HIV-1 Antiretroviral Drug Resistance in Recently Infected Patients in Abidjan, Côte d’Ivoire: A 4-Year Survey, 2002–2006

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ABSTRACT

We performed HIV-1 drug resistance genotypic analysis of viral isolates from 100 antiretroviral (ARV)-naive, recently HIV-1-infected (between 2002 and 2006) individuals from Abidjan (Côte d’Ivoire). The overall prevalence of HIV-1 variants with resistance mutations to reverse transcriptase, protease, or fusion inhibitors was 6%. The majority of isolates were CRF02_AG. Compared with a previous study carried out by our group in 2001–2002 in a similar population in Abidjan, our findings confirm the circulation and transmission of HIV-1 carrying key ARV drug resistance mutation.

INTRODUCTION

SUB-SAHARAN AFRICA HAS BEEN SEVERELY HIT by the HIV-1 pandemic but now has the opportunity to offer highly active antiretroviral therapy (HAART) to those who need it. Treatment failures under HAART are strongly associated with the emergence of resistant viral variants. Drug-resistant HIV-1 has been widely characterized in developed areas.1 In developing countries, it is necessary to investigate whether resistant mutants are circulating in untreated patients at a time when antiretroviral (ARV) drugs are more intensively introduced.

In West Africa, Côte d’Ivoire has the highest HIV-1 prevalence rate (4.7%) (http://www.unaids.org, update 2006). In this country, HAART has been available since 1998 through the UNAIDS/Côte d’Ivoire program of access to HIV/AIDS treatment drugs. In 2002, a longitudinal survey of primary ARV drug resistance in untreated patients was launched with a cohort of recent seroconverters associated with the National Blood Bank of Abidjan (Primo-CI ANRS 1220 cohort). We present here the findings of a 4-year survey.

MATERIALS AND METHODS

The procedures of the Primo-CI ANRS 1220 cohort have been described previously.2,3 In summary, enrollment in the cohort was proposed to each blood donor at the National Blood Bank of Abidjan who had a delay of less than 36 months since the estimated date of seroconversion (midpoint between the last negative and the first positive HIV test). All patients were adults and ARV drug naïve at study entry. All patients who accepted participation gave written informed consent. Blood samples were collected at inclusion to measure CD4+ cell count (FACScan; Becton Dickinson, Aalst-Erembodegem, Belgium) and plasma HIV-1 RNA load (Amplicor HIV-1 Monitor, version 1.5; Roche Diagnostics, Indianapolis, IN); threshold of

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The Primo-CI protocol was approved by the ethics committees of the National Ivorian Program on AIDS and the institutional review board of the French Agency for Research on AIDS (ANRS, France).

Since January 2002, genotype resistance tests were systematically performed on the baseline plasma samples for all HIV-1-infected patients included in the cohort. Reverse transcriptase (RT), protease (Prot), and gp41 (HR1 and HR2 domains) sequences were analyzed and aligned with consensus sequences of M subtypes (A–D, F–H, J, and K) and circulating recombinant forms (CRFs) documented in West and West Central Africa and available from the Los Alamos HIV sequence database (http://hiv-web.lanl.gov/). Phylogenetic trees were constructed for the three genes, using CLUSTAL W^4 software.
FIG. 1. (Continued)
Prot, RT, and gp41 resistance mutations were reported as listed by the International AIDS Society USA panel, update Fall 2006 (www.iasusa.org) and the genotypic resistance interpretation was performed with the ANRS algorithm, update 2006 (www.hivfrenchresistance.org).

RESULTS

From July 2002 to June 2006, 105 patients recently infected with HIV-1 (47% women) were recruited consecutively. At baseline, the mean age was 30 years, the median interval since the estimated date of seroconversion was 9.4 months (range, 2.1–35.8 months), the median CD4+/H11001 T lymphocyte cell count 445/000/9262 l (range, 145–1120/000/9262 l), and the median plasma HIV-1 level was 4.4 log10 (range, 2.3–6.3 log10). Most patients (93%) were at CDC stage A1.

At least one positive polymerase chain reaction (PCR) of the three genes (RT, protease, and gp41) was obtained for 100 patients. Five isolates could not be amplified. Phylogenetic analysis of the three genes was performed for 100 patients, showing a majority of CRF02_AG (n = 88, 88%) followed by subtype A (n = 7; 7%) and CRF06_cpx (n = 2; 2%). Six (6%) strains were intersubtype recombinants (two CRF02_AG/CRF06_cpx, two CRF02_AG/CRF09_cpx, and two CRF02_AG/CRF10_cpx) (Fig. 1).

Resistance mutations were detected in viruses from 6 of 100 (6%) patients (Table 1). In RT, the nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations M41L and K219Q, which are selected by thymidine analogs, were found in two patients and the mutation Y115F was present in one patient. Nucleoside resistance mutations were observed in two patients: K101E (one patient) and K103N; P236L (one patient). Polymorphic substitutions L100F and K65E, situated at resistance mutation loci, were also present in two patients. In the protease gene, the major resistance mutation M46L, encoding resistance to indinavir (IDV), was observed in one patient. Frequent polymorphisms observed in HIV-1 non-B subtypes were retrieved at position 36 (M36I, 97%) and position 20 (K20I, 89%). In gp41, no primary resistance mutation to enfuvirtide (T-20) was noticed after sequencing HR1 and HR2 regions of 47 strains. Frequent polymorphisms (N42S [70%] in the HR1 domain and between positions 127 and 162 in the HR2 domain, corresponding to T-20 amino acid sequence domain) were also noticed. Overall, according to the last ANRS resistance algorithm, 3 of 100 (3%) strains were resistant to at least one drug: one patient had resistance to IDV and two patients had resistance to NNRTIs (efavirenz and nevirapine).

DISCUSSION

Thus, in this population of recently HIV-1-infected adults in Abidjan, the prevalence of key drug resistance mutations was 6%, with detection of NRTI, NNRTI, and protease inhibitor (PI) resistance mutations, and 3% of patients were resistant to at least one drug.

These data are similar to those of a previous resistance study that we made in 2001–2002 in 107 untreated patients in Abidjan, and in which we found a similar (5.6%) prevalence of isolates carrying resistance mutations. The present study confirms that CRF02_AG is highly predominant in Abidjan, where a few intersubtype recombinants also circulate. It also confirms that a significant percentage of resistant variants is currently transmitted in Abidjan. In these resistant strains, the resistance pattern is in accordance with the availability of drugs in the country, where IDV was one of the first PIs to be used in the UNAIDS/Côte d’Ivoire drug access initiative, and where nevirapine was used early in mother-to-child HIV-1 transmission prevention programs. During the first years of the pilot UNAIDS/Côte d’Ivoire drug access initiative, anarchic drug distribution and nonstructured therapeutic interruption have been incriminated in HIV drug resistance spread. However, the stability of the prevalence of the drug resistance mutations between 2001–2002 and 2002–2006 also suggests that the more recent large-scale programs of access to HAART that have been launched in the country since 2002 might have had fewer consequences in terms of drug resistance spread.

As transmission of resistance mutations has important public health and clinical implications, these data plead for continuing antiretroviral resistance sentinel surveys in Côte d’Ivoire.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Resistance mutations</th>
<th>HIV-1 subtype</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Prot</td>
</tr>
<tr>
<td>1</td>
<td>—</td>
<td>K219Q</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>Y115F</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>K101E</td>
</tr>
<tr>
<td>4</td>
<td>M46L</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>—</td>
<td>K103N; P236L</td>
</tr>
<tr>
<td>6</td>
<td>—</td>
<td>M41L</td>
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</tbody>
</table>

*Protease and RT mutations: all protease and RT inhibitors mutations as listed at www.iasusa.org, update Fall 2006.
ACKNOWLEDGMENTS

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SEQUENCE DATA

The sequences described in this study have been deposited in GenBank with accession numbers EF116643 to EF116688 for gp41 sequences, EF116689 to EF116777 for protease sequences, and EF116778 to EF116864 for reverse transcriptase sequences.

REFERENCES


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