapy in PI-experienced children. **Results.** 66% of the children reached undetectable VL. The children with a new NRTI or PI or PI + NNRTI in the current regimen had a better viral response than children without these new drugs. Further, children with <6 PI had a relative odds of 2.31 of achieving undetectable VL. **Conclusions.** The authors concluded that ART including LPV/r induces beneficial effects in terms of viral outcome responses and is an effective option for salvage therapy in PI-experienced HIV-1–infected children.
8	Resino S, Bellon JM, Ramos JT, Navarro ML, Martin-Fontelos P, Cabrero E, Munoz-Fernandez MA. Salvage lopinavir-ritonavir therapy in human immunodeficiency virus-infected children. Pediatr Infect Dis J 2004; 23: 923-930.	**Study design.** Retrospective observational study. **Population and setting.** 30 PI-experienced children living with HIV from four clinical sites in Spain (1996–2003). **Intervention.** The study compared three treatment regimen arms, but only arm three is of interest for this PICO (PI-experienced children receiving LPV/r). **Results.** 71.5% of children achieved a VL of ≤400 copies/ml, and 32.4% experienced a VL rebound. Children with HIV-1 isolates with <7 protease mutations or <7 transcriptase inverse mutations at baseline achieved a VL of ≤400 copies/ml more quickly than children with HIV-1 isolates with <7 mutations. **Conclusions.** The authors concluded that ART that includes LPV/r is able to control HIV replication more efficiently than other types of classic salvage antiretroviral therapy.
9	Resino S, Bellon JM, Munoz-Fernandez MA. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with	**Study design.** Prospective observational study. **Population and setting.** 25 children living with HIV, age range 3.2 to 17.1 years, from one clinical site in Spain. **Intervention.** Children for whom a PI or NNRTI-based regimen failed and treated with LPV/r and multiple different backbones. **Results.** 47% of children achieved an undetectable VL of ≤400 copies/ml. After achieving undetectable VL, 8 of 17 children had a rebound of VL >400 copies/ml. The median (range) increase in $CD4^+$ at month 18

Brief summary of observational studies of children with no comparator arm or using obsolete regimens		
	severe-moderate immunodeficiency. J Antimicrob Chemother 2006; 57: 579-582.	was 15 (95% CI –3, 44). Adverse events during the follow-up study were reported in 15 of 25 (60%) children. **Conclusions.** The authors concluded that therapy with lopinavir/ritonavir exhibited safety and tolerability, and it was associated with substantial antiviral activity (50% of children with a VL of <400 copies/ml) and immune recovery.
10	Resino S, Resino R, Micheloud D, Gurbindo Gutierrez D, Leon JA, Ramos JT, Ciria L, de Jose I, Mellado J, Munoz-Fernandez A. Long-term effects of highly active antiretroviral therapy in pretreated, vertically HIV type 1-infected children: 6 years of follow-up. Clin Infect Dis 2006; 42: 862-869.	**Study design.** Retrospective observational study. **Population and setting.** 113 vertically infected children living with HIV, mean age 7 years, from six clinical sites in Spain (1996–2004). **Intervention.** Children having received mono- or dual-nucleoside therapy before starting ART (no specific data provided on second-line ART provided). **Results.** During the first two years of HAART, HIV-1–infected children experienced a significant increase in CD4 cell percentage and a decrease in viral load ($P < 0.05$). During their last 4 years of receiving HAART, we found a significant decrease in viral load but not an increase in $CD4^+$ cell percentage, because the $CD4^+$ cell percentage plateaued after the second year of HAART. **Conclusions.** The authors concluded that long-term HAART allowed for restoration of $CD4^+$ cell counts and control of viral loads in HIV-1–infected children. However, initiating HAART after severe immunosuppression has occurred is detrimental for restoring the $CD4^+$ cell count.
11	Rudin C, Burri M, Shen Y, Rode R, Nadal D. Long-term safety and effectiveness of ritonavir, nelfinavir, and lopinavir/ritonavir in antiretroviral-experienced HIV-infected children. Pediatr Infect Dis J 2008; 27: 431-437.	**Study design.** Prospective observational cohort study. **Population and setting.** 62 PI-experienced children living with HIV (of which 37 received LPV/r as their second-line ART) from seven clinical sites in Switzerland (1996–2003). **Intervention.** PI-experienced children receiving ritonavir, nelfinavir or LPV/r for second-line ART (the study also included PI-naive children). **Results.** Significant mean reductions in HIV-1 RNA levels were found for the PI-experience group for all three PIs at week 4 and for RTV and LPV/r at week 96. Statistically significant increases in $CD4^+$ cell counts were observed for LPV/r at week 4, with no difference between the three PI regimens at week 96. No other results reported for the PI-experienced group only. **Conclusions.** The authors concluded that long-term PI-based therapy seems to be safe and to result in durable viral and immune effectiveness in HIV-1–infected antiretroviral-experienced children.
12	Rudin C, Wolbers M, Nadal D, Rickenbach M, Bucher HC. Long-term safety and effectiveness of lopinavir/ritonavir in antiretroviral-experienced HIV-1-infected children. Arch Dis Child 2010; 95:	**Study design.** Prospective observational cohort study. **Population and setting.** 63 PI-experienced children living with HIV from seven clinical sites in Switzerland (1996–2003, 2000–2008). **Intervention.** Children treated with LPV/r-based ART participating in the cohort. **Results.** 27/46 (59%) of PI-experienced children with detectable viral loads achieved viral suppression during follow-up and, of these, 3 experienced viral rebound. The median $CD4^+$ cell increase at 48 weeks was 177 (interquartile range 21–331). **Conclusions.** The authors concluded that long-term treatment with

Brief summary of observational studies of children with no comparator arm or using obsolete regimens		
	478-481.	LPV/r-based combination ART is safe and effective in HIV-1–infected children.
13	Saez-Llorens X, Violari A, Deetz CO, Rode RA, Gomez P, Handelsman E, Pelton S, Ramilo O, Cahn P, Chadwick E, Allen U, Arpadi S, Castrejon MM, Heuser RS, Kempf DJ, Bertz RJ, Hsu AF, Bernstein B, Renz CL, Sun E. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. Pediatr Infect Dis J 2003; 22: 216-224.	**Study design.** Single-arm observational study **Population and setting.** 56 ART-experienced (24 PI-experienced) children living with HIV from locations not reported (1999). **Intervention.** Clinical trial of liquid formulation of LPV/r in combination with reverse-transcriptase inhibitors (study included both ART-naive and ART-experienced children). **Results.** 42/56 (75) of ART-experienced children achieved a VL of <400 copies/ml at 48 weeks. 5.9% had a mean relative (percentage) CD4 cell count increase and a mean absolute increase of 284 cells/mm^3 at 48 weeks (data not reported by PI-experienced versus naive). **Conclusions.** The authors concluded that the liquid co-formulation of LPV/r demonstrated durable antiviral activity and was safe and well tolerated after 48 weeks of treatment in children living with HIV.
14	Zyl GU et al. Is it time to consider third-line options in antiretroviral-experienced paediatric patients? J Int AIDS Soc 2011; 14: 55.	**Study design.** Cross-sectional study nested in a case series longitudinal study **Population and setting.** 82 children living with HIV (53 PI-experienced) from two clinical sites in South Africa (2007–2009). **Intervention.** Evaluating the prevalence of major PI resistance in children for whom ART has failed. **Results.** Fourteen (17%) of 82 ART-experienced patients had major PI mutations. Patients retained on LPV/r had lower viral loads than those switched to an NNRTI. However, two of three patients with follow-up resistance tests accumulated additional PI resistance. **Conclusions.** The authors concluded that the historical use of unboosted PI regimens contributed to a cohort of children at increased risk of having compromised first- and second-line antiretroviral regimens. Therefore, there is an urgent need for affordable access to third-line drugs for children in low- to middle-income countries.

8. Bibliography of included studies

8.1. LPV/r versus ATZ/r

Johnson M, Grinsztejn B, Rodriguez C, Coco J, DeJesus E, Lazzarin A, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. AIDS 2005;19(7):685-94. [BMS 045 STUDY]

Johnson M, Grinsztejn B, Rodriguez C, Coco J, DeJesus E, Lazzarin A, et al. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple viral failures. AIDS 2006;20(5):711-8. [BMS 045 STUDY]

8.2. LPV/r versus DRV/r

Katlama C, Esposito R, Gatell JM, Goffard JC, Grinsztejn B, Pozniak A, et al. Efficacy and safety of TMC114/ritonavir in treatment-experienced HIV patients: 24-week results of POWER 1. AIDS 2007;21(4):395-402. [POWER 1 STUDY]

Haubrich R, Berger D, Chiliade P, Colson A, Conant M, Gallant J, et al. Week 24 efficacy and safety of TMC114/ritonavir in treatment-experienced HIV patients. AIDS 2007;21(6):F11-8. [POWER 2 STUDY]

Clotet B, Bellos N, Molina JM, Cooper D, Goffard JC, Lazzarin A, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. Lancet 2007;369(9568):1169-78. [POWER 1 AND 2 STUDIES]

Arasteh K, Yeni P, Pozniak A, Grinsztejn B, Jayaweera D, Roberts A, et al. Efficacy and safety of darunavir/ritonavir in treatment-experienced HIV type-1 patients in the POWER 1, 2 and 3 trials at week 96. Antiviral Ther 2009;14(6):859-64. [POWER 1, 2 AND 3 STUDIES]

Madruga JV, Berger D, McMurchie M, Suter F, Banhegyi D, Ruxrungtham K, et al. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. Lancet 2007;370(9581):49-58. [TITAN STUDY]

De Meyer S, Lathouwers E, Dierynck I, De Paepe E, Van Baelen B, Vangeneugden T, et al. Characterization of viral failure patients on darunavir/ritonavir in treatment-experienced patients. AIDS 2009;23(14):1829-40. [TITAN STUDY]

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8.3. First-line PI/r comparison studies

8.3.1. LPV/r versus ATV/r

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8.3.2. LPV/r versus DRV/r

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9. Excluded studies with reasons

9.1. LPV/r versus ATZ/r

Cohen C, Nieto-Cisneros L, Zala C, Fessel WJ, Gonzalez-Garcia J, Gladysz A, et al. Comparison of atazanavir with lopinavir/ritonavir in patients with prior protease inhibitor failure: a randomized multinational trial. Curr Med Res Opin 2005;21(10):1683-92.

Reason: Cohen (2007) was an open-label, randomized trial of ATZ (400mg daily) compared with LPV/r (400 mg/100 mg twice daily). Because ATZ was not boosted with ritonavir, this study did not meet our inclusion criteria and was excluded from this study.

9.2. LPV/r versus DRV/r

None.