

GRADE table: PI Monotherapy

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 2008; Katlama 2009; Nunes 2007; Singh 2007 & Waters 2008.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							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)	⊕⊕○○ 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	25/499 (5%)	26/472 (5.5%)	RR 1.02 (0.5 to 2.07)	1 more per 1000 (from 28 fewer to 59 more)	⊕○○○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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	⊕⊕⊕○ 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)	⊕⊕○○ 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.

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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.