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 naive and antiretroviral 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 monotherapy with suppressed viral load (below 50 copies/ml) at follow up week 96.
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).

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**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 monotherapy arm (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 (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 monotherapy arm (25).

**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>
<thead>
<tr>
<th>Study (Patients)</th>
<th>HIV RNA &lt; 50 copies#</th>
<th>Patients with primary PI mutations</th>
<th>Efficacy at re-intensification % (N)</th>
<th>Mean CD4 count increase cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>KALESOLO (87 vs 99)</td>
<td>84 vs 88 (4.0; 90% CI: -12.4 to 4.5)</td>
<td>1 vs 0*</td>
<td>100 (6/6)</td>
<td>+98 vs +79*</td>
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<tr>
<td>OK0 (109 vs 98)</td>
<td>77 vs 77.6</td>
<td>2 vs 2</td>
<td>83 (10/12)</td>
<td>+71 vs +41*</td>
</tr>
<tr>
<td>MONOI (112 vs 113)</td>
<td>88 vs 84</td>
<td>1 vs 0 §</td>
<td>100 (5/5)</td>
<td>+70 vs +39*</td>
</tr>
<tr>
<td>MONET (127 vs 126)</td>
<td>72 vs 78 (-5.6%; 95%CI: -16.5 to +5.4)</td>
<td>1 vs 1 **</td>
<td>85 (6/7)</td>
<td>+95 vs +99</td>
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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.

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.

<table>
<thead>
<tr>
<th>MONOI study (ref. 20)</th>
<th>MONET study (ref. 27)</th>
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<tr>
<td>Proportion with HIV RNA &lt; 1 copies/ml</td>
<td>Proportion with HIV RNA &lt; 5 copies/ml</td>
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<tr>
<td>study entry % (patients)</td>
<td>week 48 % (patients)</td>
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<tr>
<td>Monotherapy arm</td>
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<tr>
<td>Triple arm</td>
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* differences not statistically significant; § data on file Janssen
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 time on 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 between 2006-2010 in France, who were treated with PI monotherapy (260 patients, 2 years of follow up), with replication in both arms (560 patients, 4-5 years of follow up).

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/mm3 or baseline HIV-1 RNA < 105 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 naive 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

35. PROTEA study, available at: http://clinicaltrials.gov/ct2/show/NCT01448707