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HIV regimens de-intensification with PI monotherapy: one size does not fit all

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ABSTRACT

Since the advent of HAART, the triple regimens have been the standard of care for the long-term treatment of HIV infection. However, clinical trials and clinical experiences have explored the option of maintaining the HIV RNA control with a single-drug regimen (boosted PI monotherapy) in subjects fully suppressed with the standard combination treatment.

The aim of this paper is to focus on the long-term data available from trials investigating the option of PI monotherapies in selected populations.

So far, three-year data suggest that patients with a prolonged HIV RNA suppression (whatever the triple regimen they were on), fully adherent to medications, with nadir CD4 count higher than 100 cells/mmc, who don't required the nucleoside backbone for specific reasons, may safely switch to a boosted-PI monotherapy as a maintenance strategy. Although all trials confirm that, in terms of plasma viral control, triple regimens may be more potent, a large proportion of subjects can be virologically controlled over time with a boosted PI only. In fact, a full HIV RNA suppression (below 1 or 5 copies/ml) is possible, even with a PI monotherapy and for a long follow up (96-144 weeks). The risk of primary mutations at failure is rare and similar to patients on PI-based triple therapy. In case of failure, re-suppression by NRTIs re-introduction is effective in almost all patients.

Open issues refer to virological control in sanctuary sites, but studies are ongoing.

Rationale for PI monotherapy

The standard treatment of HIV chronic infection is based on triple therapy as it consistently provided a potent, effective and durable response, minimizing the risk of virological failure (1-3). Several triple regimens are currently available and ranked as first line options in antiretroviral naïve patients (1-3). However, a long-term HIV control requires a life-long exposure to drugs (with toxicity and tolerability concerns) and a high financial burden for the public health care system (4,5,6). The option of maintaining a suppressed viremia with a reduced number of drugs (less drug regimens) has been explored also in the early years of HAART Era with unfavorable results, using 2 NRTIs as maintenance, after a short term induction (a few months) with PI-based regimens, (7). Insufficient drug potency and/or HIV characteristics were then perceived to be the reasons for failure with dual NRTI-based regimens.

However, the idea that maintenance treatment (when HIV RNA is suppressed) could be achieved with less than a 3-drug regimen has never been abandoned (9). Over almost 20 years of HIV pharmacology, new drugs and new drug combinations have generated alternative ideas for HIV initial and maintenance regimens. The advent of ritonavir-boosted PIs, given their intrinsic potency and the minimal risk of resistance mutations at failure, have suggested the option of preserving the HIV RNA control with boosted PI monotherapy in patients whose viremia is suppressed under triple regimens.

However, starting therapy with a PI monotherapy in naïve subjects proved to be less potent and with a higher risk of mutations compared to triple arm (10), so this option is not recommended.

The potential benefits from de-intensification to a PI monotherapy in aviremic subjects are associated to lower exposure to drugs, lower toxicity from NRTIs and lower costs. However, the potential risks are a higher proportion of failing patients (compared to the standard of care) and a higher risk of resistance mutations at failure with consequent loss of future treatment options.

The main issues when considering a treatment strategy based on a single-drug regimen are:

1. the intrinsic potency of the drug (capacity to maintain HIV RNA suppression)
2. the risk of resistance mutations at failure (loss of future options)
3. the virological efficacy of NRTIs re-introduction

4. the durability of response compared to standard HAART
5. the differential drug tissue penetration of antivirals (control in sanctuary sites)

Pilot studies and clinical trials tried to explore and answer these questions. A recent meta-analysis (11) involved six trials (both in naïve and antiviral experienced patients) showing a higher risk of failure for monotherapy arms compared to combined regimens, although a similar efficacy between arms was reported after NRTIs reintroduction was allowed. Another meta-analysis (12) included 10 trials, comparing 3 different PIs in 1189 virologically suppressed patients, confirming that subjects switching to PI monotherapy have a lower chance of maintaining HIV RNA suppression (< 50 copies/ml) compared to subjects on triple therapy, at week 48 [ITT analysis: OR: 0.94 (95% CI: 0.89-1.00), p=0.06 and PP analysis OR: 0.93 (95% CI: 0.90-0.97), p<0.001]. The reintroduction of the NRTI backbone was highly effective with 93% (41/44) of patients regaining suppression.
However, not all PIs are the same, some of them have been explored in pilot trials only and not all of them showed a similar efficacy in monotherapy trial (12).
Here we focus on the randomized switch trials with a sufficiently large sample size and with a long follow-up, in order to clarify the risks and benefits of monotherapy as maintenance treatment.

Randomized monotherapy trials

Table 1 summarizes the study design, entry criteria and duration of follow up of Kalesolo (13), OK04 (14), MONOI (15) and MONET (16) trials.
All studies were non inferiority trials, with 100 or more patients per arm. All patients had no history of previous virological failure on PI regimens, they all switched from virologically effective triple therapy (either NNRTI- or PI-based), with relative high CD4 counts and a long history of virological suppression. Two studies switched to LOP/r BID monotherapy (Kalesolo and OK04) and 2 studies to DRV/r monotherapy which was differently dosed in the two trials for the first 48 weeks, namely 600 mg BID in MONOI study and 800 mg OD in MONET study.
Table 2 compares, in the 4 trials, the efficacy results, the emergence of resistance mutations, the efficacy at NRTIs re-introduction and the CD4 count response by study arms. Monotherapy arms showed a lower efficacy, according to non-inferiority definition, in both Kalesolo and MONET study. The risk of developing primary mutations at failure was similar between arms and trials, as was the extent of immune response. Additional data on the follow up are described below.

Long term data for monotherapy arms

In Kalesolo study, 60/87 (69%) patients were still on LOP/r monotherpy with suppressed viral load (below

Table 1: Multicenter randomized trials for PI monotherapy versus triple therapy: study design and entry criteria.

Study* ***(Patients)*** Country	**Study design** (protease inhibitor)	**HIV RNA and CD4 count** at study entry **§**	**nadir CD4 count§**	**Years on HAART** (median)	**Follow up**
KALESOLO *(87 vs 99)* France	non-inferiority lower limit: -12% (LOPV/r BID)	< 50 (for 95%)^ 494 (371-630) *vs* 525 (357-688)	Not reported	7 vs 8	48 weeks
OK04 *(100 vs 98)* Spain	non-inferiority lower limit: -12% (LOP/r BID)	< 50 474 (340-660) *vs* 473 (307-673)	107 (28-216) *vs* 103 (32-214)	1.6 ***vs*** 1.5	96 weeks
MONOI *(112 vs 113)* France	non-inferiority lower limit: -10% (DRV/r **)	*< 50 585 (457-757) vs 582 (390-780)*	223 (150-320 *vs* 212 (147-283)	8.7 ***vs*** 7.8	96 weeks
MONET *(127 vs 126)* Europe	non-inferiority lower limit: -12% (DRV/r OD)	< 50 (for 95%) 571 (162-1451) *vs* 579 (163-1888)	with nadir < 200 cells/ml 39% vs 37%	7.4 ***vs*** 6.4	144 weeks

*All data are mono vs triple arm. Data are medians (IQR); BID: bis in die; ^ 5 patients with detectable HIV RNA (all with < 250 copies/ml.)
** first 48 weeks DRV= 600mg bid, then 800 mg od in both arms; § for HIV RNA: copies/ml, for CD4 count: medians (IQR) unless differently specified;

50 copies/ml) at week 96. (13)
The OK pilot study confirmed that 14/21 (67%) patients had HIV RNA <50 copies/ml with LOP/r monotherapy after 4 years (17). Similarly, the OK04 study showed that 71/100 (71%) patients were still treated effectively with LOP/r monotherapy at week 144 (ITT, M=F, Reinduction=F analysis) (18,)
Findings from MONOI study demonstrated that 91/103 (88%, ITT analysis) of patients enrolled in DRV/r monotherapy were still on the same arm with viral load < 50 copies/ml at week 96 (15). Similarly, in MONET study, DRV/r monotherapy was still effective in 88/127 (69%, ITT, TLOVR, S=F analysis) patients at week 144 (16)

Risk factors for failure in randomized trials

In virological terms, a failure is defined as loss in HIV RNA control (i.e. confirmed elevation in HIV RNA above 50 copies/ml). However, in clinical practice and in trials, a confirmed slight elevations in HIV RNA (i.e. 67 and 88 copies/ml, in two consecutive determinations) may not lead to any change in HIV regimen (16). If the following tests are persistently below 50 copies/ml, a "failing regimen" (according to study definition) would turn into a clinical success in the long term. All that is relevant for understanding the clinical meaning of "virological failure" as assessed in trials.
In multivariate analysis for the risk factors for failure in monotherapy, data show that:

- In KALESOLO study (13), only older age at baseline was associated with failure (but nadir CD4 count was not included in the model).
- In OK + OK04 studies (19) virological failure occurred in 15 out of 121 patients treated with monotherapy arms at week 48. Having more than 2 visits with missed doses reported (OR: 6.30, 95%CI: 2.00-19.6, p=0.002), a lower nadir CD4 count (OR: 4.1, 95%CI: 1.3-13.5, p=0.02) and lower haemoglobin levels (OR: 0.68, 95%CI: 0.5-0.92, p=0.013) were risk factors for failure.
- In MONOI study (20), multivariate analysis showed that a lower adherence to therapy (OR: 3.84, 95%CI: 1.29-12.49, p=0.02), lower duration of HAART (OR: 2.93, 95%CI: 1.43-6.66, p=0.006) and higher HIV DNA levels at study entry (OR: 2.66, 95%CI:1.11-7.48, p=0.04) were associated to HIV RNA elevations at week 96.
- In MONET study (21), only HCV coinfection was associated to failure in multivariate analysis at week 96 (OR: 4.35, 95%CI: 2.06 to 9.17, p<0.0001). HCV coinfected patients accounted for 12% and 19% in triple and monotherapy arm, respectively. However, the *post hoc* analysis in OK04 study (approximately 47% of patients were HIV/HCV coinfected, with well-balanced distribution between study arms) didn't show any effect of HCV coinfection on the rate of virological response by randomized group and at different analysis (22). Of note, also in an observational cohort (23) including 92 patients on DRV/r monotherapy (23.9% HCV coinfected), multivariate analysis didn't show any effect of HCV coinfection on the risk of failure at week 48.

Primary mutations, intermittent viremia and HIV-1 DNA evolution on boosted PI monotherapy

In clinical terms, the cost of failure of a given regimen is estimated on the rate of primary mutations leading to loss of treatment options. As confirmed by randomized trials (table 2), patients on monotherapy do not experience a higher rate of primary PI resistance mutations (13-16). Also for minor mutations or mutations in the gag gene, data do not support a higher risk for patients on boosted PI monotherapy arms (24,20). More importantly, the reintroduction of the NRTI backbone can re-suppress the viral load in most of the subjects (apart from the non-adherent patients).
However, all the 4 major trials (13-16) do confirm that patients on PI-monotherapy experience a higher rate of intermittent viremia (i.e. not confirmed HIV RNA >50 copies/ml) compared to triple regimens, suggesting that combination treatment is more potent and/or more forgiving than monotherapy. For instance, in MONOI trial, 59% (66/112) vs 70% (79/113) patients had HIV RNA consistently below 50 copies/ml over week 96 (p=0.10) (20). In this trial, 18.8% versus 8% of patients had 3 or more HIV RNA blips in the mono- versus triple arm, respectively (25).
Viral blips may be worrisome if they are linked with a higher risk of resistance mutations over time, or whether they may affect the CD4 count recovery or grade of immune activation. So far, data do not support a detrimental impact on the above-mentioned parameters for PI monotherapies. In particular, data from MONET and MONOI studies confirm that the more frequent "intermittent viremia" occurring in monotherapy arms does not cause a different HIV DNA evolution, a marker of the size of cellular HIV reservoir (25,26).

Single-drug regimen and "low level" viremia

As described above, the rate of patients who have HIV RNA below 50 copies/ml consistently over time is lower for monotherapy regimens compared to triple arms (13-16). Nonetheless, a boosted PI alone is able to maintain, for a long term, a "high level" (below 1 or 5 copies/ml) of viral suppression in patients fully suppressed by a long-term triple therapy. Table 3 shows the rate of patients with HIV RNA below 1 or below 5 copies/ml at study entry and later, by trials and randomized groups (15,27). In particular, in MONET trial (27) approximately 80% of patients with HIV < 50 copies/ml do maintain HIV RNA below 5 copies/ml in both mono and triple arm at week 96 (observed data), confirming the possible and persistent "high level" HIV control by a single drug.

Sanctuary sites and monotherapy

The potential insufficient drug penetration and viral control into some compartments (i.e. genital tract and cerebral tissue) by some regimens is still an open issue (28). The risk of discordant plasma/CSF viral replication has been documented in both triple (29) and monotherapy studies (30-33). In particular, in 5 patients in two monotherapy arms, CSF HIV RNA elevations were also associated with CNS symptoms (30,31).
This issue of CSF HIV control is currently under investigation by two ongoing trials:

- one large long-term cohort study in the UK. Patients were randomized to triple and monotherapy (Protease Inhibitor Monotherapy Versus Ongoing Triple-therapy in the Long Term Management of HIV Infection (PIVOT trial, 34), with a neurological substudy, investigating the rate of CSF HIV

Table 2: PI monotherapy versus triple arms in all 4 studies: efficacy results, emergence of mutations at failure, efficacy at re-intensification and immune response by study arms.

Study *(Patients)*	**HIV RNA < 50 copies#** Proportions, *(difference, CI)*	**Patients with primary PI mutations**	**Efficacy at re-intensification** % (N)	**Mean CD4 count increase** cells/mmc
KALESOLO *(87 vs 99)*	84 *vs* 88 (-4.0; 90% CI: -12.4 to 4.5) *ITT analysis ,M/C=F, 48 weeks*	1 *vs* 0*	100 (6/6)	+98 *vs* +79°
OK04 *(100 vs 98)*	77 *vs* 77.6 p value = 0.86 *ITT, M/R=F analysis , 96 weeks*	2 *vs* 2	83 (10/12)	+71 *vs* +41°
MONOI *(112 vs 113)*	88 *vs* 84 p value = 0.42 *ITT, M=ignored analysis , 96 weeks*	1 *vs* 0 §	100 (5/5)	+70 *vs* +39°
MONET *(127 vs 126)*	72 *vs* 78 (-5.6%; 95%CI: -16.5 to +5.4) *PP analysis, S=F, 144 weeks*	1 *vs* 1 **	85 (6/7)	+95 *vs* +99

All data are monotherapy versus triple arm. CI: confidence interval. S: switch, M: missing, C: change, R: reinduction, F: failure. # for primary analysis; * 1 key mutation for indinavir only; ° not statistically significant; § mutation V11I, already documented 7 years before in a stored sample; ** one patient with M184V mutation.

Table 3: HIV RNA suppression at baseline and during follow up, by trials and study arms (observed data analysis). HIV RNA cut off are different between trials.

	MONOI study (ref. 20) *Proportion with HIV RNA < 1 copies/ml*		**MONET study** (ref. 27) *Proportion with HIV RNA <5 copies/ml*	
	study entry % (patients)	week 48 % (patients)	study entry % (patients)	week 96 % (patients)
Monotherapy arm	50.5 (112)*	63 (96)	80.3 (127)	80.4 (102)
Triple arm	40.7 (113)*	66 (101)	79.1 (129)	83.3 (108)

* differences not statistically significant; § *data on file Janseen*

replication in both arms (560 patients, 4-5 years of follow up).

- a multinational and European trial (PROTEA study), enrolling patients switching to DRV/r monotherapy (260 patients, 2 years of follow up), with a subgroup undergoing lumbar puncture for CNS substudy (35).

Drug toxicity in monotherapy arms

The OK04 (14), MONET (16) and an observational study (23) reported a greater rates of dyslipidaemia in monotherapy subjects compared to patients on triple arm, despite demonstrating overall improvements in tolerability. A higher rate of discontinuation due to adverse events was reported in triple regimens (12). For lypodistrophy, whose effect is largely dependent on the type of NRTI backbone included in the triple arm, data from MONET trial do not confirm any benefit at week 96 (36). In this respect, the possible NRTIs optimization at time of study entry may have blunted the effect from switching.

PI monotherapy in the real world

Data from observational cohorts have been recently reported on the use of PI monotherapy in HIV patients, with results matching the ones from trials and confirming the clinical interest in the real world. In particular, Guiguet et al. (36) reported on 529 patients, enrolled between 2006-2010 in France, who were treated with PI monotherapy. A total of 59%, 28% and 13% were on LOP/r, DRV/r and ATV/r monotherapy, respectively. Approximately 75% had at least 12 and 49% at least 24 months of follow up. Median nadir and baseline CD4 count was 190 (Q5-Q95:13-443) and 541 (Q5-Q95: 210-116) cells/ml, respectively. Median HAART duration was 7 years. A total of 9% of the enrolled patients had a history of failure on a PI regimen. During follow up, two-thirds of the individuals had HIV RNA always below 50 copies/ml. Overall, the rate of virological failure (confirmed HIV RNA > 50 copies/ml or single HIV RNA > 50 copies followed by PI monotherapy discontinuation) was 21% (95%CI: 17-25) and 31% (95%CI: 27-37) at 12 and 24 months, respectively. In multivariate analysis, the risk of failure was higher for patients with history of AIDS, shorter duration of previous HAART, with previous failure on a PI-based regimen and for those on ATV/r monotherapy (HR:1.9, 95%CI: 1.1-3.3). Out of 73 (14%) failing patients, 35 (48%) had a genotyping test (21, 11 and 3 of them were on LOP/r, DRV/r and ATV/r, respectively) and key mutations were detected only in 4 patients, all on LOP/r monotherapy.
Santos et al. (23) reported on a retrospective cohort including 92 patients on DRV/r monotherapy for a median follow up of 73 (IQR 57-92) weeks. Median baseline and nadir CD4 count were 604 (IQR 433-837) and 238 (IQR 150-376) cells/mmc, respectively. The risk of virological failure at week 48 was assessed. Nine (9.8%) of patients had virological failure (confirmed HIV RNA > 50 copies/ml). A total of 77/92 (83.7%) maintained virological suppression at week 48. Genotyping data were available in 3/9 patients at failure, none showing DRV associated resistance mutations. Multivariate analysis didn't show any factors associated with risk of failure. Viral re-suppression was achieved in all cases with NRTIs reintroduction (6 patients) or HAART change (2 subjects) or intensified adherence (1 patient).
Cossarini et al. (37) reported on a retrospective cohort including 43 patients on ATV/r (30 subjects) or ATV 400 mg OD (13 subjects) and with a median follow up 10 (IQR 5.4 - 23.4) months. Nadir CD4 count was 312 (IQR 251- 510) cells/mmc and median time on HAART was 9.1 (IQR 6.9 -18.8) years. Some of these patients might have had a failure on previous PI regimens. Virological failure (confirmed HIV RNA >50 copies/ml) during follow up occurred in 3 patients (2 on unboosted ATV).
Neth et al. (38) reported on clinical experience in 5 aviremic children switched to LOP/r or ATV/r monotherapy with successful virological control after a mean of 20.9 months.

Guidelines recommendations for PI-monotherapy

International guidelines differ with respect to the recommendations for monotherapy option in maintenance strategy for HIV infected patients. Some guidelines do not support this strategy outside clinical trials as this option is considered to be not "non-inferior" to standard triple therapy (USA, 1,2) or data are considered insufficient to recommend its use in virologically suppressed patients (British, 39). European (3) and Italian guidelines (40) support its use as an alternative option in a selected population, namely for patients who are virologically suppressed (with PI- or NNRTI-based regimen), without a history of PI failure and able to tolerate a low-dose RTV (or for whom RTV-related drug interactions is not an issue). All that, provided that:

1. there is no need of NRTIs within the regimen (HIV-related encephalopathy? HBV coinfection?)
2. nadir CD4+ count > 100 cells/mm^{3}or baseline HIV-1 RNA <10^5 copies/mL
3. in patients with optimal adherence
4. in patients with long history for suppression

Data from randomized trials (table 1) show that median duration of successful HAART was relatively long (6-8 years for most of them), despite entry criteria for these study were less stringent. This suggest that clinicians were more confident in selecting patients with a long history of viral suppression. The analysis of predictors of failure in MONOI study (15) show that patients with longer duration of viral control are more likely to maintain suppression with PI monotherapy.

Conclusion

1. Data from clinical trials confirm that, in general, triple regimens are more potent and/or more forgiving, in both antiviral naïve and experienced patients.
2. De-intensification to a single-drug regimen, as a maintenance strategy, is a feasible option in a selected population. In fact, a large proportion of patients (approximately 69-75%) were successfully treated with PI monotherapy for a relatively long term (up to week 144) in clinical trials.
3. NRTIs reintroduction is effective for HIV RNA re-suppression in almost all patients failing monotherapy.
4. The risk of emergence of primary mutations at failure and the CD4 count increase are similar for patients in mono- *versus* triple therapy.
5. Not all PIs are the same and not all showed a similar efficacy in monotherapy strategy.
6. Not all patients responding to current triple regimens do qualify for de-intensification, even if their plasma viral load has been persistently undetectable for years.
7. The issue of HIV RNA control into sanctuaries is currently under investigation.

References

1. DHHS guidelines 2012. Available at: http://www.aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7. Accessed Nov 2012.
2. Antiretroviral Treatment of Adult HIV Infection 2012 Recommendations of the International Antiviral Society. USA Panel. JAMA 2012;308:387-402. Available at: https://www.iasusa.org/guidelines .
3. EACS Guidelines October 2011. Available at: http://www.europeanaidsclinicalsociety.org/index.php?option=com_content&view=article&id=59:eacs-guidelines&catid=37:guidelines&Itemid=41 . Accessed Nov 2012.
4. Gazzard B, Moecklinghoff C, Hill A. New strategies for lowering the costs of antiretroviral treatment and care for people with HIV/AIDS in the United Kingdom. Clinicoecon Outcomes Res. 2012;4:193-200.
5. Gazzard B, Hill A, Anceau A. Cost-efficacy analysis of the MONET trial using UK antiretroviral drug prices. Appl Health Econ Health Policy. 2011;9:217-23
6. Pasquau J, Gostkorzewicz J, Ledesma F, Anceau A, Hill A, Moecklinghoff C. Budget impact analysis of switching to darunavir/ritonavir monotherapy for HIV-infected people in Spain. Appl Health Econ Health Policy. 2012;10:139-41.
7. Pialoux G, Raffi F, Brun-Vezinet F, et al. A randomized trial of three maintenance regimens given after three months of induction therapy with zidovudine, lamivudine, and indinavir in previously untreated HIV-1-infected patients. N Engl J Med. 1998;339:1269-76.
8. Flandre P, Raffi F, Descamps D, Calvez V, Peytavin G, Meiffredy V, Harel M, Hazebrouck S, Pialoux G, Aboulker JP, Brun Vezinet F. Final analysis of the Trilège induction-maintenance trial: results at 18 months. AIDS. 2002 Mar 8;16:561-8.
9. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med. 2008;358:2095-106
10. Delfraissy JF, Flandre P, Delaugerre C, et al. Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naive HIV-infected patients. AIDS. 2008;22:385–93.
11. Bierman WF, van Agtmael MA, Nijhuis M, Danner SA, Boucher CA. HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. AIDS. 2009;23:279–91.
12. Mathis S, Khanlari B, Pulido F, et al. Effectiveness of protease inhibitor monotherapy versus combination antiretroviral maintenance therapy: a meta-analysis. PLoS ONE 2011;6(7):e22003.
13. Meynard JL, Bouteloup V, Landman R, et al. Lopinavir/ritonavir monotherapy versus current treatment

continuation for maintenance therapy of HIV-1 infection: the KALESOLO trial. J Antimicrob Chemother. 2010;65:2436-44.

14. Arribas JR, Delgado R, Arranz A, et al. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis. J Acquir Immune Defic Syndr. 2009;51:147-52.
15. Valantin MA, Lambert-Niclot S, Flandre P et al. Long-term efficacy of darunavir/ritonavir monotherapy in patients with HIV-1 viral suppression: week 96 results from the MONOI ANRS 136 study. J Antimicrob Chemother. 2012;67:691-5.
16. Arribas JR, Clumeck N, Nelson M, Hill A, van Delft Y, Moecklinghoff C. The MONET trial: week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load < 50 HIV-1 RNA copies/mL at baseline. HIV Med. 2012;13:398-405.
17. Pulido F, Delgado R, Pérez-Valero I, et al. Long-term (4 years) efficacy of lopinavir/ritonavir monotherapy for maintenance of HIV suppression. J Antimicrob Chemother. 2008;61:1359-61.
18. Pulido F, Delgado R, Arranz A, et al. Three-year Efficacy of Lopinavir/ritonavir Monotherapy in the OK04 Trial. ICAAC 2009; Poster H 1240
19. Pulido F, Pérez-Valero I, Delgado R, et al. Risk factors for loss of virological suppression in patients receiving lopinavir/ritonavir monotherapy for maintenance of HIV suppression. Antivir Ther. 2009;14:195-201.
20. Lambert-Niclot S, Flandre P, Valantin MA, et al. Factors associated with virological failure in HIV-1-infected patients receiving darunavir/ritonavir monotherapy. J Infect Dis. 2011;204:1211-6.
21. Rieger A, Banhegyi D, Schmidt W, et al. The MONET trial 96 week analysis: darunavir/ritonavir monotherapy versus DRV/r + 2NRTIs, for patients with HIV RNA < 50 copies/mL at baseline. XVIII International AIDS Conference (AIDS 2010). Vienna, July 18-23, 2010. Abstract THLBB209.
22. Pulido F, Arribas J and OK04 study group. No effect of HCV infection on virological response 96 weeks after simplification to lopinavir/ritonavir monotherapy in OK04 trial. IAS Conference 2011. Abs MOPE217
23. Santos JR, Moltó J, Llibre JM, et al. Antiretroviral simplification with darunavir/ritonavir monotherapy in routine clinical practice: safety, effectiveness, and impact on lipid profile. PLoS One. 2012;7:e37442.
24. Lambert-Niclot S, Flandre P, Valantin MA, et al. Resistant minority species are rarely observed in patients on darunavir/ritonavir monotherapy. J Antimicrob Chemother. 2012;67:1470-4.
25. Ghosn J, Delaugerre C, Flandre P, et al. Polymorphism in Gag gene cleavage sites of HIV-1 non-B subtype and virological outcome of a first-line lopinavir/ritonavir single drug regimen. PLoS One. 2011;6:e24798.
26. Ripamonti D, Arribas J, Antinori A, et al. No evidence for evolution of genotypic resistance and no changes in cellular HIV DNA levels after three years of treatment with darunavir/ritonavir, with or without nucleoside analogues: final Week 144 analysis of the MONET trial. ICAR 2012, OC67
27. Clumeck N, Arribas JR, Pulick P, et al. Low-level viraemia during treatment with darunavir/r monotherapy versus DRV/r + 2NRTIs in the MONET trial. J Int AIDS Soc. 2010;13(Suppl 4): O19.
28. Eisfeld C, Reichelt D, Evers S, Husstedt I. CSF Penetration by Antiretroviral Drugs. CNS Drugs. 2012 Nov 17.
29. Canestri A, Lescure FX, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. Clin Infect Dis. 2010;50:773-8.
30. Gutmann C, Cusini A, Günthard HF, et al. Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir. AIDS. 2010;24:2347–54.
31. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. AIDS. 2010;24:2365-74.
32. Pasquet A, Ajana F, Melliez H, Giurca C, Poissy J, Yazdanpanah Y. Central nervous system HIV replication and HIV-related pachymeningitis in a patient on protease inhibitor monotherapy despite an undetectable plasma viral load. AIDS. 2012;26:1726-8.
33. Gisslén M, Fuchs D, Hagberg L, Svennerholm B, Zetterberg H. Cerebrospinal fluid viral breakthrough in two HIV-infected subjects on darunavir/ritonavir monotherapy. Scand J Infect Dis. 2012 Jul 9.
34. PIVOT trial, available at: http://clinicaltrials.gov, identifier NCT01230580
35. PROTEA study, available at: http://clinicaltrials.gov/ct2/show/NCT01448707
36. Guiguet M, Ghosn J, Duvivier C, et al. Boosted protease inhibitor monotherapy as a maintenance strategy: an observational study in the FHDH-ANRS CO4 cohort. AIDS 2012;26:2345-2350
37. Cossarini F, Salpietro S, Galli L, et al. Monotherapy with atazanavir as a simplification strategy: results from an observational study. J Acquir Immune Defic Syndr. 2012;60:e101-3.
38. Neth O, Falcon-Neyra L, Ruiz-Valderas R, et al. Simplified human immunodeficiency virus maintenance therapy in virologically suppressed children with Ritonavir-boosted protease inhibitor monotherapy. Pediatr Infect Dis J. 2011;30:917.
39. BHIVA guidelines, available at: http://www.bhiva.org/documents/Guidelines/Treatment/2012/120430TreatmentGuidelines.pdf
40. HIV Italian guidelines, available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1793_allegato.pdf