Assessing the Paradox Between Transmitted and Acquired HIV Type 1 Drug Resistance Mutations in the Swiss HIV Cohort Study From 1998 to 2012

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Background. Transmitted human immunodeficiency virus type 1 (HIV) drug resistance (TDR) mutations are transmitted from nonresponding patients (defined as patients with no initial response to treatment and those with an initial response for whom treatment later failed) or from patients who are naive to treatment. Although the prevalence of drug resistance in patients who are not responding to treatment has declined in developed countries, the prevalence of TDR mutations has not. Mechanisms causing this paradox are poorly explored.

Methods. We included recently infected, treatment-naive patients with genotypic resistance tests performed ≤1 year after infection and before 2013. Potential risk factors for TDR mutations were analyzed using logistic regression. The association between the prevalence of TDR mutations and population viral load (PVL) among treated patients during 1997–2011 was estimated with Poisson regression for all TDR mutations and individually for the most frequent resistance mutations against each drug class (ie, M184V/L90M/K103N).

Results. We included 2421 recently infected, treatment-naive patients and 5399 patients with no response to treatment. The prevalence of TDR mutations fluctuated considerably over time. Two opposing developments could explain these fluctuations: generally continuous increases in the prevalence of TDR mutations (odds ratio, 1.13; P = .010), punctuated by sharp decreases in the prevalence when new drug classes were introduced. Overall, the prevalence of TDR mutations increased with decreasing PVL (rate ratio [RR], 0.91 per 1000 decrease in PVL; P = .033). Additionally, we observed that the transmitted high-fitness-cost mutation M184V was positively associated with the PVL of nonresponding patients carrying M184V (RR, 1.50 per 100 increase in PVL; P < .001). Such association was absent for K103N (RR, 1.00 per 100 increase in PVL; P = .99) and negative for L90M (RR, 0.75 per 100 increase in PVL; P = .022).

Conclusions. Transmission of antiretroviral drug resistance is temporarily reduced by the introduction of new drug classes and driven by nonresponding and treatment-naive patients. These findings suggest a continuous need for new drugs, early detection/treatment of HIV-1 infection.

Keywords. HIV; transmission; drug resistance; recently infected; fitness.
Transmission of human immunodeficiency virus type 1 (HIV-1) infection depends strongly on individual levels of plasma viremia [1]. When HIV-1–infected patients receive suboptimal treatment or have incomplete adherence to antiretroviral therapy (ART), drug-resistant viruses emerge and continue replicating. Therefore, the general assumption is that drug-resistant viruses are mainly transmitted from treated patients with high levels of HIV viremia due to failed treatment [2]. Modern ART reduces the viremia levels and transmissibility of HIV-1 more effectively than earlier ART [3], suggesting less emergence [4] and transmission of drug resistance mutations over time.

In recent years, the incidence and prevalence of acquired drug resistance (ADR) mutations in treated patients has indeed declined because of effective ART in various developed countries [5, 6]. However, the prevalence of transmitted drug resistance (TDR) mutations has often remained stable [7–9]. TDR mutations may cause early virological failure when patients start their first-line therapy [10]. Certain TDR mutations can persist for years in the absence of drug pressure after seroconversion [11] and have long-term potential to jeopardize the effectiveness of ART; other TDR mutations may disappear rapidly and become undetectable via population sequencing [11, 12]. Recently, transmission of minority variants harboring drug resistance mutations has been demonstrated [13]. Difficulties in detecting TDR mutations upon ART initiation might therefore compromise the treatment success achieved thus far.

In the current study, we aimed at analyzing the risk factors for TDR mutations and resolving the discrepant patterns in the prevalences of TDR mutations and ADR mutations over time. The unique data set of the Swiss HIV Cohort Study (SHCS), which is representative for ≥15 years, allows us to determine the impact of temporarily changing factors, such as numbers of available drug classes. We used population viral load (PVL) as a tool to assess the spread of drug resistance and the transmission potential of the treatment–experienced population. We focused specifically on TDR mutations during recent infections, to avoid potential bias caused by different times of TDR mutation persistence.

**METHODS**

**Study Population**

The SHCS, which has been enrolling patients since 1988, is a prospective, nationwide, clinic-based study that includes a biobank. The SHCS reflects the epidemiologic characteristics of HIV infection in Switzerland: it includes at least 53% of all cases of HIV infection ever diagnosed in Switzerland, 72% of all patients receiving ART, and 69% of the nationwide registered AIDS cases [14]. Additionally, we enrolled patients from the Zurich Primary HIV Infection study (clinical trials registration NCT00537966), which focuses on identifying and treating patients during early infection [15]. Ethical approval from all participating institutions and written informed consent from all patients was obtained [14–16].

To identify the prevalence of TDR mutations, we included recently infected, treatment-naive patients, as defined below, with a genotypic resistance test performed before 1 January 2013. The first genotypic resistance test from each recently infected, treatment-naive individual was considered. All sequences determined before 1996 were grouped together because of small sample sizes. For the association analysis, in which we tested whether the TDR mutation prevalence was associated with the PVL for nonresponding patients (defined as patients with no initial response to treatment and those with an initial response for whom treatment later failed), we included nonresponding patients enrolled from 1997 to 2011, owing to the representative availability of viral load testing since 1997.

Genotypic resistance tests were performed as part of routine clinical testing by 4 laboratories in Switzerland authorized by the Federal Office of Public Health. All laboratories perform population-based sequencing of the full protease gene and at least codons 28–225 of the reverse transcriptase gene, using commercial assays (Viroseq Vs.1, PE Biosystems; Viroseq Vs. 2, Abbott; and vircoTYPE HIV-1 Assay, Virco Lab) and in-house methods [17], and have participated in the yearly quality control evaluation by the Agence Nationale de la Recherche du SIDA since 2002. All sequences are entered into the SHCS drug resistance database, using SmartGene’s Integrated Database Network System (SmartGene, Zug, Switzerland; IDNS version 3.6.3) [18]. Additionally, we performed systematic retrospective sequencing of virus from blood samples that were stored in the biobank before routine genotyping was introduced (>11 000 sequences were retrospectively generated). Subtyping was performed on the protease and reverse transcriptase sequences, using REGA 2 (http://jose.med.kuleuven.be/genotypetool/html/subtypinghiv.html). If this method returned inconclusive results, the analysis was repeated with the Star analyzer (http://www.vgb.ucl.ac.uk/starn.shtml) [19].

TDR mutations were identified using the World Health Organization list for surveillance of transmitted HIV drug resistance [20].

**Definition of Recent Infection**

To account for potential reversion of TDR mutations in the absence of drug pressure [11, 21–25], we restricted our study population to treatment-naive patients who received their diagnosis ≤1 year after infection. We determined recent infection on the basis of satisfaction of at least one of 3 criteria. The first criterion was documented acute HIV-1 infection, as previously described [15]. The second criterion was documented seroconversion (with <1 year having passed between the last negative result and first positive result of a test to detect HIV). For those lacking the data mentioned above, the ambiguity score [26] was used as a third criterion. The ambiguity score is a measure of the viral nucleotide diversity determined using bulk sequencing, which provides an estimate of the infection duration. Sequences in which ≤0.5% of the nucleotides are ambiguous indicate that the...
genotypic resistance test was performed on a recently infected patient [26]. However, because diversity may be low in long-term HIV infections, patients with a score ≤0.5% and a CD4+ T-cell count of <200 cells/μL were excluded to reduce false positives. For validation of this method, see the Supplementary Materials.

**Viral Burden Among Nonresponders**

PVL was used to describe the viral burden of nonresponding patients for the coming year on a population level. We summed the log_{10} transformed viral loads from all nonresponding patients of a given year. For further analyses, in which we studied the transmission pattern of a specific TDR mutation, the total log_{10} transformed viral loads from nonresponding patients carrying the corresponding mutation was used. Only viral loads corresponding to a genotypic resistance test were included for these analyses because genotyping was needed to determine drug resistance mutations.

To acquire all potential treatment failures, we defined treatment failure as having a viral load of ≥400 copies/mL after receiving ART continuously for 180 days of continuous ART. Viral load measurement was not fully integrated into the clinical routine before 1997, so we included viral loads from nonresponding patients during 1997–2011. Each person contributed to each year once. If a patient had ≥2 viral load measurements within the same year, we calculated the mean for that year.

**Statistical Methods**

Potential risk factors for acquiring any TDR mutations were analyzed using logistic regression. Variables investigated were ethnicity (white, black, or other), sex (male or female), transmission group (men having sex with men, heterosexuals, injection drug users, or other), HIV-1 subtype (B or non-B), and calendar year of sampling (fitted as a continuous variable). Additionally, since we suspected that less optimal regimens resulting from fewer choices of available drugs might have influenced TDR mutation transmission, we included the number of available drug classes as an ordered categorical variable (the P value was obtained from the test for trend). In Switzerland, HIV-1 treatment can be classified into 5 eras, each separated by the introduction of a new drug class. Monoclass therapy with nucleoside analogue reverse transcriptase inhibitors (NRTIs) was used before 1996 (1 drug class; before 1997). After the introduction of unboosted protease inhibitors (PIs) in 1996, patients could obtain dual-class regimens (2 drug classes: 1997–1998). Subsequently, nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) were introduced in 1998 (3 drug classes: 1999–2000), followed by ritonavir-boosted PI (PI/r) in 2000 (4 drug classes: 2001–2008) and integrase inhibitor (InSTI) in 2008 (5 drug classes: 2009–2012). In the model, we included a binary response indicating detection of any TDR mutation from the previous year as the explanatory variable. We further studied the association for the most prevalent drug resistance mutation for each major drug class in the SHCS: M184V, L90M, and K103N for NRTIs, PIs, and NNRTIs, respectively. In this individual-mutation analysis, we fitted the model with the annual prevalence of each of these 3 transmitted mutations as outcome and the PVL of nonresponding patients carrying the corresponding mutation from the previous year as an explanatory variable. We performed sensitivity analyses that included PVLs measured during the same year as or 2 years before performance of genotypic resistance tests (Supplementary Materials).

We expressed our results with 95% confidence intervals (CIs) and 2-sided P values, with a P value of <.05 being statistically significant. Data analyses were performed with Stata 13.0 SE (StataCorp, College Station, Texas).

**Subgroup Analysis**

Considering that transmission to some SHCS patients may have occurred abroad and that the TDR mutation prevalence among those patients would be less relevant to that among treatment-experienced patients in Switzerland, we repeated the association analyses with only those patients found in Swiss transmission clusters, defined phylogenetically [27]. To summarize, HIV-1 subtype B pol sequences from 8271 SHCS patients were pooled with foreign pol sequences from the Los Alamos Sequence database (n = 36 230). Clusters were defined as clades containing ≥10 sequences and consisting of ≥80% sequences from the SHCS.

**RESULTS**

**Fraction of Genotypic Resistance Tests With Positive Results in the SHCS**

Figure 1 summarizes the fraction of TDR and ADR mutations from all 20 120 genotypic resistance tests sampled before 1 January 2013, regardless of the infection duration, stratified by treatment status (naive or experienced). Specifically, 10 504
genotypic resistance tests were from 7920 treatment-naive individuals, and 9616 genotypic resistance tests were from 4816 treatment-experienced individuals. The prevalence of ADR mutations reached a peak of 85% in 1998 and dropped continuously thereafter, reaching a plateau of approximately 38% in 2009. This strong decrease in the fraction of genotypic resistance tests positive for any drug resistance mutation for both populations is shown. The annual numbers of included genotypic resistance tests from treatment-experienced (first row; red) and treatment-naive (second row; blue) patients are listed below the graph. Linear regression analysis with fraction as the dependent variable and year as the explanatory variable showed that the fraction of drug resistance tests with positive results among treatment-experienced patients has declined substantially over time (−2.8% [95% confidence interval (CI), −3.4% to −2.2%] per year; \(P<.001\)), whereas the fraction among treatment-naive patients has not (0.3% [95% CI, .2%–.5%] per year; \(P<.001\)). Vertical bars denote 95% CIs.

**Study Population**

We identified 2421 recently infected patients (31%) from 7920 treatment-naive patients in the SHCS with ≥1 genotypic resistance test performed between 26 June 1992 and 18 December 2012. Additionally, we included 5399 who were nonresponders to ≥1 regimen during 1997–2011, presenting 18 097 yearly unique viral load measurements. For detailed patient-selection methods, see Figure 2. For details on the representativeness of the study population, see Supplementary Figure 1.

**TDR Mutation Prevalence Over Time in Recently Infected Treatment-Naive Patients and Associated Risk Factors**

Median TDR mutation prevalences fluctuated substantially over time, as follows: 9.1% (range, 2.2%–15.6%) to any drug, 5.8% (range, 2.2%–14.3%) to an NRTI, 2.5% (range, 0%–4.8%) to a PI, and 1.4% (range, 0%–5.1%) to an NNRTI (Figure 3).

We observed 2 opposing developments in the multivariable logistic model that could explain the complex fluctuations of TDR mutation prevalences (Table 1). On one hand, the overall TDR mutation prevalence dropped after introduction of new drug classes. In particular, prevalences significantly dropped after PI/r and InSTI became available. On the other hand, we found a linear increase of TDR mutation prevalences when the number of available drug classes remained constant (Figure 3). The combination of...
these 2 opposing developments resulted in TDR mutation prevalences, which increased in the absence of new drugs but decreased sharply upon introduction of new drug classes. TDR mutation prevalences predicted from this model are shown in Figure 3.

Additionally, prevalences of TDR mutations for individual drug classes showed similar but not statistically significant patterns, as mentioned above (Supplementary Table 1.1–1.3).

**Association of TDR Mutation Transmission With Viral Burden in Nonresponding Patients**

We further investigated whether TDR mutation transmission was associated with nonresponse to treatment. We fitted annual prevalences of any TDR mutation (outcome) and the PVL of nonresponding patients from the previous year (explanatory variable) with a Poisson regression model. The rate ratio (RR) was 0.91.

**Figure 2.** Patient selection profile. Numbers outside of the boxes indicate exclusions. A, Selection profile for the recently infected, treatment-naive population. We selected patients enrolled in the Swiss HIV Cohort Study (SHCS) before 1 January 2013 with genotypic resistance tests (GRTs) performed when they were treatment naive (n = 7920). Of these, we identified patients with GRTs performed during recent infection (≤1 year of infection) according to documented infection dates, seroconversions, or ambiguity score and CD4+ T-cell count. These patients constitute our basic study population (n = 2421). For further analyses, such as for the univariable and multivariable analysis in Table 1, and for the association analyses in Figure 4A–4D, 66 and 252 patients, respectively, were excluded because of additional criteria set for these analyses. Sixty-six patients did not have a clearly defined subtype, and 252 patients were not sampled during 1998–2012 (for details, see individual descriptions in Table 1 and Figure 4). B, Selection profile for the nonresponding population. We chose population viral load (PVL) as an indicator for the viral burden for nonresponding patients on a population level. PVL was defined as the sum of log10-transformed viral loads from nonresponding patients. We thus selected available viral load measurements from SHCS patients when they were treatment experienced. High viral loads (≥400 copies/mL) measured after 180 days of and during continuous therapy were included from these patients. Because viral load testing has been fully integrated into routine clinical care since 1997, values before 1997 were excluded. We calculated a yearly unique viral load from each patient (if ≥1 viral load was available per patient within the same year, the mean was used) and used these values for the association analysis reported in Figure 4E. For further association analyses, shown in Figure 4F–4H, in which we studied the transmission pattern of a specific transmitted drug resistance mutation, only viral loads corresponding to a GRT were included because genotyping was needed to determine drug resistance mutations. From viral loads with corresponding GRTs, we selected those from patients carrying M184V, L90M, or K103N for association analysis in Figure 4F, 4G, or 4H, respectively. Abbreviations: HIV-1, human immunodeficiency virus type 1; ZPHI, Zurich Primary HIV Infection study.
(95% CI, .83–.99) per 1000 increase in PVL [of sum of log_{10} transformed viral load] \((P = .033)\), indicating a 9% increase in the TDR mutation prevalence per 1000 decrease in the PVL from the previous year of non-failing patients (Figure 4A and 4E). The PVL itself decreased over time (linear regression, −318 [95% CI, −438 to −197] per year; \(P < .001\)). When we considered patients identified in Swiss transmission clusters, we found no discernible evidence for an association between TDR mutations and PVL (RR, 0.76 [95% CI, .43–1.34] per 1000; \(P = .34\)).
Together, our results suggested no or a negative association between TDR mutation prevalences and PVL of nonresponding patients from the previous year.

Transmission of the Class-Specific Drug-Resistance Mutations

**M184V, L90M, and K103N**

The above analysis pooled all TDR mutations and potentially neglected the differential behavior of individual mutations. We therefore performed individual-mutation analysis for the most prevalent drug resistance mutation for each drug class.

The prevalence of transmitted M184V increased 1.5-fold per 100 increase in the PVL from the previous year among nonresponding patients carrying M184V (RR, 1.50 [95% CI, 1.20–1.86] per 100 increase in the PVL; *P* < .001; Figure 4B and 4F). This association increased to approximately 6-fold when only TDR mutations from Swiss transmission clusters were considered (RR, 5.68 [95% CI, 1.21–26.7] per 100 increase in the PVL; *P* = .028). On the contrary, we observed a negative association between the prevalence of transmitted L90M and the PVL in nonresponding patients carrying L90M during the previous year (RR, 0.75 [95% CI, .58–.96] per 100 increase in the PVL; *P* = .022; Figure 4C and 4G); the association became stronger when TDR mutations from Swiss transmission clusters were considered (RR, 0.07 [95% CI, .01–.46] per 100 increase in the PVL; *P* = .006). For K103N, no association was detected (RR, 1.00 [95% CI, .73–1.37] per 100 increase in the PVL; *P* = .99; Figure 4D and 4H), and the RR became negative when the analysis included only patients from Swiss transmission clusters but did not reach statistical
significance (RR, 0.02 [95% CI, 0.002–1.55] per 100 increase in the PVL; P = .078).

Sensitivity analyses using PVL from different years and validation of the ambiguity score for identifying recent infections showed that our results were robust (Supplementary Tables 2, 3.1, and 3.2). For a summary of the sample sizes and methods used in each analysis, see Supplementary Table 4.

DISCUSSION

In this study, we investigated the paradox between the decrease in ADR mutation prevalence [5, 6, 28] and a nearly stable prevalence of TDR mutations [7, 8, 29–31]. If TDR mutations indeed primarily originate from nonresponding patients with ADR mutations, this discrepancy is counterintuitive. We therefore tested whether transmission of drug-resistant viruses was dependent on nonresponding patients in the SHCS, which is representative of the HIV-infected population in Switzerland, over a 15-year period. A large, treatment-naive population with clearly defined recent infection was used to calculate the TDR mutation prevalences.

Our results indicate that drug resistance transmission is predominantly driven not by nonresponding patients but, rather, by a complex mixture of both nonresponding and ART-naive patients. Although the PVL of nonresponding patients decreased continuously, TDR mutation prevalences increased over time. When specific TDR mutations were studied individually, distinct transmission patterns emerged. The prevalence of transmitted...
M184V correlated positively with PVL from nonresponding patients carrying M184V from the previous year. This association became stronger for patients included in Swiss transmission clusters. This suggests that the nonresponder population is the major transmission source for M184V. In contrast, no positive association was found for L90M or K103N. We detected a negative association between prevalences of transmitted L90M and the PVL among nonresponding patients carrying L90M from the previous year. This implies that major transmission reservoirs for these mutations are treatment-naive rather than nonresponding patients.

How can we explain such divergent transmission patterns between specific drug resistance mutations? It is most likely due to the differential fitness costs, which represent the reduced ability of a virus harboring a drug resistance mutation to replicate in the absence of the drug to which the mutation confers resistance. Generally, drug-resistant viruses will be replaced gradually by fitter viruses when drug pressure is not present, and the rate of the replacement depends on the degree of the fitness cost [32]. M184V disappears at a fast rate after transmission [11] without drug pressure, owing to its high fitness cost [33]. Therefore, M184V was rarely found in a drug-naive population, and its transmission depends on nonresponding patients. In contrast, the low-fitness-cost mutations L90M and K103N [23, 34, 35] persist longer in the absence of drug pressure [23] and may therefore persist within the ART-naive population, which thus becomes an important source for transmission of these mutations.

This interpretation is further supported by the fact that occurrence of L90M among recently infected, treatment-naive patients has increased years after the PVL from nonresponding patients carrying L90M started to decrease (Figure 4), resulting in the negative association yielded by the Poisson regression. A similar but weaker phenomenon was observed for K103N. Various combinatorial ART regimens might contribute to differences between transmission patterns of L90M and K103N. Drugs selecting for L90M, mainly saquinavir and nelfinavir, have been almost unused in Switzerland for many years, indicating circulation of transmitted L90M within the treatment-naive population. On the other hand, drugs selecting for K103N, such as efavirenz and nevirapine, are still in heavy use, implying that transmission of K103N is fueled both by nonresponding and treatment-naive patients.

Complemented by results from previous phylogenetic analyses [36–38], our study further illustrates that the treatment-naive population is a major source for ongoing transmission of low-fitness-cost mutations. Early diagnosis and treatment of HIV-1 infection is warranted to block the otherwise self-fueling mechanism of unrecognized TDR mutations, which persist in this population because of low fitness costs.

In the SHCS, TDR mutation prevalences fluctuated considerably over time. We hypothesized that introductions of new drugs had an effect on these fluctuations, because new drugs improve control of viremia in treated patients. Indeed, after each introduction of a new drug class, a drop in TDR mutation prevalence was observed: in 1997 after introduction of PI, 1999 after introduction of NNRTI; in 2001, after introduction of PI/r; and in 2009, after introduction of InSTI (Figure 3). Despite the universal and unlimited access to ART in Switzerland, TDR mutation prevalences could not be reduced over an 18-year study period (Figure 3A). Possibly, even more TDR mutations would have occurred without a constant influx of new therapy options. This highlights the importance of a drug pipeline that constantly delivers new medications.

There are several limitations to this study. Although our study was limited to a single country, we believe that our findings are generalizable to settings with similar HIV epidemics and treatment policies (for the generalizability of our findings, see the Supplementary Material). In the correlation analyses, we used measures for nonresponding patients from the previous year because we assumed that nonresponding patients could transmit drug resistance approximately within 1 year before salvage treatment is fully active. Sensitivity analyses using the PVL from the same year or 2 years before revealed results similar to those of the original model (Supplementary Table 2). Furthermore, the lack of positive associations from individual-mutation analyses of L90M/K103N does not causally prove that treatment-naive individuals are the main source for the transmission. Although unlikely because of the well-studied transmission dynamics within the SHCS [27], we cannot exclude the possibility that patients carrying the transmitted L90M/K103N in our study population might all have been infected abroad and thus that the nonresponder PVL as measured in the SHCS would not be relevant. However, the subgroup analysis including only patients from Swiss transmission clusters confirmed the same finding.

In summary, we demonstrated that transmission of antiretroviral drug resistance is temporarily reduced by the introduction of new drug classes and driven both by nonresponding and treatment-naive patients. These findings suggest a continuous need for new drugs and for early detection and treatment of HIV-1 infection to successfully control the spread of TDR mutations in the long term.

**Supplementary Data**

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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