Journal of Clinical Virology 106 (2018) 49–52

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Short communication

Evolution of HIV-1 transmitted drug resistance in Italy in the 2007–2014 period: A weighted analysis

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ARTICLE INFO

Keywords:
HIV infection
Antiretroviral resistance
Transmitted resistance
Weighted analysis

ABSTRACT

Background: Recent studies suggest that transmitted drug resistance (TDR) may be decreasing in latest years, likely because of the reduced frequency of acquired resistance. However, specific risk factors, geographical areas and special HIV-infected populations may be disproportionally affected by TDR.
Objectives: Correlates of TDR and time trends were evaluated from 2007 to 2014.
Study design: We evaluated the genotypic results of 2155 naïve patients enrolled in the I.Co.N.A cohort at 23 clinical Centers in Italy between 2007 and 2014. A weighted analysis was performed to account for the patients enrolled in the cohort in each clinical Centre at each biennium (total number of patients: 3737).
Results: Overall prevalence of TDR was 10.7%. Independent predictors of TDR were sexual risk factor (OR 2.315, p = 0.020) and non-Italian geographical origin (OR 1.57, p = 0.038). The weighted prevalence of TDR was 10.5% with a stable proportion over calendar years. Generally, TDR prevalence was numerically higher, although not significantly, in clinical Centers of metropolitan areas with more than 3 millions of residents as compared to others (11.3% vs. 9.2%). The difference in TDR prevalence between these Centers decreased in more recent years.
Conclusions: A stable frequency of TDR was observed during the most recent years in Italy, with opposite and converging trends in large metropolitan areas as compared to the rest of the country, suggesting a more homogeneous spread of TDR across the country in latest years. Concerns remain for sexual route of infection and non-Italian origin, reinforcing the need for specific prevention strategies prioritizing specific populations.

1. Background

Transmitted drug resistance (TDR) represents a major concern for the efficacy of combined antiretroviral therapy (cART) [1], even showing a stable or even decreasing trend in Europe before 2010 [2,3]. This evidence may be explained at least in part by the stable and marked decrease observed in the frequency of acquired resistance, which has been observed in several clinical settings over the last decade [4–6]. HIV-1 infected populations with different epidemiological characteristics, mainly related to the route of infection and the country of origin may be disproportionally affected by TDR [7–9]. A heterogeneous TDR prevalence is often observed in specific regions of the same country, thus representing a relevant bias in collaborative observational evaluations [2,10]. In order to overcome a possible misevaluation of TDR prevalence due to heterogeneous data sampling across several clinical settings, weighted analysis may be a useful tool

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https://doi.org/10.1016/j.jcv.2018.07.009
Received 24 October 2017; Received in revised form 6 June 2018; Accepted 25 July 2018

for more reliable estimates of TDR prevalence in national and international cohorts [11].

2. Objectives

In a retrospective national longitudinal study, we aimed determining at the time trends of TDR, taking into account epidemiological and geographical factors variously distributed across the Country. To this purpose, we investigated the temporal trends of TDR through a weighted analysis of the I.Co.N.A. (Italian Cohort Naïve for Antiretrovirals) cohort over a 8-years period.

3. Study design

The I.Co.N.A. study is a large observational study storing epidemiological, immunovirological and clinical information of patients who are enrolled when still antiretroviral naïve. We included the genotypic results obtained from 2155 naïve patients at their enrollment in 23 clinical Centers of the ICONA cohort from 2007 to 2014.

Genotyping was based on a partial HIV-1 pol sequence including RT and protease and ranging from 1000 to 1280 nucleotides, depending on the sequencing protocol used at the laboratories at each Clinical Center contributing to the cohort. The Surveillance Drug Resistance Mutation list was used to define TDR [12].

Four homogeneous time intervals (2007–2008, 2009–2010, 2011–2012 and 2013–2014) were considered. Subjects were also grouped according to the size of cities where the clinical Centers are located. A cut off of over 3 millions of residents for larger metropolitan areas was used.

Correlates of TDR were analyzed in a logistic regression model. Temporal trends in TDR were studied by means of the Chi squared test for trends.

A weighted analysis was performed to account for the possible heterogeneous distributions of TDR in areas with different rates of genotype prescription and availability. The weight was based on the number of patients enrolled in the I.Co.N.A. cohort at each clinical Center, the number of those having a genotypic test during each time interval (total number of patients enrolled in the cohort in the 23 Centers during this period: 3737).

4. Results

Over the study period, 2155 genotypic results were retrieved from naïve subjects enrolled in the ICONA cohort: 392 (18.2%), 571 (26.5%), 818 (38%) and 374 (17.4%) were obtained from patients enrolled during 2007–2008, 2009–2010, 2011–2012 and 2013–2014, respectively. Males were 1751 (81.3%) of the study population. Men having sex with men (MSM), heterosexuals, injection drug users (IDUs) and other risk factors (not referred, professional or accidental exposure to contaminated fluids, blood transfusions) accounted for 1048 (48.6%), 826 (38.3%), 133 (6.2%) and 148 (6.9%) subjects, respectively. Overall, 1452 patients (67.4%) were in follow up at 9 clinical Centers of large metropolitan areas (> 3 milions inhabitants). Non-Italian origin was reported in 435 individuals (20.2%) and their prevalence increased overtime, from 15.8% (n = 62) in 2007–2008 to 25.7% (n = 96) in 2013–2014 ($p < 0.001$).

Prevalence of any resistance mutation to antiretrovirals was 10.7% (n = 299). Resistance mutations were 6.0% (n = 130), 4.0% (n = 86) and 2.2% (n = 48) for NRTIs, NNRTIs and PIs, respectively.

Predictors of TDR were evaluated in a logistic regression model (Table 1). In the univariate analysis, a higher risk of TDR was observed in subjects with sexual risk factors (OR 1.638, p = 0.043) and, even though not significantly, in patients of non Italian origin (OR 1.341, p = 0.054) and in those enrolled in clinical Centers of larger metropolitan areas (OR 1.311, p = 0.082). Independent predictors of TDR were confirmed to be the sexual risk factors (OR 2.315, p = 0.020) and the geographical origin (OR for Italian origin 1.574, p = 0.038).

A weighted analysis was performed to correct for the number of patients enrolled in the I.Co.N.A. cohort and for those who received a genotypic test at each clinical Center during the specific time interval, showing a weighted prevalence of TDR of 10.4%. A stable weighted proportion of TDR was observed over calendar years, ranging from 10.3% in 2007–2008 to 10.7% in 2013–2014. The weighted prevalence of TDR for NRTIs, NNRTIs and PIs was 6.1%, 4.0% and 2.3%, respectively. Little and fluctuating variations of class resistance were observed over time.

According to the weighted analysis, TDR prevalence was higher in clinical Centers of larger metropolitan areas compared to those of other Italian areas, even though not significantly (11.3% vs. 9.2%, p = 0.112). Nevertheless, the difference between these Centers decreased in more recent years: the prevalence of TDR to any antiretroviral class decreased, although not significantly, from 12.0% to 10.6% in Centers of larger metropolitan areas and increased with a borderline significance from 4.8% to 10.8% in the other clinical Centers (p = 0.056).

As shown in Fig. 1, the prevalence of class resistance to NRTIs decreased from 9.2% in 2007–2008 to 4.6% in 2013–2014 in larger metropolitan areas (p = 0.039), while it did not significantly vary over time, ranging from 3.3% in 2007–2008 to 3.6% in 2013–2014 in other areas. The prevalence of TDR to NNRTIs was observed to be stable in larger metropolitan areas, with small fluctuations from 5.7% to 5.1%, while it increased from 1.8% to 5.9% in other clinical Centers (p = 0.067). No significant variation was found in PI resistance.

5. Conclusions

Temporal trends of TDR were previously evaluated in Italy from 2000 to 2010, showing a declining prevalence of resistance [4]. Our study extends these results to the period following 2010, revealing a stabilization in TDR prevalence, particularly in larger metropolitan areas. In the same time interval, a clear evidence has emerged of a marked reduction of acquired resistance in Europe and Italy [5,6]. The lack of a continuous decline in TDR observed in our study may indicate a role of the early stage infection in the transmission of HIV, suggesting a possible acquisition of TDR not only from treated subjects failing their antiretroviral therapy but also onward transmission from recently seroconverted naive individuals [13,14].

Among correlates of TDR, the route of infection has been shown to have an impact on the transmission of resistant HIV-1 strains, as the homosexual risk factor is linked with a higher TDR prevalence [7]. Moreover, special populations may also be disproportionally affected by higher prevalence of TDR, as some evidence has emerged in this study about the possible increase of TDR in migrants [8]. Even if non-B subtypes have been associated with a lower prevalence of TDR when compared to B variants [4,9], this may not be the case for some viral variants. In fact, relevant TDR prevalence was reported in subjects carrying the F1 subtype in a recent Italian survey evaluating transgender South American subjects [15].

As relevant epidemiological features are reported to be heterogeneously represented in specific regions of our country, the different proportions of subjects tested for ARV resistance among those included in different Clinical Centers of the ICONA cohort may represent a relevant bias in the effort to estimate the burden of TDR in our national setting [2].

Some limitations of our work should be acknowledged: first of all, the retrospective nature of the analysis, the huge variability in resistance testing attitudes at each Clinical Center, the variability in the number of resistance tests available at each time interval. All these factors have been only partially corrected by means of the weighted analysis. Moreover, we were not able to study the trends of resistance to integrase inhibitors, as most of patients were not tested for these mutations at baseline because of the limited usage of such drugs in the