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HIV-1 Genetic Diversity and Drug Resistance Mutations Among Treatment-Naive Adult Patients in Suriname

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3 HIV-1 genetic diversity and drug-resistance mutations among treatment-naïve adult
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5 patients in Suriname.
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52 Running head: HIV-1 subtypes and genotypes in Suriname
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Abstract (146 words)

The molecular epidemiologic profile of HIV-1 in Suriname was determined through protease (PR) and reverse transcriptase (RT) sequences obtained from HIV-1 strains collected from 100 drug-naïve HIV-1-infected persons. Subtype determination revealed that most viruses were of subtype B (94.9%) in both PR and RT genomic regions, followed by B/D recombinants (5.1%). Analysis of drug-resistance mutations showed only one transmitted drug-resistance mutation (TDRM) (V75M) in a single strain. The genetic data obtained can serve as a baseline for Suriname to monitor emerging mutations. This study reveals that the HIV-1 epidemic in Suriname is still characterized by a low TDRM rate (1%) and a low level of subtype diversity. However, both genes display a high genetic polymorphism. This high polymorphism may ultimately lead to drug resistance. Continuous monitoring of the baseline resistance is therefore a prerequisite to safeguard effective long-term treatment for people living with HIV-1 in Suriname.

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3 Introduction
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5 Suriname is located on the northeastern coast of South America, between Guyana and
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7 French Guiana, and is the smallest sovereign state on this continent, with a population of
8 nearly 550,000 inhabitants. Due to its colonial history, Suriname's population consists of a
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10 wide variety of ethnic and cultural groups. In addition, substantial migratory fluxes exist
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12 between Suriname and Europe (especially the Netherlands), but also to and from
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14 neighboring countries and the Caribbean region. In 2012, the estimated prevalence rate of
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16 adults (15- to 49-year-old age group) living with HIV/AIDS in Suriname was around 1.1%
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18 according to UNAIDS estimates.¹ The global estimated HIV prevalence in adults in the
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20 Caribbean and Latin America was 1.0% and 0.4%, respectively. In Latin America it ranged
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22 from 0.2% in Mexico to 1.4% in Belize, while in the Caribbean it ranged from < 0.1% in Cuba
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24 to 3.3% in the Bahamas. In the Netherlands, it was 0.2%.
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31 Treatment of HIV-1-infected patients in Suriname started on a very small scale in 1996,
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33 when it was confined to a specific subset of well-motivated individuals and was provided by
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35 a few specialists in internal medicine through gifts of antiretroviral (ARV) drugs from the
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37 Netherlands and the USA. With the establishment of a Revolving Fund in 2000, access to ARV
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39 treatment was broadened. National provision of ARV therapy free of charge started in 2005.
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41 The initiation and monitoring of treatment also shifted from secondary healthcare to
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43 primary healthcare in 2005. The number of HIV-1-infected patients receiving ARV therapy
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45 has thus dramatically increased since 2005, from 345 in 2005 to 1428 in 2013.² The common
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47 first-line ARV regimens use a combination of two nucleoside and one non-nucleoside reverse
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49 transcriptase inhibitors (NRTIs and NNRTIs), all targeting the reverse transcriptase enzyme of
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51 HIV-1. In 2009, the national standard first-line treatment in Suriname consisted of the
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53 combination of Zidovudine (AZT), Lamivudine (3TC) and Nevirapine (NVP). Patients who fail
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3 this first line of treatment are switched to a protease inhibitor (PI)-based regimen with a
4 backbone of NRTIs. Nevertheless, the number of different RTI and PI drugs currently
5 available in Suriname remains limited.
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10 The prevalence of transmitted drug resistance (TDR) is highly variable worldwide, with
11 rates ranging from 0% to 25%.³ The highest rates are reported in countries with a long-
12 standing use of ARV drugs. The WHO distinguishes three groups of TDR prevalence: low
13 (<5%), moderate (5–15%), and high (>15%).⁴ A systematic review of the literature showed
14 that the rates of TDR in low- and middle-income countries increased between 2003 and
15 2010, reaching a peak of 6.6% in 2009.⁵ Given that HIV-1 variants have not yet been
16 described in Suriname and ARV treatment is started without prior genotypic testing due to
17 resource limitations, knowledge of the polymorphism of HIV-1 protease (PR) and reverse
18 transcriptase (RT) as well as mutations, whether or not associated with resistance, was
19 critical. We therefore conducted a molecular study in a cohort of treatment-naïve adult
20 patients to investigate the level of natural polymorphism present in PR and RT genes,
21 determine the subtype distribution and identify potential drug-resistance-associated
22 mutations.
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43 Materials and Methods

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45 Between August and October 2009, a prospective cross-sectional study was conducted
46 using plasma samples collected from 101 HIV-1-positive adults naïve to ARV drugs.
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48 Participants included in this study were selected from the ambulatory care services of the
49 four hospitals in the capital Paramaribo (Academisch Ziekenhuis Paramaribo, Diakonessen
50 Ziekenhuis, Rooms Katholiek Ziekenhuis and 's Lands Hospitaal) and the ten largest
51 healthcare centers of the Regional Health Services, which cater to the capital and the
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3 surrounding areas. The study population consisted of ARV-naïve adult HIV-1-positive persons
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5 living in Paramaribo and the surrounding areas with a CD4 count ≤ 385 (≤ 350 including a
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7 10% range). This cut-off point was selected to include patients who were expected to start
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9 ARV treatment within one year. A minimum sample size of 70 was calculated with EPI Info
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11 (95% confidence level). For this calculation, the expected frequency of primary TDR in
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13 Suriname was set at 5%. This expected frequency was based on international figures, the
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15 relatively young epidemic and the relatively short history of widespread use of ARV in
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17 Suriname. The genotyping was performed as an additional diagnostic test for the study
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19 participants. The study was approved by the Ministry of Health's national ethics committee.
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24 Blood samples (2 × 5 mL) were drawn by venous puncture in EDTA tubes. Plasma was
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26 separated and stored at -80°C until RNA extraction for viral load measurement and
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28 genotyping. RNA was isolated from 1 mL of plasma with the Nuclisens® EasyMag®
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30 (bioMérieux, Marcy l'Etoile, France), as recommended by the manufacturer. The viral load
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32 was determined using the bioMérieux NucliSENS® EasyQ VIH-1 v1.2 kit. For genotyping, RNA
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34 was reverse-transcribed to cDNA and amplified for partial reverse transcriptase and protease
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36 genes using the ANRS (Agence Nationale de Recherche sur le Sida) consensus sets of primers
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38 (<http://www.hivfrenchresistance.org/ANRS-procedures.pdf>). The amplified products were
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40 sent to Beckman Coulter Genomics (<http://www.cogenicsonline.com>) for direct sequencing
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42 on both strands. Chromatograms were verified, analyzed, and interpreted using CEQ 2000XL
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44 software (Beckman Coulter Inc., Fullerton, CA, USA). For both PR and RT sequences, the
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46 sense and antisense strands of each fragment were aligned and compared to the wild-type
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48 HIV-1 virus HXB2 reference sequence (GenBank accession number K03455).
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54 The PR and RT nucleotide sequences obtained were aligned using MEGA5 software
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56 with known group M reference sequences pooled from the HIV-1 database
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3 (<http://hiv.lanl.gov/>). The phylogenetic trees were inferred using the Maximum Likelihood
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5 method based on the HKY85 + G model of nucleotide evolution. Subtypes were also
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7 identified at the same time on PR and RT sequences using the Calibrated Population
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9 Resistance (CPR) tool in the Stanford Database (<http://cpr.stanford.edu>) with the last
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11 updated version 6.0. The presence of drug resistance-associated mutations (DRMs) in PR and
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13 RT was detected and drug susceptibility was predicted using the French ANRS HIV-1
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15 genotypic drug resistance algorithm version 25, updated in September 2015
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17 (<http://www.hivfrenchresistance.org/2014/Algo2014.pdf>). Evidence of TDR was defined
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19 based on the WHO list for surveillance of drug-resistance mutations, which did not include
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21 resistance mutations that can occur naturally as polymorphisms in the absence of drug
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23 pressure.⁶
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31 Results

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33 One hundred and one HIV-1-infected adult naïve patients were recruited in
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35 Paramaribo. There were 55 women and 46 men. The mean age was 38 years (range, 18–62)
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37 for women and 39 (range, 23–58) for men. The viral load (VL) ranged from 25 to 10⁶
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39 copies/mL. One patient was excluded for genotyping due to a viral load below 100
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41 copies/mL. Successful amplification was observed for 99 PR and 95 RT genes. Amplification
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43 of both genes could be obtained for 94 samples. Phylogenetic analyses together with the
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45 CPR tool showed that all RT sequences (n=95) clustered with subtype B. All but five PR
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47 sequences were subtype B (95%). The five non-B PR sequences were assigned to the D
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49 subtype.
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55 PR and RT sequences were analyzed for polymorphisms, which were defined as any
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57 amino acid change compared to the B subtype consensus sequence HXB2 (Tables 1 and 2).
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3 Several major and minor mutations were detected. For PR, 82 of the 99 sequences (82.8%)
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5 analyzed harbored two or more mutations. Among them, 18% (n=17/82) of the sequences
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7 harbored five to eight mutations. Alignment of the sequences showed that overall, at least
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9 one polymorphism had occurred at 38 of 99 (38.4%) amino acid positions (Table 1). In
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11 particular, V3 displayed a fixed mutation with 100% of sequences mutated, followed by the
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13 highly polymorphic L63, S37, V77, I15, R41, T12 and I72. Some of these polymorphic amino
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15 acid substitutions corresponded to positions of secondary resistance (in descending order:
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17 V77I, I15V, L63P, M36I, D60E, I62V and H69K/Q/Y/R for those over 15% frequencies).
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19 Similarly, RT sequences exhibited polymorphic substitutions at 82 of 250 (32.8%) amino acid
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21 positions (Table 2). Substitutions found in more than 40% of the study subjects occurred at
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23 Q207, R211, E122, L214, S162, T200, V35 and I178. None of these positions corresponded to
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25 positions of drug resistance.
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31 Sequence analysis for the presence of DRMs in PR according to the French ANRS
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33 algorithm, version 25, revealed no major mutation conferring drug resistance. However, we
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35 detected one isolate carrying mutations L10V, G16E, M36I, D60E and I62V, which confer a
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37 resistance to Atazanavir (ATV) and a possible resistance to Saquinavir (SQV) (Table 3). A
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39 second isolate was detected harboring substitutions L10LV, I15V, K20R, I62V, L63P, H69Q,
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41 A71V and V77I, which together confer resistance to SQV and Lopinavir (LPV) and a possible
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43 resistance to ATV. A third isolate, carrying mutations L10I, I15V, M36I, I62V and H69Q,
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45 implicated in resistance to SQV and a possible resistance to Tipranavir (TPV), also harbored
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47 the V179D mutation on RT (see below). Other combinations of minor amino acid mutations
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49 were detected, associated with possible resistance to SQV for 16 isolates, ATV for five
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51 isolates, TPV for two and LPV for one isolate (Table 3). Finally, isolates carrying mutations
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3 associated with possible resistance to multiple drugs were identified, with SQV and ATV for
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5 two isolates, SQV and TPV for two as well as LPV and ATV for one isolate (Table 3).
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8 With regard to the presence of DRMs in RT, one isolate out of 95 (1.05%) exhibited a
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10 major DRM (V75M), conferring resistance to the NRTI Stavudine (d4T) (Table 3). This isolate
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12 did not bear resistance mutations to NNRTIs and PIs. In addition, two isolates presented the
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14 V179D mutation that confers a possible resistance to Rilpivirine (RPV), while three others
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16 presented the V106I mutation that does not confer any resistance alone, nor a possible
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18 resistance, to NRTIs or NNRTIs.
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22 According to the WHO list for surveillance of DRMs, the overall prevalence of TDR in
23
24 Suriname was 1% with only one isolate bearing a DRM to the NRTI Stavudine.
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27 28 29 Discussion

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31 This study allowed us to document the circulating HIV-1 subtypes in Suriname and
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33 present the first published data on TDR in HIV-1-infected individuals in Suriname. The most
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35 prevalent HIV-1 clade observed in Suriname is subtype B (95%), the remainder being B/D
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37 intersubtype recombinants (5%). Predominance of subtype B is also observed in neighboring
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39 countries (Venezuela, French Guiana and Northern Brazilian states) and in the Caribbean,
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41 even though its prevalence varies over a wide range across the different countries.⁷⁻¹² These
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43 results are also comparable to the Netherlands.^{13, 14}
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48 A high level of polymorphism on both PR and RT genes was found in our population.
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50 Similar results were obtained in the region, where a high genetic diversity was observed in
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52 PR and RT genes in Venezuela, French Guiana and Brazil.^{9, 10, 15} Despite the high level of
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54 polymorphism on both PR and RT genes in our cohort, the genotypic drug-resistance analysis
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56 uncovered only one drug resistance mutation for RT (V75M). The 1% level of transmitted
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3 HIV-1 drug resistance in Suriname is regarded as low according to the WHO classification.
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5 This is in line with recent results from French Guiana with a reported 4.6% prevalence of
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7 TDR, but in contrast with other countries in the region, given that the median overall TDR
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9 prevalence in Latin America and the Caribbean between 2000 and 2013 was 7.6%.^{3,9}
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12 The absence of major drug resistance mutations is consistent with an ARV-naïve
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14 population in a country where structural use of anti-HIV-1 drugs has been introduced
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16 relatively recently. These results can therefore serve as a baseline for Suriname. Since the
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18 detected V75M mutation confers resistance to Stavudine, which is only used in Suriname as
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20 an alternative drug in the first-line treatment for patients with anemia, these results become
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22 even more favorable. The practice of starting ARV treatment without prior genotypic testing
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24 is therefore not challenged in the current situation with limited resources and very low drug
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26 resistance. Nevertheless, the high degree of PR polymorphism at key amino acid positions
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28 known to be associated with drug resistance in HIV-1 subtype B is a concern for long-course
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30 PI treatment of people living with HIV-1. These results imply that PR and RT DRMs deserve
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32 monitoring to optimize first-line antiretroviral regimens in Suriname.
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4
5 Wongsokarijo).
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10 Sequence Data

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12 The GenBank accession numbers for the sequences are KX390878 to KX390977.
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17 Author Disclosure Statement

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19 The authors have no competing interests to disclose.
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2 TABLE 1. Amino acid substitutions in the HIV-1 protease of isolates from 99 patients.
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6	Number of strains	Q2	V3	P9	L10	T12	I13	K14	I15	G16	Q18	L19	K20	L33	E35	M36	S37	P39	R41	K43	K45
7	99	H1	I99	A1	I3, V4	A4, AEK1, ADN1, D2, E18, EQ1, G1, K4, N8, P3, Q3, S2	MV1, V9	E2, R11	V50	E10	H1	I23, Q1, T1, V9	R4	V2	D16	I14, L1	C2, D2, DN1, E1, H1, KN1, N71	Q1, S1	K49	R5	R2
8		1.0	100.0	1.0	7.1	48.5	10.1	13.1	50.5	10.1	1.0	34.3	4.0	2.0	16.2	15.2	79.8	2.0	49.5	5.1	2.0

13	Number of strains	R57	D60	I62	L63*	I64	E65	C67	H69	K70	A71	I72	V75	V77	P79	V82	N83	T91	I93	F99
14	99	K9	E16	V28	AP2, APS1, HP1, HPQ1, P34, PS3	L3, V28	D5, K1	H1, W1, Y2	K1, KQ1, Q16, R1, Y9	E1, N1, Q1, R4, T28	T7, V7	E2, L1, M1, MV1, T2, V37	I2	I68	H1, L1	I4	H1	N1	L31	I1
15		9.1	16.2	28.3	94.9	31.3	6.1	4.0	28.3	35.4	14.1	44.4	2.0	68.7	2.0	4.0	1.0	1.0	31.3	1.0

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20 The gray boxes show polymorphic positions (>40%) and the boxed columns point to the positions of drug-resistance mutations according to the French ANRS algorithm, v25 September 2015.
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22 Numbers after the mutated amino acid designation represent the number of strains with the respective substitution.

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24 * additional substitutions at the L63 position: A1, C8, E1, H17, HQ1, IT1, K1, N3, Q4, R2, S11, T2.
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1
2 TABLE 2. Amino acid substitutions in the HIV-1 reverse-transcriptase of isolates from 95 patients.
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Number of strains	L12	P14	M16	P19	K20	V21	Q23	W24	E28	E29	K32	L34	V35	E36	I37	T39	E40	E42	G45	K46	S48	K49	I50
95	W1	Q1	T1	Q1	I1, R3	I1	H2	R2	G1	G2	E2, R8	F1	E1, I25, IK1, IT1, M3, R1, T10	AQ1	M1	A3	D19, K1, Q1	K1	R1	N1	T2	R14	N1
	1.1	1.1	1.1	1.1	4.2	1.1	2.1	2.1	1.1	2.1	10.5	1.1	44.2	1.1	1.1	3.2	22.1	1.1	1.1	1.1	2.1	14.7	1.1

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Number of strains	E53	T58	V60	K64	K66	T69	V75	E79	K82	F87	G93	G99	K102	K104	V106	T107	V108	V118	D121	E122	D123	R125	I135
95	D1	N1	I7	R3	N1		M1	D2, G1	R2	L1	R1	R2	Q2, R1	R4	I3	S1	I1	I6	H3, Y3	K62, P2, Q2	E26, EKN, N7	K1	ATV1, L1, MV1, R3, RT1, T16, V7
	1.1	1.1	7.4	3.2	1.1	2.1	1.1	3.2	2.1	1.1	1.1	2.1	3.2	4.2	3.2	1.1	1.1	6.3	6.3	69.5	35.8	1.1	31.6

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Number of strains	I142	Q145	A158	F160	S162	S163	T165	K166	E169	F171	K173	Q174	N175	P176	D177	I178	V179	V189	G190	D192
95	K1, T2, V25	C1	S1	C1	A3, C43, HY1, N1, NY1, Y2	T1	I6	R3	D10	Y2	DN1, E2, Q1, R3, T1	E1, H4, K1, L1, R1	Y1	S1	E19, N1, NS1	L27, M13, V1	D2, T1, I24	I2	R1	E1
	29.5	1.1	1.1	1.1	53.7	1.1	6.3	3.2	10.5	2.1	8.4	8.4	1.1	1.1	22.1	43.2	28.4	2.1	1.1	1.1

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Number of strains	I195	G196	Q197	T200	I202	E204	Q207	R211	L214	T216	L228	E233	L234	H235	P236	P243	V245	E248
95	L1, V1	D1, E17, RS1, S1, V1	E1, H2, K1, KR1, L1	A44, E2, I2, S1, V1	V7	D2, K4, N3	A3, D2, DEKN1, E61, EGKR1, G5, K1, P1, T1	AT1, K63, KT2, T1	F65	P1	F1	G8, KN1	S1	I1	H17	H2, T1	E3, I2, L1, M7, Q1	D3
	2.1	22.1	6.3	52.6	7.4	10.5	80.0	70.5	68.4	1.1	1.1	9.5	1.1	1.1	17.9	3.2	14.7	3.2

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31 The gray boxes show polymorphic positions (>40%) and the boxed columns point to the positions of drug-resistance mutations according to the French ANRS algorithm, v25 September 2015.

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33 Numbers after the mutated amino acid designation represent the number of strains with the respective mutation.

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TABLE 3. Characteristics of the samples presenting drug-resistance mutations conferring resistance and/or possible resistance to ARV.

Sample	Age	Gender	VL ³	Drug resistance mutations ¹ on		Targeted drug classes ²		
				RT	PROT	NRTI	NNRTI	PI
KX390886	50	M	5,54		L10I, D60E, V77I			ATV
KX390891	25	F	4,86		G16E, D60E, I62V, V77I			ATV
KX390916	46	F	3,32		L33V, D60E, L63P			ATV
KX390937	25	M	4,48		D60E, A71T, V77I			ATV
KX390976	47	M	3,61		L10V, G16E, V77I			ATV
KX390879	38	M	4,41		K20R, L63P, A71T, V77I			LPV
KX390894	45	F	4,61		L10I, L63P, A71V, V77I			LPV, ATV
KX390883	48	M	5,48		I15V, I62V, L63P, A71V, V77I			SQV
KX390885		M	4,60		I15V, I62V, L63P, H69Q, A71V, V77I			SQV
KX390906	45	M	5,40		I15V, I62V, L63P, A71V, V77I			SQV
KX390911	47	F	4,59		I15V, I62V, L63P, V77I			SQV
KX390914	43	F	4,28		I15V, I62V, L63P, H69Q, A71T, V77I			SQV
KX390920	47	F	4,08		I15V, I62V, V77I			SQV
KX390922	46	M	4,30		I15V, I62V, L63P, V77I			SQV
KX390931	29	F	5,15		I15V, I62V, L63P, V77I			SQV
KX390932	51	F	4,89		I15V, I62V, A71T, V77I			SQV
KX390938	52	F	4,11		I15V, I62V, L63P, H69Q, A71T			SQV
KX390878	30	F	3,71		I15V, I62V, H69Q, V77I			SQV
KX390943	50	F	4,18		I15V, I62V, L63P, H69K, A71V			SQV
KX390949	30	F	5,20		I15V, K20R, V77I			SQV
KX390953	22	F	5,80		I15V, I62V, L63P, H69KQ, V77I			SQV
KX390963	58	M	5,76		I15V, K20R, M36I			SQV
KX390971	35	M	5,49		I15V, I62V, L63P			SQV
KX390895	31	M	5,53		I15V, G16E, D60E, I62V, V77I			SQV, ATV
KX390940	31	M	4,38		I15V, G16E, M36I, D60E, I62V			SQV, ATV
KX390934	46	M	4,40		L10V, G16E, M36I, D60E, I62V			SQV, ATV
KX390890	38	M	5,60		L10V, I15V, K20R, I62V, L63P, H69Q, A71V, V77I			SQV, LPV, ATV
KX390933	25	F	3,81	V179D	L10I, I15V, M36I, I62V, H69Q		RPV	SQV, TPV
KX390959	27	M	5,72		I15V, M36I, D60E, I62V, L63P, H69R, V77I			SQV, TPV
KX390972	36	F	3,99		I15V, M36I, I62V, H69Y			SQV, TPV
KX390958	23	M	3,70		M36I, L63P, H69Y			TPV
KX390961	51	M	4,08		I15V, M36I, L63P, H69Q, V77I			TPV
KX390962	30	F	4,57	V75M	G16E, V77I	D4T		
KX390967	45	M	4,53	V179D	I15V, L63P, V77I		RPV	

¹ according to the French ANRS algorithm, version 25, September 2015. Major resistance mutations are in bold.

² Resistance to ARV drugs is indicated in bold, possible resistance is in plain text.

³ VL, viral load (log₁₀ copies/mm³)