

## Considerations on 3<sup>rd</sup> Line ART

### Studies on Boosted PIs

There are multiple trials comparing boosted PIs in treatment-experienced patients that were outside the scope of this review (see Table in **Appendix 2**). 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, multicentre open-label trial comparing indinavir/ritonavir (800/100 mg) twice daily plus 2 NRTIs to saquinavir/ritonavir (1000/100 mg) twice daily plus 2 NRTIs in 306 patients and was powered to show equivalence between arms (80% chance that 95% CI of the difference in virological failure would exclude a difference >15% in either direction). Most patients (61%) were PI experienced and 25% were ART naïve. 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 ( $p=0.009$ ). There was no difference in the time to virological 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 2 NRTIs to SQV/r (1000/100 mg) twice daily plus 2 NRTIs in 324 treatment-experienced 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 (when discontinuation = failure) compared to 39% in the SQV/r arm ( $p=0.005$ ). 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) at 48 weeks analysis occurred in those patients on ATV/r, TPV/r and LPV/r (72.4%, 68.2% and 54.4% response, respectively). Discontinuations due to adverse events was highest in the IDV group (22.8%) compared to all others ( $p=0.03$ ). In multivariate analysis, the number of protease inhibitor mutations at baseline was associated with lower virologic response at week 24 (OR= 0.77, 95% CI 0.68-.87;  $p<0.001$ ).

### Use of new drugs in heavily experienced patients

Recent studies in resource-limited settings suggest there will be an ongoing need for expanded ART options in 3<sup>rd</sup> line. The proportion of patients on second line in resource limited settings are estimated between ~1-5% (Renaud Thery 2007; Egger 2008; Pujades Rodriguez 2008). 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, urban versus rural location, among other factors (A. Calmy, personal communication; Egger 2008; Davies 2009). Recent unpublished data suggests failure rates on second-line of 18.8% (personal communication, A. Calmy shared on condition of confidentiality until publication). 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 including etravirine in resource limiting settings (**Sungkanuparph 2008**), suggesting newer options for PI intolerant patients, or potentially for heavily experienced patents.

**Table 4** contains selected trials of Etravirine, Raltegravir or Darunavir in highly treatment-experienced patients.

**Table 4.** Studies 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	Fagan 2009	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	ASIER	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 + OBT vs. placebo + OBT  OBT=optimized background therapy	ANCHMARK-1,	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

**Appendix 2** Table of Boosted PI Trials in **ART experienced** patients

Comparison	Trial name	Publications	Follow up	Outcomes/Notes
ATV/r v LPV/r	ATAZIP	Mallolas 2009 Soriano 2008	48 weeks	* In ATAZIP, 48 week analysis showed similar efficacy and better lipid parameters in ATV/r arm
	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 Madrugá 2007	48 weeks	* DRV/r non-inferior to LVP/r in treatment experienced patients with similar safety profile
ATV/r v ATV	ARIES	Johnson 2009 (IAS)	144	*Non-inferiority of ATV to ATV/r after induction
	SWAP	Coatell 2007	48	*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 OBV (p<.0001). GI side effects and raised transaminase and lipids in TPV/r arm.
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## SUMMARY

### Second line failure findings

Failure rates on second-line therapy are estimated to be ~5-15%. In general, response with second line regimens including boosted PIs has been encouraging. 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. Despite a comprehensive search, very few studies were identified of relevance. One trial suggests no difference in virological outcomes among those maintaining lamivudine on 2<sup>nd</sup> line regimens compared to those who do not (low quality of evidence). Observational data supports this finding.

### Boosted PI comparisons

Single trials evaluating comparison of lopinavir/ritonavir to darunavir/ritonavir, atazanavir/ritonavir or fosamprenavir/ritonavir in ART **naïve** patients showed non-inferiority of all 3 PIs when compared to lopinavir/ritonavir (low to moderate quality evidence).

### Boosted PI monotherapy

There is low quality evidence that patients on monotherapy have lower virologic response than patients on combination ART. There were no other significant differences in critical or important outcomes (although non-critical outcomes such as Grade 2 adverse events, lipodystrophy 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 cART. Accessibility of monitoring and reinitiation 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.

### Ongoing Second-line trials

Trial ID	Location	population	intervention and comparator	Outcomes	end date
NCT 00928187 (2LADY)	Burkina Faso, Cameroon, Senegal	450 adults with 1st line failure on NNRTI and 2NRTI	2nd line with: FTC/TDF+LPV/r or ABC+ddl+LPV/r	HIV RNA <50 copies/ml (48 weeks) and clinical outcomes	2012

			or FTC/TDF + Darunavir/r		
NCT 00931463 (SECOND- LINE)	48 sites (global)	550 adults with failure on NNRTI + 2NRTI	2nd line with: LPV/r +2NRTI or LPV/r + raltegravir	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	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 2 <sup>nd</sup> line	monotherapy or LPV/r-based therapy	efficacy and safety	2009
NCT 00988039 (EARNEST)	Malawi, Uganda, Zimbabwe	120 patients >12 years with failure on first line NNRTI + 2NRTI	LPV/r monotherapy or LPV/r + RAL or LPV/r + 2NRTI	clinical, virologic, immunologic control at 96 weeks	2013