Low Rate of Virological Failure and Maintenance of Susceptibility to HIV-1 Protease Inhibitors with First-Line Lopinavir/Ritonavir-Based Antiretroviral Treatment in Clinical Practice

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Keywords:	human immunodeficiency virus type 1, lopinavir/ritonavir, first-line antiretroviral therapy, genotypic resistance, virologic failure

Table 1a. Multivariable Cox regression analysis: predictors of virological failure beginning from month 6 after treatment initiation (n=548).

HIV-RNA measured at or after 6 months							
factor		>50 copies/ml			>500 copies/ml		
		RH	95% CI	p-value	RH	95% CI	p-value
year of birth (per 1-year increase)		0.994	(0.958-1.03)	0.725	1.024	(0.983-1.066)	0.264
gender	male vs. female	0.649	(0.298-1.415)	0.277	0.575	(0.248-1.336)	0.198
	unknown vs. female	1.041	(0.128-8.463)	0.970	1.374	(0.17-11.079)	0.765
mode of HIV transmission	homo/bisexual vs. heterosexual	1.264	(0.524-3.046)	0.602	1.368	(0.53-3.534)	0.517
	intravenous drug user vs. heterosexual	0.512	(0.105-2.498)	0.408	1.519	(0.432-5.346)	0.515
	other/unknown vs. heterosexual	1.236	(0.558-2.737)	0.602	1.156	(0.477-2.802)	0.748
calendar year of HAART initiation (per more recent)		0.919	(0.719-1.174)	0.497	0.978	(0.733-1.304)	0.878
backbone HAART	abacavir+lamivudine vs. tenofovir+emtricitabine	0.362	(0.079-1.65)	0.189	0.197	(0.025-1.533)	0.121
	zidovudine+lamivudine vs. tenofovir+emtricitabine	1.142	(0.47-2.773)	0.769	0.991	(0.375-2.619)	0.986
	other backbone vs. tenofovir+emtricitabine	1.592	(0.403-6.299)	0.507	1.936	(0.402-9.323)	0.410
	tenofovir+lamivudine vs. tenofovir+emtricitabine	0.275	(0.056-1.361)	0.114	0.754	(0.206-2.767)	0.671
baseline CD4+ cell count cells/mm3 (per log higher)		0.844	(0.656-1.087)	0.190	0.892	(0.679-1.173)	0.414
baseline HIV-RNA load cp/ml (per log10 higher)		0.844	(0.529-1.348)	0.479	1.790	(1.097-2.921)	**0.020**
lopinavir GRS (per 10 points higher)		0.975	(0.912-1.042)	0.450	0.945	(0.89-1.003)	0.064
backbone GRS (per 10 points higher)		1.002	(0.979-1.026)	0.849	1.038	(1.017-1.06)	**0.0003**

Table 1b. Multivariable Cox regression analysis: predictors of virological failure beginning from month 3 after treatment initiation (n=548).

HIV-RNA measured at or after 3 months							
Factor		>50 copies/ml			>500 copies/ml		
		RH	95% CI	p-value	RH	95% CI	p-value
year of birth (per 1 year increase)		1.018	(0.991-1.045)	0.2012	1.032	(1.002-1.063)	**0.0365**
gender	male vs. female	1.233	(0.679-2.239)	0.4915	0.918	(0.504-1.67)	0.7784
	unknown vs. female	1.497	(0.339-6.605)	0.5941	0.468	(0.06-3.63)	0.4677
mode of HIV transmission	homo/bisexual vs. heterosexual	0.875	(0.468-1.634)	0.6751	0.827	(0.407-1.678)	0.5984
	intravenous drug user vs. heterosexual	0.202	(0.046-0.892)	**0.0348**	1.065	(0.433-2.621)	0.8909
	other/unknown vs. heterosexual	0.935	(0.517-1.69)	0.8228	1.223	(0.673-2.225)	0.5091
calendar year of HAART initiation (per more recent)		0.974	(0.805-1.178)	0.7859	1.101	(0.903-1.343)	0.3402
backbone HAART	abacavir+lamivudine vs. tenofovir+emtricitabine	0.255	(0.077-0.849)	**0.0259**	0.111	(0.015-0.824)	**0.0316**
	zidovudine+lamivudine vs. tenofovir+emtricitabine	0.895	(0.467-1.716)	0.7386	1.138	(0.585-2.212)	0.7041
	other backbone vs. tenofovir+emtricitabine	1.546	(0.505-4.737)	0.4457	2.015	(0.646-6.291)	0.2275
	tenofovir+lamivudine vs. tenofovir+emtricitabine	0.897	(0.397-2.029)	0.7948	1.199	(0.485-2.967)	0.6938
baseline CD4+ cell count cells/mm3 (per log higher)		0.875	(0.732-1.047)	0.145	0.967	(0.795-1.176)	0.7382
baseline HIV-RNA load cp/ml (per log10 higher)		1.127	(0.799-1.589)	0.4968	1.901	(1.312-2.754)	**0.0007**
lopinavir GRS (per 10 points higher)		0.997	(0.958-1.039)	0.9007	0.999	(0.966-1.032)	0.9361
backbone GRS (per 10 points higher)		1.001	(0.983-1.02)	0.8793	1.021	(1.005-1.037)	**0.0101**

RH = relative hazard; HAART = highly active antiretroviral therapy; GRS = Stanford's 6.0.1 genotypic resistance score

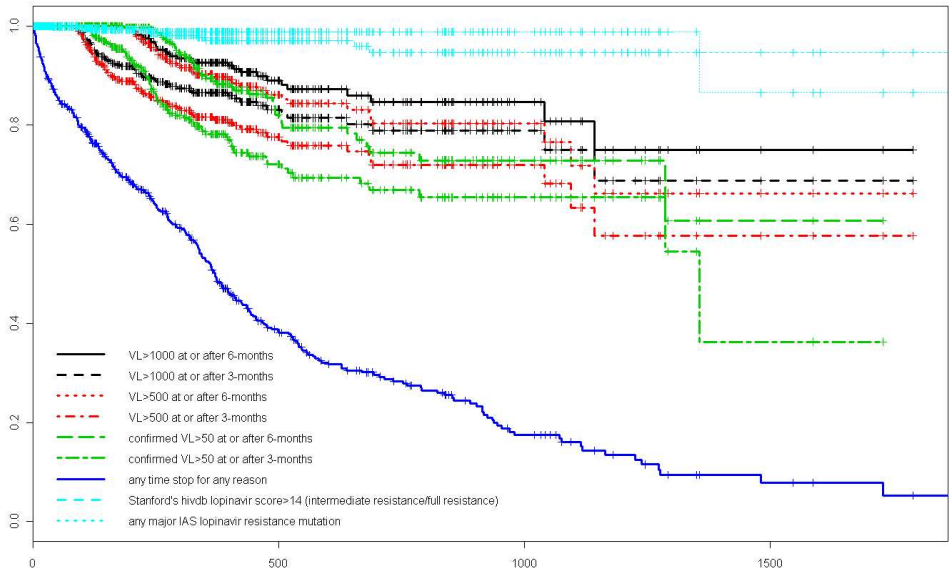
Table 2. Evolution of protease and reverse transcriptase resistance mutations under lopinavir/ritonavir plus 2 nucleoside/tide reverse transcriptase inhibitors pressure in 36 previously naive patients with available baseline and follow-up HIV-1 genotype. Substitutions emerging during treatment are in bold.

patient	nrti[a]	Baseline HIV-RNA load Log10 copies/ml	Baseline genotype[b]	Follow-up genotype[b]	LPV/rtv susceptbility (baseline/follow-up)[c]
1	3TC TDF	6.76	PR: 63P RT:	PR: 63P RT: **41L 70R 101Q 103N 181C 210W 215F 215Y 219E 221Y 225H 238T**	S/S
2	FTC TDF	5.72	PR: 63P RT:	PR: 63P RT: **184I**	S/S
3	3TC TDF	5.18	PR: 10F 20T 46I 54V 63P 71T 73T 84V 90M RT: 41L 70R 74V 103N 118I 184V 215F 219Q 228H	PR: 10F 20T 46I 54V 63P 71T 73T 84V 90M RT: 41L 70R 74V 103N 118I 184V 215F 219Q 228H	I/I
4	FTC TDF	5.53	PR: 16E 20R 36I RT:	PR: 16E 20R 36I RT:	S/S
5	3TC AZT	5.12	PR: 36I 60E RT: 101Q	PR: 36I 60E RT: 101Q **184V**	S/S
6	FTC TDF	5.70	PR: 20M 77I RT:	PR: 77I RT:	S/S
7	FTC TDF	4.93	PR: 13V 63P 77I RT:	PR: 13V 63P 77I RT:	S/S
8	FTC TDF	5.86	PR: 10I 11I 20V 32I 33F 36I 43T 63P 71V 73S 82A 89V 90M RT: 215D	PR: 10I 20V 32I 33F 36I 43T **46I 47V 54V** 63P 71V 73S 82A 89V 90M RT: **44D 118I 184V 215Y**	R/R
9	FTC TDF	6.25	PR: 36I 63P RT:	PR: 63P RT:	S/S
10	3TC AZT	5.17	PR: 63P 71T RT:	PR: 63P 71T RT:	S/S
11	FTC TDF	5.70	PR: 10V 13V 16E 20M 35G 36L RT:	PR: 10V 13V 16E 20M 35G 36L RT:	S/S
12	FTC TDF	4.77	PR: 82I RT:	PR: **36I** 82I RT:	S/S
13	FTC TDF	5.70	PR: 63P 77I RT: 333D	PR: 63P 77I RT: 333D	S/S
14	3TC AZT	4.17	PR: 36I 93L RT:	PR: 36I **63P** 93L RT:	S/S
15	3TC AZT	4.18	PR: 10I 13V 36I 58E 60E RT: 103N 184I 184V	PR: 10I 13V 36I 58E 60E RT: 103N 184V	S/S
16	D4T DDI	5.17	PR: 10I 46I 60E 63P 73T 77I 84V 90M 93L RT: 41L 67N 101E 181C 190A 215Y 219Q 228H	PR: 10F **20I 36I** 46I **54V** 60E 63P 73T 84V 90M 93L RT: 41L 67N 101E **108I 118I** 181C 190A **210W** 215Y 219R **221Y**	I/I

17	3TC D4T	4.56	PR: 10F 33I 35G 36I 46I 63P 71V 73S 83D 84V 90M RT: 41L 44D 67N 74I 74V 103N 118I 181C 210W 215Y 219R	PR: 10F **20V** 36I 46I **54V** 63P 71V 73S 84V 90M RT: 41L 44D 67N 74V **101Q** 118I **184V** 210W 215Y 219R	I/I
18	3TC AZT	5.31	PR: 13V 16A 58E 60E 77I RT: 179D	PR: 13V 16A 58E 60E 77I RT: 179D	S/S
19	3TC AZT	5.26	PR: 60E 63P 71T 77I RT: 106I 138G 179I	PR: 60E 63P 71T 77I RT: 106I 138G	S/S
20	D4T TDF	5.17	PR: 10F 35D 36I 54V 63P 71I 84V 93L RT: 41L 67G 74V 101P 184V 210W 215Y	PR: 10F 35D 36I **46I** 54V 63P 71I 84V 93L RT: 41L 67G 74V 101P 210W 215Y	I/I
21	3TC AZT	5.69	PR: 71T 77I RT:	PR: **35D** 71T 77I RT:	S/S
22	D4T TDF	5.46	PR: 10F 63P 77I RT:	PR: 63P RT:	S/S
23	3TC AZT	5.17	PR: 63P 77I 93L RT:	PR: 63P 77I 93L RT:	S/S
24	3TC TDF	5.03	PR: 36I 63P RT: 103R	PR: 36I 63P RT: 103R	S/S
25	3TC TDF	5.70	PR: 20I 36I RT:	PR: **10F 13V** 20I **20M** 36I **63P 77I 82I** RT: **184V 215C 215S 215Y**	S/S
26	3TC AZT	5.00	PR: 13V RT:	PR: 13V RT:	S/S
27	3TC TDF	5.56	PR: 10V 20V 36I 47V 54V 63P 71V 73S 82A 89V 90M RT: 215F 215S	PR: 10V 20V 36I 47V 54V 63P 71V 73S 82A 89V 90M RT: 215F 215S **215Y**	R/R
28	3TC AZT	4.59	PR: 20R 35D 36I RT:	PR: 20R 35D 36I RT:	S/S
29	3TC ABC	5.85	PR: 13V 20I 35N 36L 60E 63P RT:	PR: **10I** 13V 20I 36L 60E 63P RT:	S/S
30	FTC TDF	5.31	PR: 63P RT:	PR: 63P RT:	S/S
31	3TC AZT	4.20	PR: RT: 67N 219Q	PR: RT: 67N 219Q	S/S
32	FTC TDF	5.44	PR: 63P 93L RT:	PR: 63P 93L RT:	S/S
33	FTC TDF	7.00	PR: 10V 13V RT:	PR: 10V 13V RT:	S/S
34	FTC TDF	5.81	PR: 60E 63P RT:	PR: 60E 63P RT:	S/S
35	FTC TDF	5.17	PR: 63P 71V 93L RT: 69A 179I	PR: 71V 93L RT:	S/S
36	FTC TDF	4.91	PR: 10I 46L 93L RT: 118I 333E	PR: 10I 46L 93L RT: 118I	S/S

[a]3TC, lamivudine; ABC, abacavir; AZT, zidovudine; D4T, stavudine; DDI, didanosine; FTC, emtricitabine; TDF, tenofovir.
[b]PR, protease; RT, reverse transcriptase.
[c]S, susceptible (Stanford's score <=14); I, intermediate resistance (Stanford's score from 15 to 59); R, high-level resistance (Stanford's score >=60).

Figure 1. Kaplan-Meier curves of survival rates with respect to a virological failure at or after 3 or 6 months using different HIV-RNA thresholds (>1000, >500 and >50 cp/ml), to a Stanford's lopinavir genotypic resistance score >14 (intermediate/full resistance), to an accumulation of at least one major IAS resistance mutation to lopinavir/ritonavir, and to a therapy discontinuation (at any time for any reason) end-point.



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370x244mm (96 x 96 DPI)

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Running head: First-line lopinavir/ritonavir HAART

Abstract

Protease inhibitor (PI)-resistant HIV-1 has hardly ever been detected at failed boosted PI-based first-line antiretroviral regimens in clinical trials. However, this phenomenon has not been investigated in clinical practice. To address this gap, data from patients starting a first-line lopinavir/ritonavir (LPV/rtv)-based therapy with available baseline HIV-1 RNA load, a viral genotype and follow-up viral load after 3 months and 6 months of treatment were extracted from the Italian Antiretroviral Resistance Cohort Analysis (ARCA) observational database. Based on survival analysis, 39 (7.1%) and 43 (7.8%) of the 548 examined patient cases had an HIV-1 RNA >500 and >50 copies/ml, respectively, after 6 months of treatment. Cox proportional hazard models detected baseline HIV-1 RNA (RH 1.79, 95%CI 1.10-2.92 per 1-$\log_{10}$ increase, P = 0.02) and resistance to the nucleoside backbone (RH 1.04, 95%CI 1.02-1.06 per 10-point increase using the Stanford HIVdb algorithm, P < 0.001) as independent predictors of HIV-1 RNA at >500 copies/ml, but not at the >50 copies/ml cutoff criteria. Higher baseline viral load, older patient age, heterosexual route of infection and use of tenofovir/emtricitabine were predictors of failure at month 3 using the 50-copy and/or 500-copy threshold. Resistance to LPV/rtv did not occur or increase in any of the available 36 follow-up HIV-1 genotypes. Resistance to the nucleoside backbone (M184V) developed in four cases. Despite the likely differences in patient population and adherence, both the low rate of virological failure and the lack of development of LPV/rtv resistance documented in clinical trials are thus confirmed in clinical practice.

Key Words

human immunodeficiency virus type 1; boosted protease inhibitor; lopinavir/ritonavir; first-line antiretroviral therapy; antiretroviral drug resistance; virologic failure.

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Introduction

Ritonavir-boosted protease inhibitors (PIs) have been used successfully for years and still remain a key component of highly active antiretroviral therapy (HAART). A major advantage of boosted PIs in first-line therapy is the very low risk of selecting drug-resistant HIV-1 variants at virological failure, as shown in multiple clinical trials [Bartlett et al., 2006; Gupta et al., 2008; Lima et al., 2008; Molina et al., 2008; Ortiz et al., 2008; Mills et al., 2009]. This feature is, in fact, the main argument made by experts favouring boosted PI over non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line therapy because NNRTIs select typically for NNRTI-resistant virus at failure [Riddler et al., 2008]. In addition, resistance to the backbone nucleoside reverse transcriptase inhibitors (NRTIs) occurs less frequently with a boosted PI compared to an NNRTI-based therapy [Soulié et al., 2009].

While the latest treatment guidelines recommend other boosted PIs for first-line HAART [DHHS, 2009], lopinavir/ritonavir (LPV/rtv) has been the most widely used PI owing to its long-standing availability, unique heat-stable co-formulation, efficacy and safety profiles [Oldfield et al., 2006]. In order to evaluate virological response to first-line LPV/rtv-based therapy and confirm its low propensity for selecting resistance mutations in HIV-1 protease in clinical practice, a targeted analysis was carried out using the Italian Antiretroviral Resistance Cohort Analysis (ARCA) observational database. ARCA (www.hivarca.net) is a nationwide initiative started in 2002 which retrospectively and prospectively collates clinical and virological data from HIV-1-infected patients followed at 105 centres. The data include demographics, hepatitis B and C status, AIDS-defining events, antiretroviral treatment, viral load, CD4+ T cell counts, HIV-1 genotype. The oldest HIV-1 genotype entry is dated back to 1991. At the time of this study, data from 19,984 patients were available.

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Patients and Methods

First-line treatments comprised of LPV/rtv plus two NRTIs were extracted from the ARCA database. All patients with available HIV-1 genotype and HIV-1 RNA load at baseline were included and all HIV-1 RNA load data available from the treatment start date to the latest follow-up time were collected. The rate of treatment failure and development of drug resistance were evaluated by survival analyses using the cases with at least one follow-up HIV-1 RNA load measurement obtained after 3 months and after 6 months of uninterrupted treatment. Information on HIV-1 genotype obtained between 30 days after treatment start and 90 days after LPV/rtv discontinuation was also included, if no other PI was administered after LPV/rtv.

The Stanford HIVdb version 6.0.1 (http://hivdb.stanford.edu/) algorithm was used to calculate genotypic resistance scores (GRS). HIVdb scores below 10 are classified as full drug susceptibility, from 10 to 14 as potential low-level resistance, from 15 to 29 as low-level resistance, from 30 to 59 as intermediate resistance and >59 as high-level resistance. This five-level system was converted to a three-category classification by grouping scores up to 14 as susceptibility, 15 to 59 as intermediate resistance and >59 as complete resistance. A continuous numeric GRS scale was used in the multivariable analysis in order to minimise the number of parameters to be optimised: results are showed per 10 points higher, which roughly corresponds to a one-category increase in the Stanford HIVdb categorisation.

Survival analysis using the Kaplan-Meier method and Cox proportional hazard models was performed using the following outcome measures: having an HIV-1 RNA load >500 and >50 copies/ml at 3 months after treatment initiation; an HIV-1 RNA load >500 and >50 copies/ml at 6 months after treatment initiation; intermediate or full LPV/rtv resistance defined as a GRS >14; and the presence of at least one major LPV/rtv resistance mutation according to the 2009 IAS-USA list (i.e. V32I, I47A/V or V82A/F/S/T) [Johnson et al., 2009]. Cases not reaching the specific

endpoint were censored at the regimen discontinuation date or at the latest available HIV-1 RNA or HIV-1 genotype if the regimen was not discontinued. After adjusting for the other explanatory variables, the Cox model provides an estimate of the treatment effect on the remaining data with no outcome event. In addition, the model allows estimating the outcome event hazard for each individual, based on his/her baseline variables.

Results

The ARCA database contained 1,141 patients who were treated with first line LPV/rtv-containing HAART regimens. Of these, 549 (48%) did not have a baseline genotype and were excluded from the analysis. The remaining 592 patients had baseline median (IQR) CD4+ T cell counts and HIV-1 RNA load of 127 (48-255) cells/mm^3 and 5.20 (4.80-5.60) $\log_{10}$ copies/ml, respectively. The median (IQR) calendar year of LPV/rtv initiation was 2006 (2004-2007). The NRTI backbones employed most frequently were tenofovir plus emtricitabine (37.5%), zidovudine plus lamivudine (34.3%), abacavir plus lamivudine (12.2%), and tenofovir plus lamivudine (10.6%).

At baseline, 15 (2.5%) and 1 (0.2%) patients presented with a LPV/rtv intermediate and resistant GRS, respectively. The prevalence of genotypes carrying at least one major IAS mutation associated to LPV/rtv resistance was 7.3% (n=43). Intermediate and full resistance to at least one NRTI were detected in 5.4% and 2.5% of the cases, with 1.8% showing intermediate and 5.7% full resistance to at least one NNRTI; and 1.8% and 2.0% to at least one PI, respectively. When looking at the GRS of the treatment provided, the prevalence of regimens with all fully active drugs (i.e. no drug with a GRS >14) was 93%, while 2.9% of regimen were composed by either at least one drug with full resistance or two drugs with intermediate resistance. Ten (1.7%) genotypes were found with both intermediate-level resistance to LPV/rtv and to at least one of the other drugs in the backbone.

Forty-four (7.4%) of the 592 patients had not have a follow-up HIV-1 RNA measurement after 3 or 6 months hence were excluded from subsequent incidence and survival analyses. Following 3- and 6 months therapy, 74 (13.5%) and 39 (7.1%) patients had an HIV-1 RNA >500 copies/ml, respectively. Using the more stringent criterion, the number of cases with a confirmed HIV-1 RNA >50 copies/ml after 3 and 6 months were 77 (14%) and 43 (7.8%), respectively.

According to Kaplan-Meier analysis (Fig. 1) the estimated proportion of patients with an HIV-1 RNA below 500 copies/ml was 0.90 (95% CI 0.86-0.94) at one year and 0.80 (0.74-0.87) at two years, with an incidence rate of 0.23 (0.17-0.32) per 1,000 person-years of follow-up. With the 50-copy threshold, the probability to remain virological failure-free was 0.90 (0.85-0.93) at one year and 0.73 (0.65-0.81) at two years, with an incidence rate of 0.26 (0.19-0.35) per 1,000 person-years of follow-up. The incidence rate of therapy discontinuation for any reason was 1.8 (1.7-2.1) per 1,000 person-years of follow-up. The probability of continuing the first-line LPV/rtv-based regimen was 0.51 (0.46-0.56) at one year and 0.28 (0.24-0.34) at two years. Notably, 26% of the 324 LPV/rtv therapy discontinuations at any follow-up time were owing to toxicity, 17% to treatment simplification, 3% to adherence problems, whereas 33% were on other grounds and 21% were stopped owing to unspecified reasons.

Multivariable Cox analysis showed that at 6 months a higher baseline HIV-1 RNA load and a higher NRTI backbone GRS were independent predictors of having viremia at >500 copies/ml, but not at >50 copies/ml (Table 1a). Factors predictive of virological failure at 3 months using the 500-copy and/or the 50-copy threshold were higher baseline viral load, older patient age, use of tenofovir/emtricitabine vs. abacavir/lamivudine and heterosexual vs. intravenous route of infection (Table 1b). However, drug users had less frequent visits, thus viral load monitoring, compared to other transmission groups (not shown). This may explain the apparently lower risk of short-term failure for drug users.

Follow-up of HIV-1 genotype was available for a total of 36 patients. Mutations associated with decreasing susceptibility to NRTIs, NNRTIs and PIs were detected at baseline in seven, five and six patients, respectively, with three patients harboring triple-class resistant virus. Overall, genotyping was carried out after a median of 220 days (IQR 102-348) from LPV/rtv initiation. Median HIV-1 RNA and CD4+ T cell count at the time of follow-up genotype were 3.64 (IQR 2.56-4.67) $\log_{10}$ copies/ml and 207 (120-432) cells/mm^3. Eight (22.2%) viral genotype tests were

performed after LPV/rtv discontinuation. Paired analysis of the baseline and follow-up genotypes revealed very limited selection of protease mutations (Table 2). There were no changes in Stanford HIVdb LPV/rtv susceptibility category in any case. Among the 30 patients with a LPV/rtv-sensitive baseline genotype, only one was found with more than one additional minor PI mutation (patient 25: L10F, I13V, L63P, V77I, V82I) but this did not have any impact on the predicted LPV/rtv susceptibility. In some other cases, the baseline and follow-up genotype differed for one minor mutation, either acquired or lost. Resistance mutation I54V, contributing to resistance to LPV/rtv, was observed in three cases with pre-existing LPV/rtv resistance. In one of the four cases harboring a virus populations with intermediate resistance to LPV/rtv at baseline (patient 20), the major PI mutation M46I was identified at the follow-up stage. Moreover, major LPV/rtv mutations M46I and I47V were found in one of the two patients (patient 8) with a virus that was already highly resistant to LPV/rtv at baseline. There were four cases with NRTI resistance mutations, namely M184I/V with or without a more extensive set of NRTI resistance mutations. In one of these patients, the follow-up HIV-1 genotype also contained NNRTI resistance mutations as a result of NNRTI therapy following discontinuation of LPV/rtv. Overall, 30 of the 36 (83.3%) follow-up genotypes were susceptible to LPV/rtv and to at least another PI, 33 (91.7%) were susceptible to NNRTIs and to at least two NRTIs.

Discussion

The use of boosted PIs as first-line HAART has been shown to be a valuable treatment option in clinical trials with virological failure being comparable or slightly higher than with NNRTI-based therapy [Riddler et al., 2008; Soriano et al., 2009; Daar et al., 2010]. However the residual number of effective drugs at failure has been generally far higher with boosted PIs [Bartlett et al., 2006; Gupta et al., 2008; Lima et al., 2008]. Although the underlying mechanism is not completely understood, it has been acknowledged that not only boosted PI failures devoid any major protease mutations but also resistance to the NRTI backbone is typically minimized by an apparently increased genetic barrier to resistance. Notwithstanding the excellent performance in clinical trials, evaluation of virological response and development of drug resistance with first-line boosted PI treatment in the different context of clinical practice is advisable. Larger heterogeneity and lower adherence rate of the patient population may introduce variables affecting the success of a treatment regimen based mostly on a high genetic barrier. Moreover, genotypic resistance assays in clinical trials are performed typically at the first sign of virological failure, while they may be delayed in clinical practice owing to practical constraints.

The analysis of a large multicentric observational cohort confirms both a very low rate of virologic failure, which is in some cases driven by pre-existing resistance, and a negligible selection of drug resistance in patients undergoing a LPV/rtv-based first-line regimen. The results shown with respect to the 6-month follow-up, which is more relevant in the current clinical settings, and for the 3-month end-point, which could be of interest in the evaluation of the predictors of early failure. Although the number of follow-up genotypes was limited, clinical trials of drug-naive patients have generated comparably low numbers of genotypic information at failure [Gupta et al., 2008]. In addition, patients with transmitted PI-resistant virus are generally excluded from boosted PI-based first-line treatment trials while such patients are encountered in clinical practice

[Geretti, 2007] and may benefit from boosted PI therapy. Interestingly, it was observed that decreased susceptibility to the NRTI backbone appeared to compromise treatment more than decreased susceptibility to LPV/rtv. This highlights the potency of this high-genetic barrier PI, although the low number of cases with resistance at baseline may have hampered the detection of minor effects.

According to the genotypic susceptibility profile at failure, for the vast majority of patients a fully active regimen can be still based on a boosted PI or consisting of two NRTI plus one NNRTI. While novel drug classes are being considered for convenient and potentially less toxic first-line treatment, boosted PIs, particularly LPV/rtv, maintain an excellent and hardly achievable efficacy record of in terms of suppression of virus replication and limitation of drug resistance evolution. In addition, recent trial data suggest better tolerability and/or higher potency for the currently recommended boosted PIs compared to LPV/rtv [Madruga et al., 2007; Molina et al., 2008]. While this strengthens the importance of the PI class as a cornerstone in HAART, future analysis of large cohort data will be required to confirm such advantages in clinical practice.

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