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Evolution of transmitted HIV-1 drug resistance in HIV-1-infected patients in Italy since 2000 to 2010

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Abstract

Prevalence and predictors of Transmitted Drug Resistance (TDR), defined as the presence of at least one WHO surveillance drug resistance mutation (SDRM), were investigated in antiretroviral-naïve HIV-1infected patients, with a genotypic resistance test (GRT) performed ≤6 months before starting cART between 2000 and 2010.

3163 HIV-1 sequences were selected (69% subtype B). Overall, the prevalence of TDR was 12% (13.2% subtype B, 9% non-B). TDR significantly declined overall and for the single drug classes.

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Transparency Declaration

All Authors have nothing to declare in the period of research leading up to this publication and with specific reference to this paper. MC, SDG, RC received funds for speaking, consultancy, advisory board membership, travel from MSD, J-C, Abbott, ViiV Healthcare, Gilead Science, BMS outside the present work.

MC was an employee of BMS from May 2010 to February 2011 and resigned before starting the present work.

Older age independently predicted an increased odd whereas a more recent GRT, a higher HIV-RNA and C- versus B-subtype lower odds of TDR.

Keywords

Resistance epidemiology; Antiretroviral therapy; transmitted resistance; chronic HIV infection; recent HIV infection

Introduction

The introduction of combination Antiretroviral Therapy (cART) has allowed to obtain high rates[1-5] of success in controlling the replication of HIV. In Italy, the prevalence of TDR ranged from 5.9% to 15.1% in two studies between 1992 and 2007[6, 7]. We had analyzed the temporal trends and predictors of TDR in Italy in a previous study between 1996 and 2007[8].

The present study aimed to extend the follow-up of our previous work[8] and to evaluate possible predictors and trends of TDR prevalence in the Italian population from 2000 to 2010.

Materials and Methods

Sequences from HIV-1 infected, treatment naïve patients with a GRT performed ≤6 months before starting cART from 2000 to 2010 were retrieved from the ARCA database[www.hivarca.net,8] and from separate databases at the Catholic University of Sacred Heart (CUSH) and at the University Hospital "Spedali Civili" of Brescia, Italy. For each patient, only the first genotype was considered. We defined an "acute/recent" infection if the first HIV positive test was obtained within 1-18 months since the last available negative test or if a primary HIV infection (PHI) could be demonstrated and a "non acute/non recent" infection when the time between an HIV negative and a subsequent positive test was longer than previously stated or when no negative test was available. TDR was defined as the detection of at least one mutation among those indicated in the WHO-recommended SDRM list updated in 2009 (available at: http://hivdb.stanford.edu/pages/WHOResistanceList.html) [9].

HIV-1 subtyping was automatically performed upon sequence upload by BLAST[8].

The changes in the prevalence of TDR per calendar year were evaluated with χ^2 test for trend; logistic regression analysis was used in order to evaluate the predictors of TDR.

Results

A total of 3,163 (65% from ARCA, 14% from CUSH and 21% from Brescia) protease and reverse transcriptase sequences obtained between 2000 and 2010 from treatment-naive patients were analyzed. Two hundred twenty-six (7%) of 3,163 patients were diagnosed with an acute or recent HIV infection.

The evolution of patients characteristics over time is shown in table 1.

The overall prevalence of any drug resistance mutation in patients with “non acute/non recent” infection was 11.7%; NRTI, NNRTI and major PI resistance mutations were detected in 7.4%, 5% and 2.9% of patients, respectively. The prevalence of any drug resistance mutations was significantly reduced in 2010 versus 2000 (8.2% vs 24.1%, p<0.001). The proportion of patients presenting any major IAS mutation associated to NRTI resistance, NNRTI resistance and PI resistance in this subgroup is shown in figure 1a.

The overall proportion of non-B strains increased from 18% in 2000 to 24% in 2010 (p<0.001); the prevalence of unknown subtypes was also increased from 5% to 18% (p<0.001) (see figure 1b). The CRF02_AG subtype showed an increase from 3/62 (5%) to 10/169 (6%, p=0.67) and F1 increased from 3/62 (5%) to 8/169 (5%, p=0.81). Among Italian natives, 310/2224 (13%) carried non-B viral strains; the prevalence of these subtypes increased over calendar years (11% in 2000–2003, 14% in 2004–07, 19% in 2008–10; overall p=0.01), peaking in 2009 (51/251, 25%).

The overall prevalence of subtype B HIV-1 strains was 69%. The prevalence of TDR was higher in B- than in non-B subtype (13% vs. 9%, p=0.002) carriers. The prevalence of TDR in subtype B and non-B was 8% and 5% for NRTIs (p=0.003), 6% and 3% for NNRTIs (p<0.001), and 3% each for PIs (p=0.94); the changes over calendar year in the trends for B and non-B subtypes is shown in figure 1c-d.

In patients diagnosed with an acute or recent HIV infection from 2000 to 2010 the overall prevalence of any drug resistance mutation was 14%; NRTI, NNRTI and major PI resistance mutations were detected in 7%, 7% and 3% of patients, respectively. Subtype B HIV-1 was detected in 185/226 (82%) samples; the most frequently observed non-B subtype was F1 (5%).

At multivariable logistic regression analysis, older age independently predicted higher odds of transmitted drug resistance mutations. More recent calendar year, higher plasma HIV-RNA and infection with non subtype B strains independently predicted reduced odds of TDR (see table 1b).

Discussion

This is an observational study aiming to analyze the prevalence of TDR in HIV-infected patients in three large Italian Cohorts. The declining trend in the prevalence of any TDR mutation that we had observed[8] was confirmed until 2010.

We observed a significantly increased proportion of treatment naïve patients carrying non-B subtype HIV-1 in the last 10 years. This confirms our previous observation reporting an increased prevalence of non subtype B strains over two decades (1983-2006) in Brescia[10].

At multivariate analysis, we observed a lower risk of TDR in patients tested for GRT in a more recent calendar year, probably as an effect of the improvement in the management of cART. The lower risk of TDR in patients with higher baseline viral load could be related to

the higher fitness of wild-type HIV[11]. Finally, the lower prevalence of TDR in non-B subtype infected subjects is in line with the lower exposure to cART in countries where these subtypes are prevalent. We acknowledge that the surveillance list of resistance mutations for non-B subtypes is still being completely defined; anyway, we referred to the last available 2009 list[9] where a considerable amount of mutations were added to those previously recognized.

The analysis of TDR in patients with acute or recent HIV infection is of great interest but is limited by the low rates of documented seroconversion or diagnosed PHIs.

The high proportion of patients with unknown duration of HIV infection is an important confounder, but this is difficult to overcome as in clinical practice the proportion of patients with a recent negative test at the diagnosis of HIV infection always represents a minority. Finally, a relevant part of subtypes could not be determined, particularly in recent years.

In conclusion, the prevalence of TDR is declining in our multicentric cohort; this probably reflects the improvement in the management and prescription of antiretroviral drugs and the availability of new drugs.

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MC wrote the first draft of the manuscript, also performing the appropriate literature search. CT contributed to the data interpretation and to the final version of the submitted draft. EMT, LA, AR, VM, NM, G Penco, BB, G Punzi, PC, G Parruti, PB, AG all contributed to the data collection. LM contributed to the data collection and to the editing of the final draft. RC edited the final draft. SDG conceived and designed the study, performed the statistical analyses and interpretations, and contributed to writing the first draft of the manuscript.

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Appendix

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The following centers currently contribute clinical and laboratory data to the ARCA database initiative.

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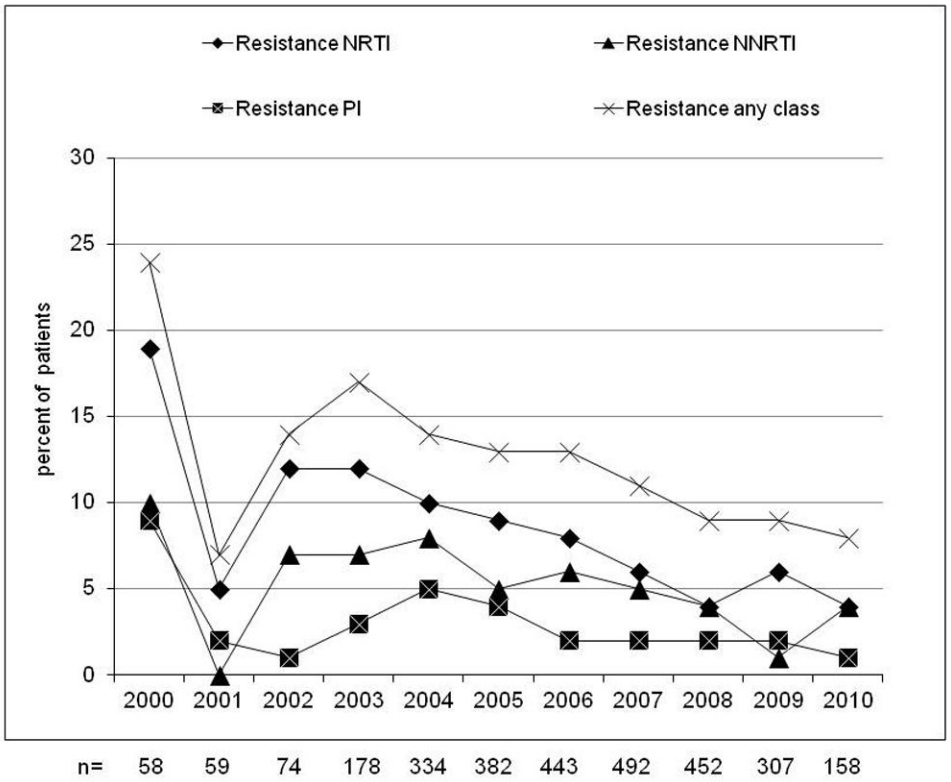

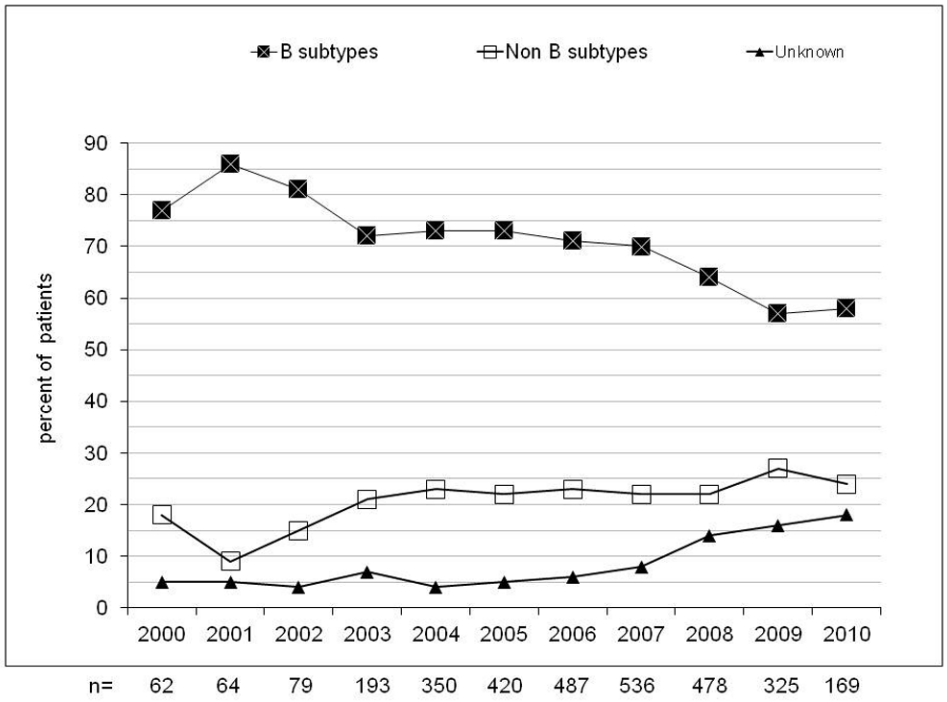

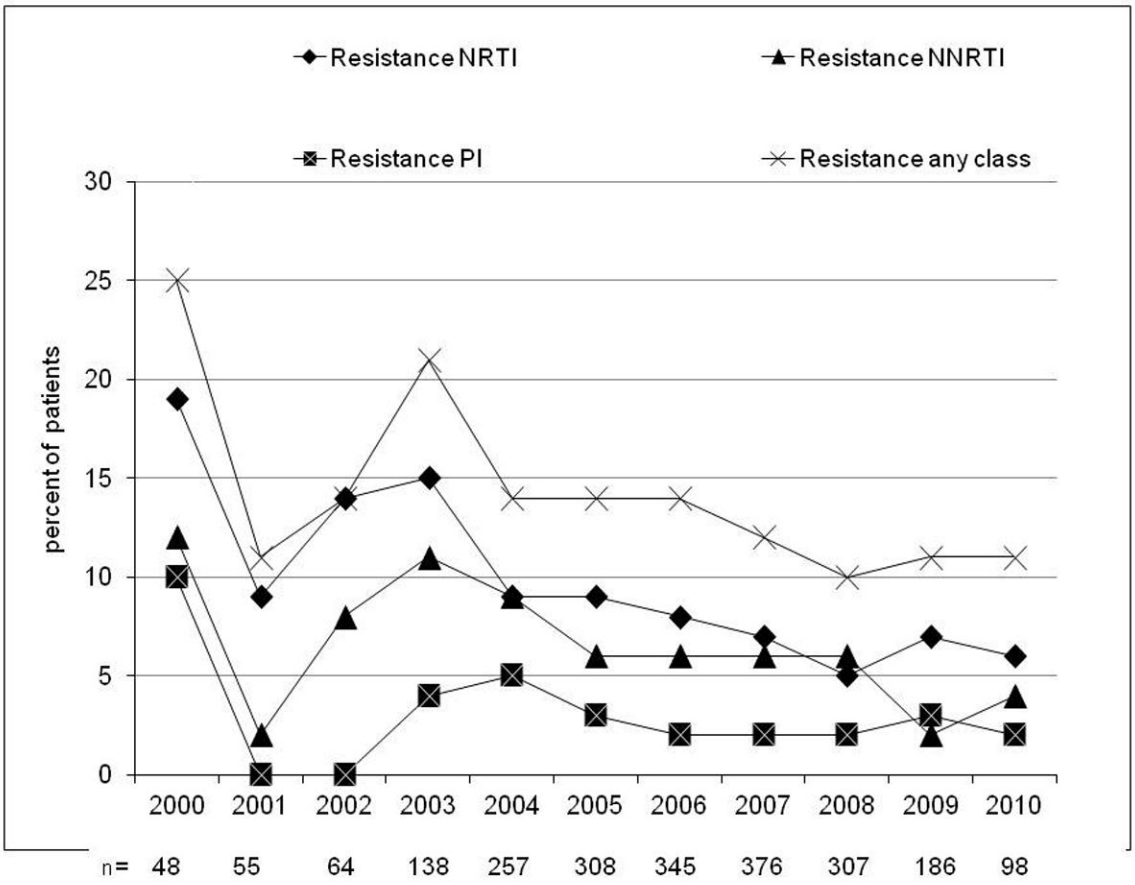

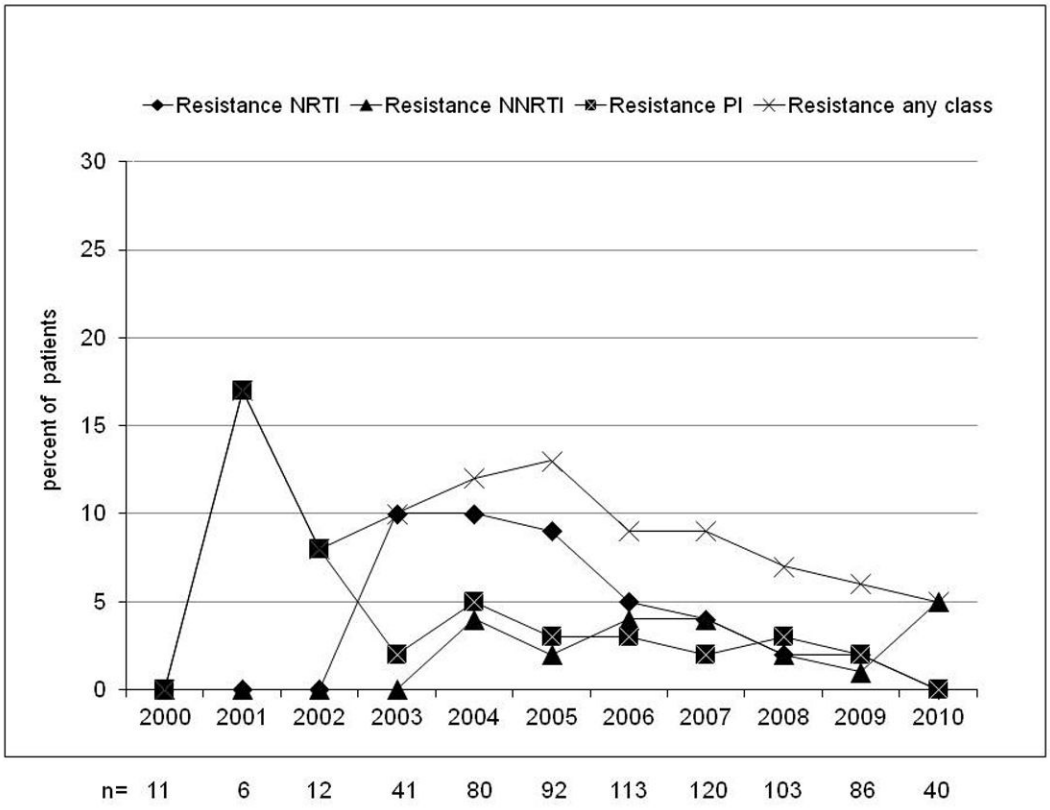

Figure 1.

Evolution of resistance (at least one major IAS mutation) by calendar year from 2000 to 2010 in naive patients with non acute/non recent infection (A, n=2,937), evolution of the prevalence of B, non-B and unknown subtypes (B) and evolution of the prevalence of drug resistance in B subtype (C) and in non-B subtypes (D). NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

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Table 1

Descriptive characteristics of general population and of patients among different quartiles

	Total population N=3163	**2000-2003 N=398**	**2004-2007 N=1793**	**2008-2010 N=972**	**p-value**
Median Age (IQR) (years)	37 (30-43)	35 (30-41)	37 (30-43)	38 (31-46)	0.001
Male sex (%)	74	71	73	76	0.07
Median calendar year at genotyping (IQR)	2006 (2005-2008)				
Risk factors					
Heterosexual contacts (%)	40	38	27	40	0.80
Homosexual contacts (%)	26	25	27	26	0.93
Injecting drug use (%)	11	14	12	9	0.002
Other or unknown (%)	23	23	20	25	0.05
Country of birth					
Italy (%)	81	61	70	78	<0.001
Sub-Saharan Africa (%)	8	4	8	8	0.007
Latin America and Caribbean (%)	5	5	4	3	0.30
Eastern Europe (%)	3	4	2	2	0.72
Other (%)	3	5	4	3	0.58
Patients followed at sites					
Northern Italy (%)	46	45	54	41	<0.001
Central Italy (%)	50	50	37	36	<0.001
Southern Italy and islands (%)	4	5	9	23	<0.001
Subtype, n (%)					
B	69	77	72	61	0.002
Non B	22	18	23	24	
Unknown	9	6	6	16	
Distribution of NonB Subtypes, %					
F1	17.3	23.7	18.9	13.6	

	Total population N=3163	2000-2003 N=398	2004-2007 N=1793	2008-2010 N=972	p-value
02_AG	15.8	15.1	19.5	11	
C	14	14	13.6	14.4	
G	6.2	5.4	8.3	13.7	
Other (<5% each)	18.5	17.1	19.6	7.4	
Unknown	28.2	24.7	20.1	39.9	
VL median (IQR) (log copies/ml)	4.58 (4.04-5.15)	4.42 (3.89-5.12)	4.61 (4.06-5.16)	4.58 (4.04-5.16)	0.006
CD4 median (IQR) (cells/mm3)	357 (201-518)	361 (185-557)	360 (226-527)	342 (161-503)	0.02

b: Predictors of TDR in all samples

	Univariate analysis		Multivariate analysis	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Sex (male versus female)	0.95 (0.74-1.22)	0.71	0.84 (0.58-1.21)	0.35
Calendar year (per more recent)	0.90 (0.86-0.94)	<0.001	0.93 (0.87-0.99)	**0.03**
Age (per 10 years more)	1.01 (0.99-1.02)	0.19	1.19 (1.04-1.36)	**0.01**
Risk category:				
Heterosexual contact (reference)	1.00		1.00	
Homosexual contact	1.25 (0.96-1.64)	0.09	1.04 (0.73-1.47)	0.84
Injecting drug use	1.08 (0.74-1.58)	0.68	0.95 (0.62-1.46)	0.83
Other	5.58 (0.92-33.6)	0.06	2.87 (0.56-14.6)	0.20
Unknown	0.69 (0.44-1.09)	1.12	2.25 (0.22-22.6)	0.49
CD4 at GRT (per 100 cells/mm3 higher)	1.06 (1.02-1.11)	0.003	1.04 (0.99-1.09)	0.17
HIV-1 RNA at GRT (per 1 log10 copies/mL higher)	0.76 (0.66-0.88)	<0.001	0.80 (0.67-0.95)	**0.01**
Clinical site:				
Northen Italy	0.96 (0.77-1.21)	0.74	0.92 (0.67-1.25)	0.59
Central Italy (reference)	1.00		1.00	
Southern Italy	0.65 (0.44-0.96)	0.03	0.78 (0.52-0.72)	0.30
Origin:				
Italian (reference)	1.00		1.00	
Sub-Saharan Africa	0.45 (0..25-0.81)	0.008	0.75 (0.32-1.72)	0.49

Latina America and Caribbean	0.91 (0.53-1.59)	0.76	0.90 (0.48-0.70)	0.75	
Eastern Europe	0.58 (0.23-1.46)	0.25	0.69 (0.24-1.99)	0.49	
Other	1.87 (1.08-3.23)	0.02	1.91 (1.02-3.59)	0.04	
Subtype:					
B (reference)	1.00		1.00		
C	0.35 (0.16-0.76)	0.008	0.31 (0.11-0.88)	**0.03**	
F1	0.82 (0.50-1.35)	0.44	0.95 (0.53-1.72)	0.87	
G	0.34 (0.10-1.09)	0.07	0.21 (0.03-1.61)	0.13	
CRF02_AG	0.65 (0.37-1.42)	0.13	0.56 (0.23-1.39)	0.21	
Other	0.70 (0.50-0.97)	0.03	0.81 (0.53-1.22)	0.31	
Non B-Subtype	0.64 (0.48-0.86)	0.003	-	-	
Duration of HIV infection:					
Acute/recent vs Non acute/non recent	1.19 (0.80-1.77)	0.38	1.14 (0.73-1.79)	0.56	