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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

Mattia Cf Prosperi, Maurizio Zazzi, Grazia Punzi, Laura Monno, Grazia Colao, Paola Corsi, Simona Di Giambenedetto, Genny Meini, Valeria Ghisetti, Stefano Bonora, et al.

► To cite this version:

Mattia Cf Prosperi, Maurizio Zazzi, Grazia Punzi, Laura Monno, Grazia Colao, et al.. 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. *Journal of Medical Virology*, 2010, 82 (12), pp.1996. 10.1002/jmv.21927 . hal-00589435

HAL Id: hal-00589435

<https://hal.science/hal-00589435>

Submitted on 29 Apr 2011

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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

Journal:	<i>Journal of Medical Virology</i>
Manuscript ID:	JMV-10-1726.R2
Wiley - Manuscript type:	Research Article
Date Submitted by the Author:	08-Jul-2010
Complete List of Authors:	<p>Prosperi, Mattia; Catholic University of Sacred Heart, Clinic of Infectious Diseases Zazzi, Maurizio; University of Siena, Molecular Biology Punzi, Grazia; Bari University Hospital, Microbiology and Virology Monno, Laura; Bari University Hospital, Clinical Infectious Diseases Colao, Grazia; Careggi University Hospital, Microbiology and Virology Corsi, Paola; Careggi University Hospital, Unit of Infectious Diseases Di Giambenedetto, Simona; Catholic University of Sacred Heart, Clinic of Infectious Diseases Meini, Genny; University of Siena, Molecular Biology Ghisetti, Valeria; A. Savoia Hospital, Microbiology and Virology bonora, stefano; university of Torino, infectious diseases Pecorari, Monica; Modena University Hospital, Microbiology and Virology Gismondo, Maria Rita; L. Sacco University Hospital, Microbiology and Virology Bagnarelli, Patrizia; Ancona University Hospital, Microbiology and Virology Carli, Tiziana; Grosseto General Hospital, Unit of Infectious Diseases De Luca, Andrea; Sacro Cuore Catholic University, Institute of Infectious Diseases; University Hospital of Siena, Infectious Diseases Unit</p>
Keywords:	human immunodeficiency virus type 1, lopinavir/ritonavir, first-line antiretroviral therapy, genotypic resistance, virologic failure

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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 Log ₁₀ copies/ml	Baseline genotype ^b	Follow-up genotype ^b	LPV/rtv susceptibility (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

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^a3TC, lamivudine; ABC, abacavir; AZT, zidovudine; D4T, stavudine; DDI, didanosine; FTC, emtricitabine; TDF, tenofovir.

^bPR, protease; RT, reverse transcriptase.

^cS, susceptible (Stanford's score ≤ 14); I, intermediate resistance (Stanford's score from 15 to 59); R, high-level resistance (Stanford's score ≥ 60).

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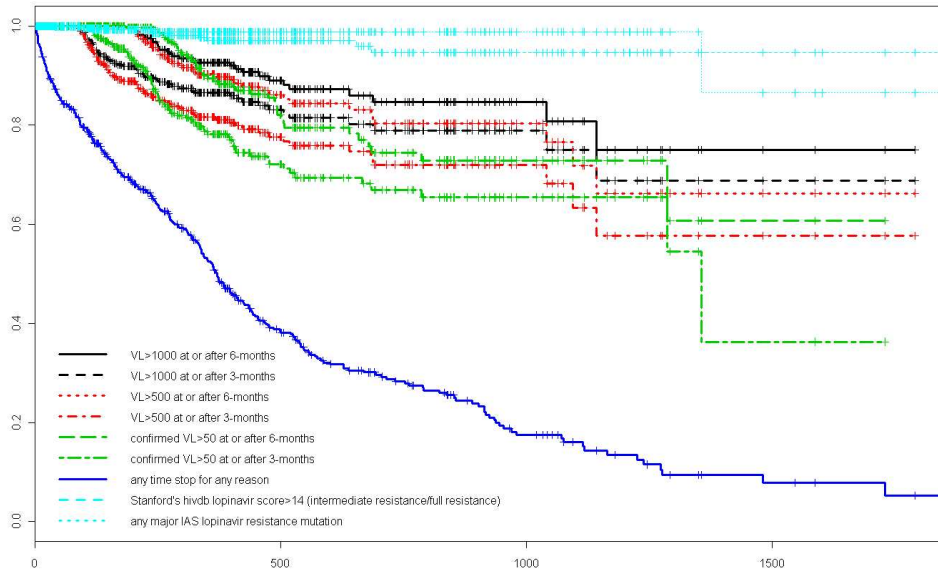


Figure 1. Kaplan-Meier curves of survival rates with respect to a virological failure at or after 3 or 6 months using different HIV-RNA thresholds (>1000 , >500 and >50 cp/ml), to a Stanford's lopinavir genotypic resistance score >14 (intermediate/full resistance), to an accumulation of at least one major IAS resistance mutation to lopinavir/ritonavir, and to a therapy discontinuation (at any time for any reason) end-point.
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1 1 **Low Rate of Virological Failure and Maintenance of Susceptibility to HIV- 2 2 **1 Protease Inhibitors with First-Line Lopinavir/Ritonavir-Based 3 3 **Antiretroviral Treatment in Clinical Practice******

8 5 Mattia CF Prosperi¹, Maurizio Zazzi², Grazia Punzi³, Laura Monno⁴, Grazia Colao⁵, Paola Corsi⁶, Simona Di
9 6 Giambenedetto¹, Genny Meini², Valeria Ghisetti⁷, Stefano Bonora⁸, Monica Pecorari⁹, Maria Rita
10 7 Gismondo¹⁰, Patrizia Bagnarelli¹¹, Tiziana Carli¹², and Andrea De Luca^{1,13}, for the ARCA Collaborative Group.

13 9 ¹Clinic of Infectious Diseases, Catholic University of Sacred Heart, Rome, Italy

14 10 ²Department of Molecular Biology, University of Siena, Siena, Italy

15 11 ³Microbiology and Virology, Bari University Hospital, Bari, Italy

16 12 ⁴Clinical Infectious Diseases, Bari University Hospital, Bari, Italy

17 13 ⁵Microbiology and Virology, Careggi University Hospital, Florence, Italy

18 14 ⁶Unit of Infectious Diseases, Careggi University Hospital, Florence, Italy

20 15 ⁷Microbiology and Virology, A. Savoia Hospital, Turin, Italy

21 16 ⁸Unit of Infectious Diseases, A. Savoia Hospital, Turin, Italy

22 17 ⁹Microbiology and Virology, Modena University Hospital, Modena, Italy

23 18 ¹⁰Microbiology and Virology, L. Sacco University Hospital, Milan, Italy

24 19 ¹¹Microbiology and Virology, Ancona University Hospital, Ancona, Italy

25 20 ¹²Unit of Infectious Diseases, Grosseto General Hospital, Grosseto, Italy

26 21 ¹³Infectious Diseases Unit, Siena University Hospital, Siena, Italy

29 23 Correspondence to:

30 24 Mattia Prosperi, PhD

31 25 Clinic of Infectious Diseases

32 26 Catholic University of Sacred Heart

33 27 Largo F. Vito, 1 – 00168 - Rome, Italy

34 28 E-mail: ahnven@yahoo.it

38 31 **Running head:** First-line lopinavir/ritonavir HAART

1
2 32 **Abstract**

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7 34 Protease inhibitor (PI)-resistant HIV-1 has hardly ever been detected at failed boosted PI-based
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10 35 first-line antiretroviral regimens in clinical trials. However, this phenomenon has not been
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12 36 investigated in clinical practice. To address this gap, data from patients starting a first-line
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14 37 lopinavir/ritonavir (LPV/r) therapy with available baseline HIV-1 RNA load, a viral
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17 38 genotype and follow-up viral load after 3 months and 6 months of treatment were extracted from
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20 39 the Italian Antiretroviral Resistance Cohort Analysis (ARCA) observational database. Based on
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22 40 survival analysis, 39 (7.1%) and 43 (7.8%) of the 548 examined patient cases had an HIV-1 RNA
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25 41 >500 and >50 copies/ml, respectively, after 6 months of treatment. Cox proportional hazard
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27 42 models detected baseline HIV-1 RNA (RH 1.79, 95%CI 1.10-2.92 per 1- \log_{10} increase, $P = 0.02$) and
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30 43 resistance to the nucleoside backbone (RH 1.04, 95%CI 1.02-1.06 per 10-point increase using the
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32 44 Stanford HIVdb algorithm, $P < 0.001$) as independent predictors of HIV-1 RNA at >500 copies/ml,
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35 45 but not at the >50 copies/ml cutoff criteria. Higher baseline viral load, older patient age,
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37 46 heterosexual route of infection and use of tenofovir/emtricitabine were predictors of failure at
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40 47 month 3 using the 50-copy and/or 500-copy threshold. Resistance to LPV/r did not occur or
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42 48 increase in any of the available 36 follow-up HIV-1 genotypes. Resistance to the nucleoside
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45 49 backbone (M184V) developed in four cases. Despite the likely differences in patient population
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47 50 and adherence, both the low rate of virological failure and the lack of development of LPV/r
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50 51 resistance documented in clinical trials are thus confirmed in clinical practice.

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57 54 **Key Words**

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60 55 human immunodeficiency virus type 1; boosted protease inhibitor; lopinavir/ritonavir; first-line
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57 antiretroviral therapy; antiretroviral drug resistance; virologic failure.

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58 **Word count:** Abstract 249; Text 2,097.

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2 59 **Introduction**

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7 61 Ritonavir-boosted protease inhibitors (PIs) have been used successfully for years and still
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10 62 remain a key component of highly active antiretroviral therapy (HAART). A major advantage of
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12 63 boosted PIs in first-line therapy is the very low risk of selecting drug-resistant HIV-1 variants at
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14 64 virological failure, as shown in multiple clinical trials [Bartlett et al., 2006; Gupta et al., 2008; Lima
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16 65 et al., 2008; Molina et al., 2008; Ortiz et al., 2008; Mills et al., 2009]. This feature is, in fact, the
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18 66 main argument made by experts favouring boosted PI over non-nucleoside reverse transcriptase
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20 67 inhibitor (NNRTI)-based first-line therapy because NNRTIs select typically for NNRTI-resistant virus
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22 68 at failure [Riddler et al., 2008]. In addition, resistance to the backbone nucleoside reverse
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24 69 transcriptase inhibitors (NRTIs) occurs less frequently with a boosted PI compared to an NNRTI-
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26 70 based therapy [Soulié et al., 2009].

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32 71 While the latest treatment guidelines recommend other boosted PIs for first-line HAART
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34 72 [DHHS, 2009], lopinavir/ritonavir (LPV/r) has been the most widely used PI owing to its long-
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36 73 standing availability, unique heat-stable co-formulation, efficacy and safety profiles [Oldfield et al.,
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38 74 2006]. In order to evaluate virological response to first-line LPV/r-based therapy and confirm its
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40 75 low propensity for selecting resistance mutations in HIV-1 protease in clinical practice, a targeted
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42 76 analysis was carried out using the Italian Antiretroviral Resistance Cohort Analysis (ARCA)
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44 77 observational database. ARCA (www.hivarca.net) is a nationwide initiative started in 2002 which
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46 78 retrospectively and prospectively collates clinical and virological data from HIV-1-infected patients
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48 79 followed at 105 centres. The data include demographics, hepatitis B and C status, AIDS-defining
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50 80 events, antiretroviral treatment, viral load, CD4+ T cell counts, HIV-1 genotype. The oldest HIV-1
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52 81 genotype entry is dated back to 1991. At the time of this study, data from 19,984 patients were
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54 82 available.

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7 87 First-line treatments comprised of LPV/rtv plus two NRTIs were extracted from the ARCA
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10 88 database. All patients with available HIV-1 genotype and HIV-1 RNA load at baseline were included
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12 89 and all HIV-1 RNA load data available from the treatment start date to the latest follow-up time
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15 90 were collected. The rate of treatment failure and development of drug resistance were evaluated
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17 91 by survival analyses using the cases with at least one follow-up HIV-1 RNA load measurement
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20 92 obtained after 3 months and after 6 months of uninterrupted treatment. Information on HIV-1
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22 93 genotype obtained between 30 days after treatment start and 90 days after LPV/rtv
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25 94 discontinuation was also included, if no other PI was administered after LPV/rtv.

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27 95 The Stanford HIVdb version 6.0.1 (<http://hivdb.stanford.edu/>) algorithm was used to
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30 96 calculate genotypic resistance scores (GRS). HIVdb scores below 10 are classified as full drug
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32 97 susceptibility, from 10 to 14 as potential low-level resistance, from 15 to 29 as low-level
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35 98 resistance, from 30 to 59 as intermediate resistance and >59 as high-level resistance. This five-
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37 99 level system was converted to a three-category classification by grouping scores up to 14 as
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40 100 susceptibility, 15 to 59 as intermediate resistance and >59 as complete resistance. A continuous
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42 101 numeric GRS scale was used in the multivariable analysis in order to minimise the number of
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45 102 parameters to be optimised: results are showed per 10 points higher, which roughly corresponds
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47 103 to a one-category increase in the Stanford HIVdb categorisation.

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50 104 Survival analysis using the Kaplan-Meier method and Cox proportional hazard models was
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52 105 performed using the following outcome measures: having an HIV-1 RNA load >500 and >50
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55 106 copies/ml at 3 months after treatment initiation; an HIV-1 RNA load >500 and >50 copies/ml at 6
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57 107 months after treatment initiation; intermediate or full LPV/rtv resistance defined as a GRS >14;
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60 108 and the presence of at least one major LPV/rtv resistance mutation according to the 2009 IAS-USA
109 list (i.e. V32I, I47A/V or V82A/F/S/T) [Johnson et al., 2009]. Cases not reaching the specific

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2 110 endpoint were censored at the regimen discontinuation date or at the latest available HIV-1 RNA
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5 111 or HIV-1 genotype if the regimen was not discontinued. After adjusting for the other explanatory
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7 112 variables, the Cox model provides an estimate of the treatment effect on the remaining data with
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10 113 no outcome event. In addition, the model allows estimating the outcome event hazard for each
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12 114 individual, based on his/her baseline variables.

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2 117 **Results**

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7 119 The ARCA database contained 1,141 patients who were treated with first line LPV/rtv-
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10 120 containing HAART regimens. Of these, 549 (48%) did not have a baseline genotype and were
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12 121 excluded from the analysis. The remaining 592 patients had baseline median (IQR) CD4+ T cell
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15 122 counts and HIV-1 RNA load of 127 (48-255) cells/mm³ and 5.20 (4.80-5.60) log₁₀ copies/ml,
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17 123 respectively. The median (IQR) calendar year of LPV/rtv initiation was 2006 (2004-2007). The NRTI
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20 124 backbones employed most frequently were tenofovir plus emtricitabine (37.5%), zidovudine plus
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22 125 lamivudine (34.3%), abacavir plus lamivudine (12.2%), and tenofovir plus lamivudine (10.6%).
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25 126 At baseline, 15 (2.5%) and 1 (0.2%) patients presented with a LPV/rtv intermediate and
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27 127 resistant GRS, respectively. The prevalence of genotypes carrying at least one major IAS mutation
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30 128 associated to LPV/rtv resistance was 7.3% (n=43). Intermediate and full resistance to at least one
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32 129 NRTI were detected in 5.4% and 2.5% of the cases, with 1.8% showing intermediate and 5.7% full
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35 130 resistance to at least one NNRTI; and 1.8% and 2.0% to at least one PI, respectively. When looking
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37 131 at the GRS of the treatment provided, the prevalence of regimens with all fully active drugs (i.e. no
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40 132 drug with a GRS >14) was 93%, while 2.9% of regimen were composed by either at least one drug
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42 133 with full resistance or two drugs with intermediate resistance. Ten (1.7%) genotypes were found
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45 134 with both intermediate-level resistance to LPV/rtv and to at least one of the other drugs in the
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47 135 backbone.
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50 136 Forty-four (7.4%) of the 592 patients had not have a follow-up HIV-1 RNA measurement
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52 137 after 3 or 6 months hence were excluded from subsequent incidence and survival analyses.
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55 138 Following 3- and 6 months therapy, 74 (13.5%) and 39 (7.1%) patients had an HIV-1 RNA >500
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57 139 copies/ml, respectively. Using the more stringent criterion, the number of cases with a confirmed
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60 140 HIV-1 RNA >50 copies/ml after 3 and 6 months were 77 (14%) and 43 (7.8%), respectively.

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2 141 According to Kaplan-Meier analysis (Fig. 1) the estimated proportion of patients with an
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5 142 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
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7 143 two years, with an incidence rate of 0.23 (0.17-0.32) per 1,000 person-years of follow-up. With the
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10 144 50-copy threshold, the probability to remain virological failure-free was 0.90 (0.85-0.93) at one
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12 145 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-
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15 146 years of follow-up. The incidence rate of therapy discontinuation for any reason was 1.8 (1.7-2.1)
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17 147 per 1,000 person-years of follow-up. The probability of continuing the first-line LPV/rtv-based
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20 148 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
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22 149 324 LPV/rtv therapy discontinuations at any follow-up time were owing to toxicity, 17% to
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25 150 treatment simplification, 3% to adherence problems, whereas 33% were on other grounds and
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27 151 21% were stopped owing to unspecified reasons.

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30 152 Multivariable Cox analysis showed that at 6 months a higher baseline HIV-1 RNA load and a
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32 153 higher NRTI backbone GRS were independent predictors of having viremia at >500 copies/ml, but
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35 154 not at >50 copies/ml (Table 1a). Factors predictive of virological failure at 3 months using the 500-
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37 155 copy and/or the 50-copy threshold were higher baseline viral load, older patient age, use of
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40 156 tenofovir/emtricitabine vs. abacavir/lamivudine and heterosexual vs. intravenous route of
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42 157 infection (Table 1b). However, drug users had less frequent visits, thus viral load monitoring,
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45 158 compared to other transmission groups (not shown). This may explain the apparently lower risk of
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47 159 short-term failure for drug users.

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50 160 Follow-up of HIV-1 genotype was available for a total of 36 patients. Mutations associated
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52 161 with decreasing susceptibility to NRTIs, NNRTIs and PIs were detected at baseline in seven, five
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55 162 and six patients, respectively, with three patients harboring triple-class resistant virus. Overall,
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57 163 genotyping was carried out after a median of 220 days (IQR 102-348) from LPV/rtv initiation.
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60 164 Median HIV-1 RNA and CD4+ T cell count at the time of follow-up genotype were 3.64 (IQR 2.56-
165 4.67) log₁₀ copies/ml and 207 (120-432) cells/mm³. Eight (22.2%) viral genotype tests were

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2 166 performed after LPV/rtv discontinuation. Paired analysis of the baseline and follow-up genotypes
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5 167 revealed very limited selection of protease mutations (Table 2). There were no changes in Stanford
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7 168 HIVdb LPV/rtv susceptibility category in any case. Among the 30 patients with a LPV/rtv-sensitive
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10 169 baseline genotype, only one was found with more than one additional minor PI mutation (patient
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12 170 25: L10F, I13V, L63P, V77I, V82I) but this did not have any impact on the predicted LPV/rtv
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15 171 susceptibility. In some other cases, the baseline and follow-up genotype differed for one minor
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17 172 mutation, either acquired or lost. Resistance mutation I54V, contributing to resistance to LPV/rtv,
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20 173 was observed in three cases with pre-existing LPV/rtv resistance. In one of the four cases
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22 174 harboring a virus populations with intermediate resistance to LPV/rtv at baseline (patient 20), the
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25 175 major PI mutation M46I was identified at the follow-up stage. Moreover, major LPV/rtv mutations
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27 176 M46I and I47V were found in one of the two patients (patient 8) with a virus that was already
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30 177 highly resistant to LPV/rtv at baseline. There were four cases with NRTI resistance mutations,
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32 178 namely M184I/V with or without a more extensive set of NRTI resistance mutations. In one of
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35 179 these patients, the follow-up HIV-1 genotype also contained NNRTI resistance mutations as a
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37 180 result of NNRTI therapy following discontinuation of LPV/rtv. Overall, 30 of the 36 (83.3%) follow-
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40 181 up genotypes were susceptible to LPV/rtv and to at least another PI, 33 (91.7%) were susceptible
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42 182 to NNRTIs and to at least two NRTIs.
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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

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2 209 [Geretti, 2007] and may benefit from boosted PI therapy. Interestingly, it was observed that
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5 210 decreased susceptibility to the NRTI backbone appeared to compromise treatment more than
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7 211 decreased susceptibility to LPV/rtv. This highlights the potency of this high-genetic barrier PI,
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10 212 although the low number of cases with resistance at baseline may have hampered the detection of
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12 213 minor effects.

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15 214 According to the genotypic susceptibility profile at failure, for the vast majority of patients
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17 215 a fully active regimen can be still based on a boosted PI or consisting of two NRTI plus one NNRTI.
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20 216 While novel drug classes are being considered for convenient and potentially less toxic first-line
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22 217 treatment, boosted PIs, particularly LPV/rtv, maintain an excellent and hardly achievable efficacy
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25 218 record of in terms of suppression of virus replication and limitation of drug resistance evolution. In
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27 219 addition, recent trial data suggest better tolerability and/or higher potency for the currently
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30 220 recommended boosted PIs compared to LPV/rtv [Madruga et al., 2007; Molina et al., 2008]. While
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32 221 this strengthens the importance of the PI class as a cornerstone in HAART, future analysis of large
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35 222 cohort data will be required to confirm such advantages in clinical practice.

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Acknowledgements

This work was supported, in part, by an unrestricted educational grant from Abbott Virology to ARCA. The sponsor played no role in study design, data analysis and manuscript revision. ARCA is supported by educational grants by Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Gilead Sciences, Janssen-Cilag Tibotec division. The study was supported partly by the European Community's Seventh Framework Programme (FP7/2007-2013) under the project "Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN)" - grant agreement number 223131. We are very grateful to Andrea Petroczi (Kingston University, UK) for critical reading of the manuscript.

The ARCA collaborative group

Andrea Giacometti (ANCONA - Clinica di Malattie Infettive), Luca Butini (ANCONA - Immunologia Clinica), Romana del Gobbo (ANCONA - Malattie Infettive), Stefano Menzo (ANCONA - Virologia), Danilo Tacconi (AREZZO - Malattie Infettive), Giovanni Corbelli (ASCOLI PICENO - Malattie Infettive), Stefania Zanussi (AVIANO - Centro di Riferimento Oncologico), Laura Monno (BARI - Clinica Malattie Infettive Università), Grazia Punzi (BARI - Virologia), Franco Maggiolo (BERGAMO - Malattie Infettive), Annapaola Callegaro (BERGAMO - Microbiologia e Virologia), Leonardo Calza (BOLOGNA - Malattie Infettive S. Orsola), Maria Carla Re (BOLOGNA - UO Microbiologia, Lab. Retrovirus), Raffaele Pristerà (BOLZANO - Malattie Infettive), Paola Turconi (BRESCIA - Fleming Labs), Antonella Mandas (CAGLIARI - Centro S.I.D.A., Policlinico Universitario), Sauro Tini (CITTA' DI CASTELLO - Medicina Generale), Alessia Zoncada (CREMONA - Malattie Infettive), Elisabetta Paolini (CREMONA - Servizio Immunoematologia e Medicina Trasmfusionale), Giorgio Amadio (FERMO - Malattie Infettive), Laura Sighinolfi (FERRARA - Malattie Infettive AOU S. Anna), Giuliano Zuccati (FIRENZE - Centro MTS), Massimo Morfini (FIRENZE - Ematologia CAREGGI), Roberto Manetti (FIRENZE - Immunoallergologia CAREGGI), Paola Corsi (FIRENZE - Malattie Infettive CAREGGI), Luisa Galli (FIRENZE - Malattie Infettive Pediatria Meyer), Massimo Di Pietro (FIRENZE - Malattie Infettive SM Annunziata), Filippo Bartalesi (FIRENZE - Malattie Infettive Università), Grazia Colao (FIRENZE - Virologia CAREGGI), Andrea Tosti (FOLIGNO - Malattie Infettive / SERT), Antonio Di Biagio (GENOVA - Clinica Malattie Infettive AOU S. Martino), Maurizio Setti (GENOVA - Clinica Medica Immunologia), Bianca Bruzzone (GENOVA - Laboratorio di Igiene Ospedale S. Martino), Giovanni Penco (GENOVA - Malattie Infettive Ospedali Galliera), Michele Trezzi (GROSSETO - Malattie Infettive), Anna Orani (LECCO - Malattie Infettive), Riccardo Pardelli (LIVORNO - Malattie Infettive), Michele De Gennaro (LUCCA - Malattie Infettive), Alessandro Chiodera (MACERATA - Malattie Infettive), Alfredo Scalzini (MANTOVA - Malattie Infettive Ospedale 'C. Poma'), Loredana Palvarini (MANTOVA - Virologia), Paolo Almi (MASSA - Malattie Infettive), Giovanni Todaro (MESSINA - Malattie Infettive), Antonella d'Arminio Monforte (MILANO - Clinica Malattie Infettive AO S. Paolo), Paola Cicconi (MILANO - Clinica di Malattie Infettive Ospedale S. Paolo), Stefano Rusconi (MILANO - Dipart. Scienze Cliniche, Sez. Malattie Infettive - Università degli Studi), Maria Rita Gismondo (MILANO - Laboratorio Microbiologia Ospedale L. Sacco (Dipart. Scienze Cliniche, Sez. Malattie Infettive)), Maria Rita Gismondo (MILANO - Laboratorio Microbiologia Ospedale L. Sacco (Prima Divisione Malattie Infettive)), Valeria Micheli (MILANO - Laboratorio Microbiologia Ospedale L. Sacco (Seconda Divisione Malattie Infettive)), Maria Luisa Biondi (MILANO - Laboratorio di diagnostica molecolare infettivologica AO S. Paolo), Nicola Gianotti (MILANO - Malattie Infettive San Raffaele), Amedeo Capetti (MILANO - Prima Divisione Malattie Infettive Ospedale L. Sacco), Paola Meraviglia (MILANO - Seconda Divisione Malattie Infettive Ospedale L. Sacco), Enzo Boeri (MILANO - Virologia HSR), Cristina Mussini (MODENA - Clinica Malattie Infettive), Monica Pecorari (MODENA - Virologia), Alessandro Soria (MONZA - Malattie Infettive), Laura Vecchi (MONZA - UO Microbiologia AO S. Gerardo), Maurizio Santirocchi (NARNI - SERT), Diego Brustia (NOVARA - Malattie Infettive AO Maggiore), Paolo Ravanini (NOVARA - Virologia), Federico Dal Bello (PADOVA - Virologia), Nino Romano (PALERMO - Centro Riferimento AIDS Università), Salvatrice Mancuso (PALERMO - Servizio Riferimento Regionale Diagnosi AIDS), Carlo Calzetti (PARMA - Divisione Malattie Infettive ed Epatologia Azienda Ospedaliera), Renato Maserati (PAVIA - Ambulatorio Clinica Malattie Infettive S. Matteo), Gaetano Filice (PAVIA - Clinica Malattie Infettive e Tropicali), Fausto Baldanti (PAVIA - Virologia S. Matteo), Daniela Francisci (PERUGIA - Malattie Infettive), Giustino Parruti (PESCARA - Malattie Infettive), Ennio Polilli (PESCARA - Virologia Pescara), Daria Sacchini (PIACENZA - Malattie Infettive), Chiara Martinelli (PISA - Malattie Infettive), Rita Consolini (PISA - Pediatria I Università), Linda Vatteroni (PISA - Virologia), Angela Vivarelli (PISTOIA - Malattie Infettive), Daniele Dionisio (PISTOIA - Virologia), Alessandro Nerli (PRATO - Malattie Infettive), Lucia Lenzi (PRATO - Virologia), Giacomo Magnani (REGGIO EMILIA - Malattie Infettive), Patrizia Ortolani (RIMINI - Malattie Infettive RIMINI), Massimo Andreoni (ROMA - Cattedra Malattie Infettive Tor Vergata), Guido Palamara (ROMA - IRCCS S. Gallicano), Caterina Fimiani (ROMA - Immunologia Clinica Umberto I), Lucia Palmisano (ROMA - Istituto Superiore di Sanità), Andrea De Luca (ROMA - Istituto di Clinica Malattie Infettive Cattolica), Simona Di Giambenedetto (ROMA - Laboratorio virologia Cattolica), Vincenzo Vullo (ROMA - Malattie

1
2 280 Infettive e Tropicali La Sapienza - Umberto I), Ombretta Turriziani (ROMA - Medicina Sperimentale e Patologia -
3 281 Sezione Virologia - La Sapienza), Marco Montano (ROMA - Virologia per Malattie Infettive Tor Vergata), Giovanni
4 282 Cenderello (SAN REMO - Malattie Infettive), Angela Gonnelli (SIENA - Malattie Infettive), Maurizio Zazzi (SIENA -
5 283 Virologia), Michele Palumbo (TERNI - Malattie Infettive), Valeria Ghisetti (TORINO - Laboratorio di Virologia, Ospedale
6 284 Amedeo di Savoia), Stefano Bonora (TORINO - Malattie Infettive Amedeo di Savoia), Palma Delle Foglie (TRENTO -
7 285 Malattie Infettive), Cristina Rossi (TREVISO - Malattie Infettive), Federica Poletti (VERBANIA - Malattie Infettive
8 286 VERBANIA), Vincenzo Mondino (VERBANIA - Virologia), Marina Malena (VERONA - Centro di Medicina Preventiva-ULSS
9 287 20), Emanuela Lattuada (VERONA - Malattie Infettive).
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