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Running title: Residual viremia: a virological marker

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Summary:

Protease inhibitor (PI) monotherapy is a potential approach to alleviate antiretroviral treatment. We pooled the results of three PI/r monotherapy trials and demonstrate that ultrasensitive viral load is a useful virological marker to select the best candidates for PI/r monotherapy.

Abstract

Background: We pooled the results of three randomized trials that compared the efficacy of PI/r monotherapy and standard triple therapy as maintenance therapy and evaluated: 1) the distribution of ultrasensitive viral load (USVL) at week 96 (W96), 2) factors associated with virological success (VL<50 copy/mL) at W96, and 3) factors associated with USVL<1 copy/ml (c/ml) at W96.

 Methods: Virological failure was defined as two consecutive measurements of HIV-1 RNA viral load >50 copies/mL and was analyzed in intention-to-treat. USVL was measured with commercial standard Roche assay. A logistic model was used to investigate which variables were predictive of VF. The Fisher exact test was used to investigate differences in USVL at W96

Results: Among 609 patients, 73% were male with a median age of 44.4 years (IQR 39.8-52.1), the treatment duration was four years, (2.4-7.6), baseline CD4/CD8 ratio 0.8 (0.6-1.10), baseline CD4 cell count 564/mm3 (422-707), and 59% presented a baseline USVL<1 copy/mL. At W96, the proportion of USVL<1 copy/mL was significantly lower for PI/r monotherapy than triple therapy (65% versus 74%; p=0.04). Overall, baseline USVL<1 copy/mL, triple therapy, and being female were associated with an USVL<1 copy/mL at W96 (p<0.0001, p=0.049 and p=0.006). For PI/r monotherapy, receiving DRV/r rather than LPV/r was associated with an USVL<1

copy/mL at W96 (p=0.03). Factors associated with virological success at W96 were higher baseline CD4 cell count (p=0.034) and baseline USVL<1 copy/mL (p=0.0005).

Conclusion: Although PI/r monotherapy is not widely recommended, this strategy is still sometimes used and USVL determination for virologically-controlled patients may help to select the best candidates for PI/r monotherapy.

Introduction

International guidelines for initial therapy recommend a three-antiretroviral regimen with drugs from at least two classes[1–4]. Treatment optimization and simplification are recommended by French guidelines in cases of virological success, under certain conditions[5]. Protease inhibitor monotherapy is a potential switch strategy to standard combination antiretroviral therapy (cART) in cases of drug toxicity or to avoid it. Indeed, extended use of triple therapy is associated with adverse events, such as renal and cardiovascular toxicities, drug-drug interactions, long-term adherence problems, and a long-term risk of selection of HIV-1 drug resistance [6–8].

A recent review of PI/r monotherapy trials concluded than PI/r monotherapy is associated with a higher risk of elevated plasma HIV-1 RNA levels than triple therapy[8], but it also showed re-suppression of HIV-1 RNA after intensification with

NRTIs. Thus, the switch-included analysis showed the efficacy of PI/r monotherapy to be comparable to that of triple therapy [8]. The largest study conducted on PI/r-MT (PIVOT) showed that this strategy, with regular viral load monitoring and prompt reintroduction of combination treatment in case of virological rebound, preserved future treatment options and did not change overall clinical outcomes or the frequency of toxic effects[9].

The maintenance of virological efficacy is not the only concern surrounding the use of PI/r monotherapy. Indeed, the long-term consequences of persistent residual viremia are yet to be determined and may include not only virological rebound, but also the emergence of resistance mutations and the persistence of immune activation and inflammation. Two clinical trials have shown that ultrasensitive viral load (USVL) (> 1 copy/mL) was individually associated with virological failure in the PI/r monotherapy arm[10,11]. Thus, it is necessary to refine selection criteria to choose the best candidates for PI/r monotherapy.

We combined data from three randomized trials (Kalesolo IMEA 030, Dream ANRS 140, and Monoi ANRS 136) and performed a pooled analysis. Our objective was to determine: 1) the distribution of ultrasensitive viral load (USVL) at week 96 (W96), 2) the virological and clinical characteristics associated with virological failure (VF) at W96, and 3) the factors associated with an USVL < 1 copy/ml at W96 in a large population receiving either PI/r monotherapy or standard triple therapy. These data

may be useful for the evaluation of USVL as a virological marker to choose treatment strategies.

Methods

Study design

The study was composed of three randomized clinical trials that evaluated the efficacy of PI/r monotherapy *vs* standard triple therapy: Monoi, Dream, and Kalesolo [10–12] (Table 1). The protocols were approved individually by an ethics committee (Comité de Protection des Personnes Ile de france V, Paris, France) and the appropriate French health authority (Agence Nationale de Sécurité du Medicament et Produits de Santé). All participants gave their written informed consent. The trials were conducted in accordance with the Declaration of Helsinki. Trial Registration: clinicaltrials.gov Identifier for Monoi: NCT00421551, Dream: NCT00946595, Kalesolo: NCT00140751.

Virological methods

Plasma HIV-1 RNA was quantified using the Cobas AmpliPrep/CobasTaqMan HIV-1 assay version 2.0 (Roche Diagnostics; lower detection limit of 20 copies/mL). Below this cutoff, the assay indicates the qualitative detection of pHIV-1 RNA in the range of 1 to 20 copies/mL. Residual viremia was measured at baseline and W96: USVL was between 1 and 20 copies/mL when a signal was detected and below 1 copy/mL when there was no detected signal. The measure of USVL was centralized for each trial.

Statistical Analysis

VF was defined as two consecutive measurements of HIV-1 RNA viral load > 50 copies/mL and analyzed in intention-to-treat. Patient characteristics are presented as medians and the interquartile range for continuous variables and percentages for categorical variables. We investigated age, time since HIV diagnosis (year), ART duration (years), CD4 and CD8 cell counts at baseline, sex, transmission group, assigned ARV treatment group, CD4/CD8 ratio, and US VL at baseline as potential risk factors for VF and USVL > 1 copy/ml at W96 using regression logistic models. A series of univariate models were fitted to the data and all variables providing $p < 0.20$ were retained to be potentially included in the final multivariate models. Final models were selected using a stepwise procedure keeping variables with a $p < 0.05$. Fisher's exact test was used to investigate differences in USVL at W96.

Results

Patient characteristics

We analyzed data on a total of 609 patients at baseline (D0) and W96 (225 from the Monoi trial, 197 from the Dream trial, and 187 from the Kalesolo trial). Only patients with an available measurement of USVL at baseline and W96 were considered for analysis. Patient characteristics are described in Table 2, overall and by trial. Among the 609 patients, 73% were male with a median age of 44.4 years (IQR 39.8-52.1), the

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duration of ARV treatment was five years, (IQR 2.8-9.9), the baseline CD4/CD8 ratio

0.8 (IQR 0.6-1.10), the baseline CD4 cell count 564/mm^3 (IQR 422-707), and 59% had a

baseline USVL <1 copy/mL (table 3). There were no significant differences in the

baseline patient characteristics between the trials.

Efficacy according to USVL

The distribution of USVL is shown in table 3. At baseline, the proportion of USVL< 1

copy/mL was similar in each trial (58%, 59% and 60% in Monoi, Dream and kalesolo

respectively). Morever in each trial, the proportion the proportion of USVL< 1

copy/mL was similar between PI/r monotherapy arm and tritherapy arm. At W96,

the proportion of USVL < 1 copy/mL was significantly lower for PI/r monotherapy

than standard triple therapy in the pooled-analysis (65% *vs* 74%; p = 0.04). We also

found this significant difference individually in the Dream and Kalesolo trials but not

the Monoi trial. There was no difference in the USVL distribution between NNRTI or

PI-based triple therapy. Moreover, there was a significant difference at W96 when we

compared the distribution of USVL in monotherapy strategies between LPV/r and

DRV/r (57% *vs* 76%, respectively, p = 0.0014).

Factors associated with virological success at W96 (VL<50 copies/mL)

We studied factors associated with treatment strategy failure by univariate and

multivariate analyses (Table 4). Overall, factors associated with virological success at

W96 were higher baseline CD4 cell counts (p = 0.034) and baseline USVL < 1 copy/mL

(p = 0.0005) by multivariate analysis. Moreover, baseline USVL < 1 copy/mL was also associated with virological success at W96 for patients receiving triple therapy (p = 0.002).

Factors associated with a USVL < 1 copy/mL at W96

Overall, baseline USVL < 1 copy/mL, triple therapy regimen, and being female were associated with an USVL < 1 copy/mL at W96 (p < 0.0001, p = 0.049, and p = 0.006, respectively) (Table 5). Among patients receiving PI/r monotherapy, DRV/r, rather than LPV/r, was associated with an USVL < 1 copy/mL at W96 (p = 0.03). Among patients receiving DRV/r monotherapy, 84% with an USVL < 1 copy/mL at baseline retained an USVL < 1 copy/mL at W96 compared with 65% for patients receiving LPV/r monotherapy (p=0.02). Among patients with detectable baseline USVL (USVL ≥ 1 copy/mL), 47% still had a detectable USVL at W96 in the DRV/r monotherapy group *vs* 53% for the LPV/r monotherapy group but this difference is not statistically significant (Figure 1).

Discussion:

This is the first analysis of USVL in three pooled PI/r monotherapy trials of treated and controlled patients. This retrospective study compared the efficacy of PI/r monotherapy *vs* triple therapy, as well as the efficacy of DRV/r monotherapy *vs* LPV/r monotherapy and PI-based triple therapy *vs* NNRTI-based triple therapy. This study confirmed the superior efficacy of triple therapy for virological success (failure

was defined as two consecutive VL > 50 copies/mL). These results are consistent with those of all PI/r monotherapy clinical trials. PI/r monotherapy was associated with a higher risk of low level HIV-1 RNA viral load than triple therapy in a meta-analysis of 13 randomized clinical trials with 2,303 virologically-suppressed patients at baseline [8]. Moreover, the sub-Saharan Africa Mobidip trial showed similar results in a different context: a dual–therapy maintenance strategy with boosted PI and lamivudine showing superiority to boosted PI monotherapy alone for the prevention of VF[13]. Multiple studies have identified a number of factors associated with failure of PI/r-MT, including nadir and baseline CD4 cell counts, proviral HIV DNA, duration of viral suppression, previous failure of ART, HCV co-infection, PI/r in the baseline cART, residual viremia levels at the time of switch, hemoglobin levels, age, VL at cART initiation, gender, and mode of HIV transmission[14–22].

Our study focused on USVL or residual viremia. Indeed, reduction of HIV-1 RNA levels to less than 50 copies/ml is frequently achieved during combination antiretroviral therapy. However, residual low-level viremia has been detected under the detection threshold of assays in 33 to 80% of cases [23–28]. Notably, this persistent viremia may be present several years into therapy [24]. Two theories may explain RV in patients on HAART [29]. In the first, RV may represent ongoing cycles of replication that continue at a low level because of the non-suppressive effects of the drugs. In the second, HAART stops all ongoing cycles of replication, and RV reflects the release of virus from stable reservoirs, such as the latent reservoir in

resting CD4 T cells. The long-term consequences of persistent low-level viremia are not known, although there is growing interest in the chronic inflammatory component of HIV infection which can be observed among those who have residual viraemia [30,31] . In our study USVL was measured with commercial standard Roche assay and limit of this measure was a lack of reproducibility of molecular assays as such low-levels of replication combining in vitro assays variations and in vivo infection dynamics .

Our results on the USVL are in accordance with the better efficacy of triple therapy, which was previously shown in the Monark study in cART-naïve patients[32]. Indeed, residual viral replication was more frequent with LPV/r monotherapy (32%) than triple therapy (18%) at week 60, despite a limited number of patients.

DRV/r is an appropriate candidate for PI/r monotherapy due to its high genetic barrier[33], high potency in wildtype and resistant HIV strains, and good pharmacokinetic profile[34]. DRV/r potency was efficient not only on virological response, but also on residual viremia. Other studies on maintenance strategies have demonstrated a varying impact on residual viremia depending on the ARV used. Among treated patients exhibiting virological success, an NNRTI-containing regimen, specifically NVP, better controlled residual viremia than other combination regimens[25,28,35]. The USVL at W96 in our study suggests that LPV/r may be less potent than DRV/r. Indeed, DRV/r has been shown to be more efficient than LPV/r, even in triple therapy strategies, such as those in trials comparing DRV/r to LPV/r,

either with a TDF/FTC backbone in cART-naïve patients[36] or in patients already receiving an NRTI or NNRTI backbone[37]. In cART-naïve patients, the Artemis study demonstrated that virological response to once-daily DRV/r was both statistically non-inferior and superior to the virolgical response to LPV/r at week 96. In already treated patients, the Titan study showed that VF (HIV-1 RNA > 400 copies/mL) with DRV/r (13.8%) was nearly half that with LPV/r (25.6%). Thus, the non-inferiority of DRV/r over LPV/r was maintained at 96 weeks and the difference in response was statistically significant[36].

In this large study, a detectable baseline residual viremia and lower baseline CD4 cell count were associated with VF at W96. Few studies have not highlighted the association between low level viremia or very low level viremia and VF but the threshold was not as low as in our study (<1copy/mL)[23,38–40] .Our results are in accordance with many studies that have shown an increased risk of VF in patients with detectable residual viremia [26,27,35,41–43]. A more recent study on 1,055 patients with two years of follow-up demonstrated a 50% lower risk of VF for patients carrying an USVL < 1 copy/mL than those with an USVL between 1 and 20 copies/mL and between 20 and 50 copies/mL[44]. In the Monet trial, patients with baseline HIV RNA < 5 copies/mL showed the highest rates of sustained HIV RNA suppression < 50 copies/mL on DRV/r monotherapy[21]. We can regret not to have the duration of viral suppression before randomization, indeed it would have been interesting to assess a link with USVL.

In conclusion, baseline USVL appears to be a useful virological marker to predict residual viremia and VF at W96 for patients under PI/r monotherapy, as well as for those under triple therapy. Although PI/r monotherapy is not widely recommended, this strategy is still used and remains an alternative option. Virological markers are thus required to define good candidates for such a strategy and we recommended that clinicians consider USVL before choosing PI/r monotherapy treatment for their patients.

Conflict of interest

S.L has receveid travel grants from ViiV Healthcare. J.L.M has receveid travel grants from Gilead Sciences, Merck Laboratories MSD, Janssen Pharmaceuticals and has received honoraria for invited talks from Gilead Sciences, Merck Laboratories MSD A. G. M. has received honoraria for advisories or invited talks or conferences and research grants from, Gilead Sciences, Merck Laboratories MSD and ViiV Healthcare. C.K has received grant support from Merck Laboratories MSD, Janssen Pharmaceuticals and ViiV Healthcare. P.M.G has received grant support from BMS and Janssen Pharmaceuticals, personal fees as member of symposia faculty from

BMS, Abbvie Labs, and Mylan and honoraria for participation on international boards from Gilead Sciences and ViiV Healthcare. L.M.J have received honoraria from Gilead Sciences, Merck Laboratories MSD, Janssen Pharmaceuticals and ViiV Healthcare. The other authors have none to declare.

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Table 1. Description of clinical trials

Clinical trial	Description	Arms
Monoi ANRS 136	96 weeks; randomized, multicenter, open-label trial; 32 clinical sites in France; First phase of DRV/r 600/100 mg twice daily for 8 weeks as a component of a triple drug regimen	DRV/r Monotherapy 600/100 mg twice daily
		DRV/r plus 2 NRTIs
Dream ANRS 140	98 weeks; randomized, multicenter, open-label, non-inferiority; 36 clinical sites in France	LPV/r Monotherapy 400/100mg twice daily
		EFV plus TDF/FTC 600/245/200 mg once daily
Kalesolo IMEA 30	96 weeks	LPV/r Monotherapy

randomized, multicenter, open-label, non-inferiority; 23 clinical sites in France	400/100 mg twice daily Current cART (1NRTI+3TC+PI/r or NNRTI)		

Table 2. Patient characteristics

	Pooled Analysis	Monoi	Dream	Kalesolo
Number of patients	609	225	197	187
Age (y), median [IQR]	44.4 [39.8-52.1]	46 [40.5-53.9]	44.5 [39.2-52.8]	43.1 [39-49.9]
Sex				
Male	446 (73.36)	170 (75.56)	138 (70.05)	138 (74.19)
Female	162 (26.64)	55 (24.44)	59 (29.95)	48 (25.81)
Time since HIV diagnosis (y), median [IQR]	9.1 [4.6-15]	10.7 [5.0-15.7]	7.7 [4.4-11.9]	9.6 [4.7-15.6]
ART duration (y), median [IQR]	5.0 [2.8-9.9]	8.3 [3.7-11.2]	5.0 [3.1-11]	3.2 [1.9-6.1]
Number of patient with VL ≤50copies/mL at D0, n [%]	556 [92.51]	213 [94.67]	181 [95.26]	162 [87.10]
Number of patient with VL ≤50copies/mL at W96 , n [%]	494 [95.00]	211 [93.78]	162 [94.19]	118 [95.93]
CD4 cell count at D0, cells/mL, median [IQR]	564[422-707]	583 [428-763]	596 [463-725]	517 [384-659]
CD4/CD8 ratio at D0, median [IQR]	0.8 [0.6-1.10]	0.8 [0.6-1.1]	0.8 [0.6-1.1]	0.5 [0.4-0.6]
CD4 cell count at W96, cells/mL, median [IQR]	604.5 [464-797]	645 [488-860]	612 [471-811]	581 [444-746]
CD4/CD8 ratio at W96, median [IQR]	0.9 [0.63-1.23]	0.9 [0.8-1.2]	0.8 [0.6-1.2]	0.8 [0.6-1]

Table 3. Distribution of USVL at baseline and W96

Pooled Analysis					
USVL		Mono Therapy	Tri Therapy	All	P value
D0 (N=574)	**≥1 copy/mL (%)**	110 (40)	125 (42)	235 (41)	0.6718
	<1 copy/mL (%)	165 (60)	174 (59)	339 (59)	
W96 (N=501)	**≥1 copy/mL (%)**	87 (35)	66 (26)	153 (31)	**0.00419**
	<1 copy/mL (%)	163 (65)	185 (74)	348 (69)	

Monoi					
USVL		Mono Therapy	Tri Therapy	All	P value
D0 (N=225)	**≥1 copy/mL (%)**	45 (40)	49 (43)	94 (42)	0.6857
	<1 copy/mL (%)	67 (60)	64 (57)	131 (58)	
W96 (N=225)	**≥1 copy/mL (%)**	27 (24)	30 (27)	57 (25)	0.7595
	<1 copy/mL (%)	85 (76)	83 (73)	168 (75)	

Dream					
USVL		Mono Therapy	Tri Therapy	All	P value
D0 (N=185)	**≥1 copy/mL (%)**	38 (41)	37 (40)	75 (41)	1
	<1 copy/mL (%)	55 (59)	55 (60)	110 (59)	

W96 (N=160)	**≥1 copy/mL (%)**	34 (41)	18 (24)	52 (33)	**0.0283**
	<1 copy/mL (%)	50 (59)	58 (76)	108 (67)	

Kalesolo

USVL		Mono Therapy	Tri Therapy	All	P value
D0 (N=164)	**≥1 copy/mL (%)**	27 (39)	39 (41)	66 (40)	0.7491
	<1 copy/mL (%)	43 (61)	55 (59)	98 (60)	
W96 (N=116)	**≥1 copy/mL (%)**	26 (48)	18 (29)	44 (38)	**0.0375**
	<1 copy/mL (%)	28 (52)	44 (71)	72 (62)	

Pooled Monotherapy

USVL		Mono LPV/r	Mono DRV/r	All	P value
D0 (N=275)	**≥1 copy/mL (%)**	65(40)	45 (40)	110 (40)	1
	<1 copy/mL (%)	98 (60)	67 (60)	165 (60)	
W96 (N=250)	**≥1 copy/mL (%)**	60 (43)	27 (24)	87 (35)	**0.0014**
	<1 copy/mL (%)	78 (57)	85 (76)	163 (65)	

Table 4. Factors associated with virological success (VL < 50 copies/mL) at W96

Multivariate analysis			
Overall			
Variable	OR	95%CI	p-value
CD4 cell count (per increase of 100)	1.09	1.0-1.2	0.034
USVL < 1 cp *vs* ≥ 1 cp at D0	1.92	1.3-2.8	0.0005

Monotherapy Group			
CD4 cell count (per increase of 100)	1.22	1.1-1.4	0.002
Triple Therapy Group			
USVL < 1 cp *vs* ≥ 1 cp at D0	2.23	1.3-3.7	0.002

Table 5. Factors associated with an USVL < 1 copy/mL at W96

Multivariate analysis			
Overall			
Variable	OR	95%CI	p-value
Female *vs* male	2.07	1.2-3.5	0.006
Tri *vs* Mono	1.51	1.0-2.3	0.049
USVL < 1 cp *vs* ≥ 1 cp at D0	2.31	1.5-3.5	<.0001
Monotherapy Group			
Female *vs* male	2.35	1.2-4.7	0.02
DRV *vs* LPV	1.93	1.1-3.5	0.03
USVL < 1 cp *vs* ≥ 1 cp at D0	2.86	1.6-5.1	0.0004
Triple therapy Group			
USVL < 1 cp *vs* ≥ 1 cp at D0	2.0	1.1-3.6	0.02

Figure 1: Distribution of USVL at baseline and W96 in PI/r monotherapy strategy according PI used a) DRV: darunavir b) LPV: lopinavir
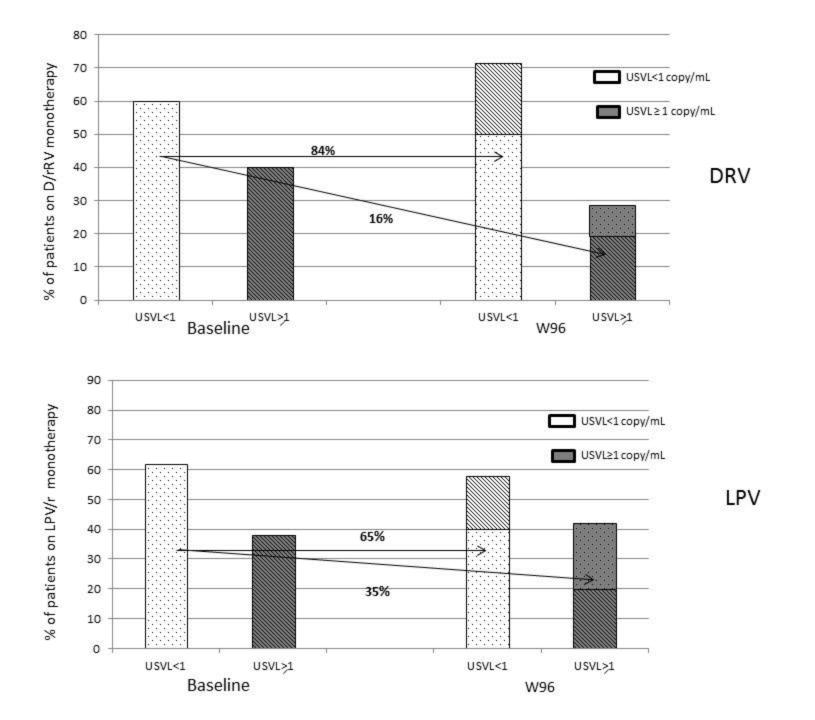
Figure 1