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Short communication

Prevalence of resistance-associated mutations in newly diagnosed HIV-1 patients in Greece☆

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Abstract

The prevalence of HIV-1 drug resistance mutations in naïve patients has been previously shown to differ greatly with the geographic origin. The purpose of this study was to prospectively estimate the prevalence of HIV-1 drug resistance in Greece by analyzing a representative sample of newly HIV-1 diagnosed patients, as part of the SPREAD collaborative study. Protease (PR) and partial reverse transcriptase (RT) sequences were determined from 101 newly diagnosed HIV-1 patients, in Greece, during the period September 2002–August 2003, representing one-third of the total newly diagnosed HIV-1 patients in the same time period. The prevalence of HIV-1 drug resistance was estimated according to the IAS-USA mutation table taking into account all mutations in RT and only major mutations in PR region. The overall prevalence of resistance was 9% [95% confidence interval (CI): 4.2–16.2%]. The prevalence of mutations associated with resistance to NRTIs was 5% (95% CI: 1.6–11.2%), for NNRTIs was 4% (95% CI: 1.1–9.8%), while no major resistance mutations were found in PR. No multi-class resistance was detected in the study population. The prevalence of resistant mutations in the recent seroconverters was 22%. For two individuals, there was clear evidence for transmitted resistance based on epidemiological information for a known source of HIV-1 transmission. The prevalence of the HIV-1 non-B subtypes and recombinants was 52%.
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Until now, there are several drugs available for treating HIV-1 infection belonging to four classes, targeting the protease, reverse transcriptase (RT), and envelope genes of the virus (Yeni et al., 2004; EACS European guidelines, 2003), while several other drugs are under development and clinical evaluation. One of the main obstacles of HAART is the development of drug resistance, which not only diminishes the therapeutic effect of treatment, but additionally due to the cross-resistance within a drug class, it compromises alternative therapeutic options (Lorenzi et al., 1999; Durant et al., 1999; Hirsch et al., 2003). Thus, for the better clinical management of HIV-1 infection, resistance testing has become a standard of care strongly recommended for treated patients when virological failure happens (Hirsch et al., 2003; Vandamme et al., 2004).

Transmission of resistance has been documented to occur and according to previous studies (Hecht et al., 1998; Boden et al., 1999; Little et al., 1999; Wensing et al., 2003) differs with the geographic origin (Vandamme et al., 2004; Descamps et al., 2001; Perno et al., 2001; Yerly et al., 1999; Little et al., 2002; Violin et al., 2004). Given that primary resistance is associated with a prolonged time to viral suppression (Little et al., 2002), updated guidelines recommend resistance testing for all patients with recent HIV infection (<6–12 months according to the Euroguidelines and IAS-USA panel, respectively) (Hirsch et al., 2003; Vandamme et al., 2004). Moreover for chronically infected patients recommendations are based, mainly on the prevalence of resistance among untreated individuals within the local population (Hirsch et al., 2003; Vandamme et al., 2004).

Results of previous studies differ greatly in the prevalence of documented resistance among treatment patients in Europe, whereas different methodology – sampling strategy, time of infection, definition of resistance, etc. – was used in each of them (Descamps et al., 2001; Perno et al., 2001; Yerly et al., 1999; Van Vaerenbergh et al., 2001; Magiorkinis et al., 2002; Birk and Sönnerborg, 1998). Preliminary results on the estimation of the overall resistance-associated mutations across Europe, based on retrospectively collected data sampled in the time period 1996–2002, reported 10.5% with substantial differences between countries (Wensing et al., 2003). This figure is similar to the estimated prevalence −8%—of viral isolates showing reduced antiretroviral-drug susceptibility among newly diagnosed patients, in 10 US cities during 1997–2001 (Weinstock et al., 2004) or the prevalence 12% of recently infected patients with major drug resistance mutations in 10 North American cities (Little et al., 2002).

It was our purpose to prospectively estimate the prevalence of HIV-1 drug resistance in Greece by analyzing a representative sample of newly HIV-1 diagnosed patients during September 2002–August 2003. For this purpose, 11 HIV/AIDS Clinics in Athens recruited newly diagnosed HIV-1 infected patients in the period September 2002–August 2003, for the analysis of the prevalence of genotypic drug resistance in untreated patients in Greece as part of the SPREAD (strategy to control SPREAD of HIV-drug resistance) collaborative study (http://www.spread-europe.org). The inclusion criteria for the study were: (1) patients diagnosed HIV-1 seropositive for a first time (newly diagnosed HIV-1 infected patients) and (2) they should have not received any antiretroviral medication in the past. The identification of all newly diagnosed HIV-1 infections was further confirmed for all patients by the National HIV/AIDS Surveillance System at the Hellenic Center for infectious diseases control.

In the period September 2002–August 2003, 101 newly diagnosed HIV-1 patients were recruited in the study representing 32% of the total newly diagnosed HIV-1 patients, in Greece in 2003, according to the National HIV/AIDS Surveillance System (http://www.keel.org.gr). HIV-1 RNA was isolated using Gentra PURESCRIPT® RNA purification kit (Gentra Systems Inc., USA) according to manufacturer's recommendation. The HIV-1 partial RT (amino acids 41-223) and the complete PR region of *pol* were characterized by using the TRUGENE® HIV-1 genotyping test, according to the manufacturer's recommendations (Bayer AG, Germany). Resistance mutations were identified according to the IAS-USA mutation table updated in 2004 (Johnson et al., 2004). The prevalence of HIV-1 drug resistance was estimated by taking into account all mutations in RT and only major mutations in PR region (Johnson et al., 2004). Secondary mutations in PR were not counted as molecular indicators associated with resistance given their high prevalence particularly for some of the HIV-1 non-B subtypes (Vandamme et al., 2004; Kantor and Katzenstein, 2003; Turner et al., 2004).

All PR and partial RT sequences were aligned with reference sequences, including all previously characterized HIV-1 subtypes and circulating recombinant forms (CRFs) available at http://hiv-web.lanl.gov (Kuiken et al., 2002), using CLUSTAL W (v. 1.74) (Thompson et al., 1994). HIV-1 subtypes and recombinants were determined by phylogenetic analysis using Bayesian method under the general time reversible (GTR) model including a Γ distributed rates heterogeneity among sites, as implemented in MrBayes (v. 3.0) (Huelsenbeck et al., 2001), bootscanning analysis as implemented in Simplot (3.2 beta version) (http://sray.med.som.jhmi.edu/Raysoft/Simplot) and maximum likelihood method under the Tamura–Nei model including Γ rates, as implemented in TREE-PUZZLE program (v. 5.2) (Schmidt et al., 2002). For Bayesian inference, metropolis coupled markov chains Monte Carlo (MC^3) chains run for 10^6 generations with a burnin of 1×10^5.

To confirm that the sample of patients included in this study was representative of the total population of newly HIV-1 diagnosed patients in Greece in 2003, we compared the distribution of age, gender and transmission group between the two populations using the *t*-test or χ^2-test, as appropriate. The presence of association between specific mutations and HIV-1 subtype was examined by the χ^2-test.

Blood samples were collected prospectively from 101 patients diagnosed HIV-1 seropositive for a first time at 11 HIV/AIDS clinics in Athens. The characteristics of the 101 individuals participating in the study are shown in Table 1.

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