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Letter to the Editor

# Prevalence of acquired resistance mutations in a large cohort of perinatally infected HIV-1 patients☆

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Data of drug resistance mutations (DRMs) within the Italian vertically infected population are scarce. The aim of the present work was to assess the prevalence of DRMs in this setting. We retrospectively analysed HIV-1 *pol* sequences of vertically infected patients obtained from the Italian Antiviral Response Cohort Analysis (ARCA) database (https://www.dbarca.net/). Our queries were restricted to adults. DRMs were interpreted using the Stanford HIVDB resistance interpretation algorithm (https://hivdb.stanford.edu/hivdb/by-mutations/). Any modification of antiretroviral therapy after initiation was considered a change in the therapeutic regimen. Data from a total of 94 patients were analysed (Fig. 1). Patient clinical characteristics are summarized in Table 1. The population was exposed to a median of five different antiretroviral regimens (range, 1–35 regimens). Data about the ongoing antiretroviral regimen were recovered for 73 patients (78%). Fourteen (15%) had no DRMs. At least one major DRM to nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs) was found in 74 cases (79%), to nonnucleoside reverse transcriptase inhibitors (NNRTIs) in 61 (65%) cases, to protease inhibitors (PIs) in 33 cases (35%) and to integrase strand transfer inhibitor (INSTIs) in 7 (7%).

The most common DRM in the N(t)RTI class was M184V/I (62/94, 66%); in NNRTIs, K103N/S (39/94, 41%); in PI, M46I/L (26/94, 28%); and in INSTI, Q148H (3/94, 3%) (Fig. 2).

Dual class resistance was seen in 39 (41%) of 94 patients, including simultaneous DRMs to N(t)RTI and NNRTI in 30 (32%), to N(t)RTI and PI in 8 (9%) and to N(t)RTI and INSTI in 1 (1%). Susceptibility to one or fewer class of drugs was seen in 25 (27%) of 94 cases, including concomitant DRMs to N(t)RTI, NNRTI and PI in 19 (20%) and N(t)RTI, NNRTI, PI and INSTI in 6 (6%) of 94 patients.

More than half (50/94, 53%) of patients had concomitant DRMs that conferred moderate to high resistance to all N(t)RTIs, 33 (35%) to all NNRTIs, 11 (12%) to all PIs and 3 (3%) to all INSTIs. One quarter of patients (25/94, 27%) had concomitant moderate to high resistance to N(t)RTI and NNRTI, while 8 (8%) had concomitant moderate to high resistance to N(t)RTIs, NNRTIs and PIs.

☆ This paper is dedicated to the memory of our friend and colleague A. De Luca, MD.

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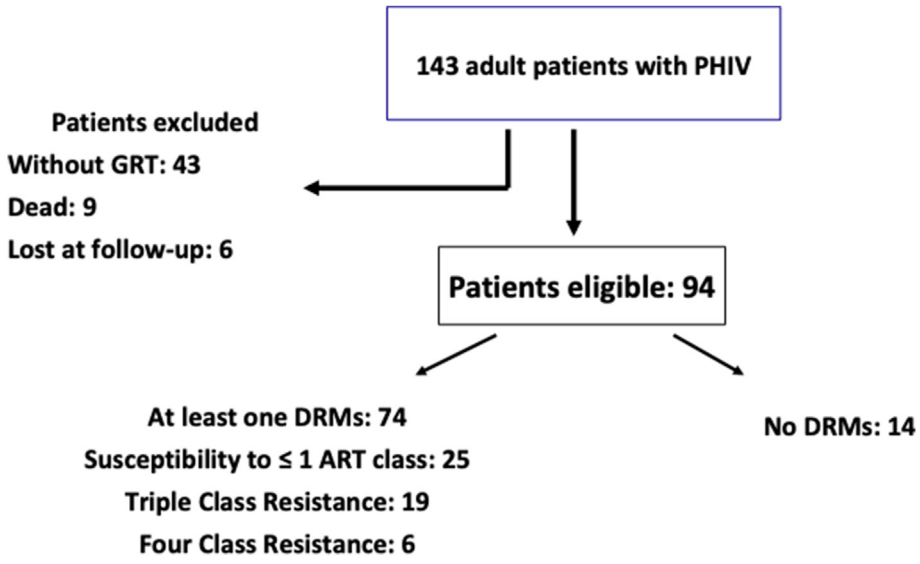


**Fig. 1.** Patient disposition. ART, antiretroviral therapy; DRM, drug resistance mutation; GRT, genotypic resistance test; PHIV, perinatal HIV-1.

According to univariate analysis, patients with limited treatment options were more likely to have a CD4 nadir <200 cells/mm$^3$ (hazard ratio (HR) 3.1; 95% confidence interval (CI) 1.2–8.1; p 0.021), last available CD4 cell count <200 cells/mm$^3$ (HR 5.5; 95% CI 1.2–25.1; p 0.028) and last available HIV RNA >50 copies/mL (HR 3.0; 95% CI 1.2–7.7; p 0.023). They were also more likely to have a history of exposure to more than ten different antiretroviral regimens (HR 5.9; 95% CI 1.8–19.0; p 0.003) and to be receiving current treatment with a salvage multiple-class drug regimen (HR 13.2; 95% CI 2.3–73.8; p 0.003).

In multivariate analysis, limited treatment options, i.e. susceptibility to one or fewer classes of antiretrovirals, remained significantly associated with previous exposure to more than ten antiretroviral regimens (HR 4.4; 95% CI 1.0–18.0; p 0.049) and with last available HIV RNA >50 copies/mL (HR 3.0; 95% CI 1.1–10; p 0.032).

In this retrospective analysis of the prevalence and characteristics of HIV-1 *pol* mutations in a cohort of Italian patients with vertically acquired HIV-1 infection, major DRMs to N(t)RTIs, NNRTIs and PIs were present in 79%, 65% and 35% of cases, respectively, thus showing higher DRM prevalence than in the adult population [1,2]. Similarly, dual-, triple- and all-class resistance was observed in 41%, 20% and 6% of our patients, respectively. Genotyping results may not be available for the perinatally infected population, particularly for those born and managed in the mid-1990s through the mid-2000s, which could lead to an underestimation of DRM prevalence in the cohort. In high-income settings, 30% to 40% of vertically infected children develop virologic failure over time, however [3]. In our study, a quarter of patients had limited treatment options. They were more likely to have had more than ten previous antiretroviral regimens and were about three times more likely than others to have detectable HIV RNA at the last follow-up. Notably, 7% of the cohort already harboured at least an INSTI resistance mutation.

This study highlights how patients vertically infected with HIV-1 develop a high prevalence of DRMs at long-term follow-up, as has been shown in other studies [4–7]. Such patients pose a therapeutic challenge, which highlights the need for new therapies as well as new strategies aimed at preserving drug susceptibility to current and upcoming antiretroviral classes and at optimizing adherence to therapy [8].

**Table 1**
Demographics of 94 perinatal HIV-infected patients in ARCA cohort

| Characteristic | Value |
|---|---|
| Age | |
| 18–24 years | 30 (32) |
| 25–29 years | 34 (36) |
| ≥30 years | 30 (32) |
| Ethnicity | |
| White | 88 (94) |
| African | 4 (4) |
| Hispanic | 2 (2) |
| Sex | |
| Male | 46 (49) |
| Female | 48 (51) |
| Serology | |
| HCV-Ab[a] | 10 (11) |
| HBsAg[b] | 1 (1) |
| Last virus load | |
| ≤50 copies/mL | 56 (60) |
| >50 copies/mL | 38 (40) |
| Virus load zenith >100 000 copies/mL[c] | 49 (59) |
| Last CD4$^+$ count | |
| <200 cells/mm$^3$ | 8 (8) |
| 200–499 cells/mm$^3$ | 25 (27) |
| ≥500 cells/mm$^3$ | 61 (65) |
| CD4$^+$ nadir <200 cells/mm$^3$[d] | 15 (16) |
| No. of regimen switches (ART and cART) | |
| 1–5 | 55 (58) |
| 6–10 | 24 (25) |
| ≥11 | 15 (16) |
| Last available ART regimen[e] | |
| Monotherapy | 6 (8) |
| Dual therapy | 4 (5) |
| 2 N(t)RTIs | 16 (22) |
| 2 N(t)RTI + INSTI | 5 (7) |
| 2 N(t)RTI + PI | 17 (23) |
| 2 N(t)RTI + NNRTI | 17 (23) |
| Multiregimen | 8 (11) |

ART, antiretroviral therapy; cART, combined antiretroviral therapy; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; INSTI, integrase strand transfer inhibitors; N(t)RTI, nucleos(t)ide inhibitors; NNRTI, nonnucleoside inhibitors; PI, protease inhibitor.

[a] Percentages calculated on total of available HCV serology ($n = 88$).
[b] Percentages calculated on total of available HBV serology ($n = 91$).
[c] Percentage calculated on total of available HIV virus load zenith values ($n = 83$).
[d] Percentage calculated on total of available CD4$^+$ nadir values ($n = 93$).
[e] Percentages calculated on total of last available ART regimen ($n = 73$).

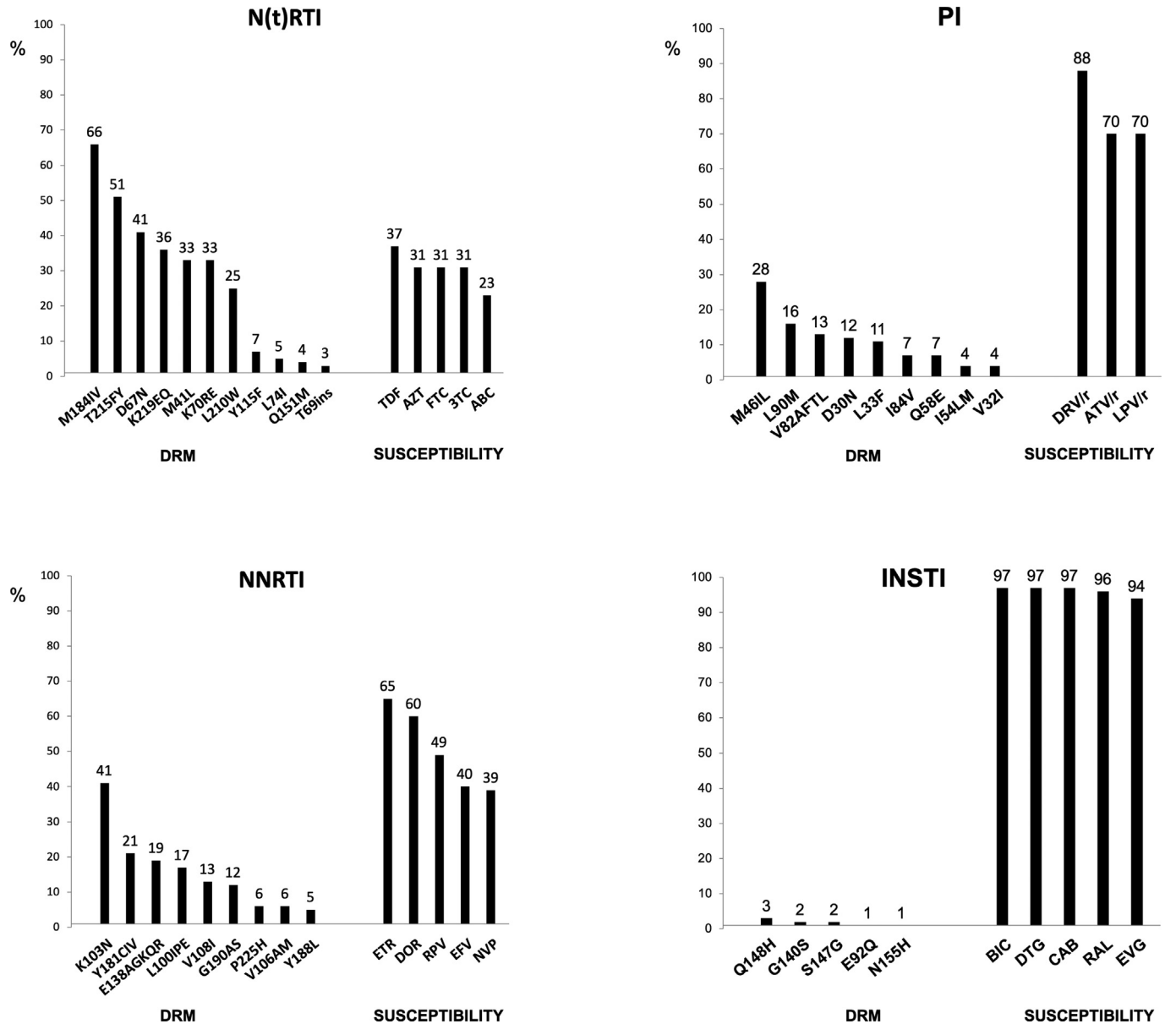


**Fig. 2.** Prevalence of DRM and residual susceptibility to antiretroviral therapy. 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; BIC, bictegravir; CAB, cabotegravir; DOR, doravirine; DRM, drug resistance mutation; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitors; LPV, lopinavir; N(t)RTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitors; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir;/r, ritonavir booster; RPV, rilpivirine; TDF, tenofovir.

## Transparency declaration

All authors report no conflicts of interest relevant to this article.

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