B R I E F   R E P O R T

Successful Prevention of Transmission of Integrase Resistance in the Swiss HIV Cohort Study

Alexandra U. Scherrer,[1,2] Wan-Lin Yang,[1,2] Roger D. Kouyos,[1,2] Jürg Böni,[2] Sabine Yerly,[3] Thomas Klimkait,[5] Vincent Aubert,[7] Matthias Cavassini,[8] Manuel Battegay,[6] Christoph Hauser,[9] Alexandra Calmy,[4] Patrick Schmid,[10] Enos Bernasconi,[11] and Huldrych F. Günthard[1,2]; for the Swiss HIV Cohort Study

[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, [2]Institute of Medical Virology, University of Zurich, [3]Laboratory of Virology, Division of Infectious Diseases, [4]HIV/AIDS Unit, Infectious Disease Service, Geneva University Hospital, [5]Department of Biomedicine, University of Basel, [6]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, [7]Division of Immunology and Allergy, [8]Division of Infectious Diseases, University Hospital Lausanne, [9]Department of Infectious Diseases, Berne University Hospital, University of Berne, [10]Division of Infectious Diseases, Cantonal Hospital St. Gallen, and [11]Division of Infectious Diseases, Regional Hospital Lugano, Switzerland

The prevalence of integrase strand transfer inhibitor (INSTI)–transmitted drug resistance (TDR) may increase with the increasing use of INSTIs. We analyzed the prevalence of INSTI TDR in the Swiss HIV Cohort Study (2008–2014). In 1 of 1316 drug-naive samples (0.1%), a major INSTI TDR mutation was detected. Prevalence was stable, although INSTIs were increasingly used. We showed that this is in contrast to the introduction of previous drug classes, in which more treatment failures with resistant strains occurred and TDR was observed more rapidly. We demonstrated on a population-level that it is possible to avoid TDR to a new drug class for years.

Keywords. HIV-1 drug resistance; integrase; transmission of drug resistance; prevalence; population viral load.

Integrase strand transfer inhibitors (INSTIs) are increasingly prescribed to treat human immunodeficiency virus (HIV)–infected patients [1]. With the increasing use of INSTIs and subsequent treatment failures on INSTIs, the number of transmitted INSTIs resistance is expected to increase, as observed for other drug classes [2, 3]. The risk of transmission of drug resistance is particularly high in populations where treatment-experienced patients are not receiving suppressive antiretroviral treatment (ART) [2].

Despite increasing use of INSTIs, transmission of INSTI resistance has not been widely reported [4, 5]. There are some anecdotal cases in which the transmission of major INSTI resistance was reported [6, 7]. Minor resistance mutations are most likely polymorphic and occur more often in non–B subtype HIV infections, compared with subtype B infections [4, 5].

We aimed to analyze the prevalence of transmitted INSTI resistance in the Swiss HIV Cohort Study (SHCS) and to identify risk factors for its occurrence. In addition, we intended to specify the transmission potential for INSTI resistance in the SHCS population and to set it in historical context.

METHODS

Study Population

We used data from the SHCS and the SHCS drug resistance database. The SHCS is an ongoing, nationwide, multicenter, clinic-based observational study [8]. The SHCS is highly representative and includes 85% of newly infected patients and at least 75% of patients receiving antiretroviral treatment in Switzerland [2, 8]. Sequences from genotypic drug resistance tests (GRTs) are stored in a central database (SmartGene; Integrated Database Network System, version 3.6.14) [2]. Subtypes were defined using REGA HIV-1 Subtyping (V3.0; available at: http://dbpartners.stanford.edu:8080/RegaSubtyping/stanford-hiv/typingtool#). If results were inconclusive, the analysis was repeated with Comet subtyping (V1.0; available at: http://comet.retrovirology.lu/). The SHCS has been approved by the ethical committees of all participating institutions, and written informed consent has been obtained from all participants [8].

The SHCS drug resistance database contained 1724 GRTs from the HIV-1 integrase gene, of which 1168 were prospectively and 556 retrospectively sequenced. A total of 1521 of 1724 GRTs were from INSTI-naive patients, and 1057 of 1724 were from treatment-naive patients. The retrospective sequencing was done systematically. All available samples from patients for whom HIV infection was diagnosed during 2008–2011 were sequenced, as well as baseline samples from drug-experienced patients who started INSTI-containing treatment and patients who experienced a treatment failure on INSTIs.

INSTI Resistance

To estimate the prevalence of transmitted INSTI resistance up to 2014, we included 1316 patients who had ≥1 GRT performed for the integrase gene before the first exposure to an INSTI (earliest GRT per patient chosen). Samples retrieved before 2008 were summarized together as a group. We considered drug resistance mutations listed by the International Antiviral Society–USA in 2015 and differentiated between minor mutations (T66AK, L74 M, E92G, T97A, E138AK, G140AS, and R263K) and major mutations (T66I, E92Q, F121Y, Y143CHR, S147G, Q148HKR, and N155H) [9].

We performed a logistic regression analysis, adjusted for HIV subtype, to quantify the impact of calendar year on transmitted INSTI resistance.

To account for potential reversion of transmitted drug resistance mutations in the absence of drug pressure, we performed a subanalysis that included only GRTs from recently infected, treatment-naive patients. A recent infection was defined as follows (details are described elsewhere [2]): acute HIV-1 infection described by the physician, documented seroconversion (<1 year between the last negative test result and first positive test result), or an ambiguity score of ≤0.5% combined with a CD4$^+$ T-cell count of >200 cells/μL [10].

Transmission Potential of Drug Resistance
To estimate the transmission potential of INSTI resistance and to put our findings into historical context, we compared different aspects of the period after the introduction of INSTI (2008–2014) to the periods after introduction of nonnucleoside reverse transcriptase inhibitors (NNRTIs) (1998–2004), unboosted protease inhibitors (PIs) (1996–2002), and ritonavir-boosted PIs (PI/r; 1999–2005). We differentiated unboosted PIs and PI/r because of the better potency of PIs/r. We compared the number of patients receiving the specific drug classes, the number of patients with no response to specific drug classes, and the number of patients detected with ≥1 drug resistance mutation affecting the specific drug class. Additionally, we compared 3 different types of population viral load (PVL): (1) PVL after first exposure to the specific drug class (after ≥120 days of continuous treatment), (2) PVL after treatment failure on a specific drug class, and (3) PVL after detection of the first major drug resistance mutation affecting the specific drug. To calculate the PVL, we summed the log$_{10}$-transformed viral loads from the respective patients. Each patient contributed to each year once. If a patient had ≥2 measurements within the same year, we calculated the mean of the log$_{10}$-transformed viral load.

Treatment failure was defined as ≥1 viral load of ≥500 HIV-1 RNA copies/mL (after 180 days of continuous treatment or previous viral suppression) followed by a treatment change or stop. Statistical analyses were performed with Stata SE, version 14.0 (StataCorp, College Station, Texas).

RESULTS

Transmission of INSTI Resistance Mutations
INSTI resistance mutations were rarely detected among INSTI-naive patients (Supplementary Appendix 1). Only 1 major mutation was found (1 of 1316 [0.1%]). It was T66I, found in a sample retrieved in 2001. In 38 of 1316 samples (2.9%), viruses were found with minor INSTI resistance mutations. The most common minor mutations were L74 M (17 of 1316 [1.3%]) and T97A (16 of 1316 [1.2%]). Minor mutations were more common in subtype non-B infections as compared to subtype B infections (24 of 466 [5.2%] vs 14 of 850 [1.6%]; $P < .001$, by the Fisher exact test). The detected minor mutations were most likely polymorphic. They were already present before (in 4 of 157 samples [2.6%]) the introduction of INSTIs in

Switzerland (28 February 2008). We found no evidence for an increase in prevalence of minor mutations in the years after the introduction of INSTIs. The yearly prevalence was 2.4% (95% confidence interval [CI], .6%–5.9%), 3.8% (95% CI, 1.4%–8.2%), 2.4% (95% CI, 0.8%–5.4%), 3.6% (95% CI, 1.8%–6.6%), 2.5% (95% CI, 0.8%–5.8%), 1.3% (95% CI, 0.2%–4.7%), and 3.9% (95% CI, 1.5%–8.4%) during 2008–2014. The odds ratio (OR) per calendar year was 0.98 (95% CI, .8–1.2) when performing a logistic regression adjusted for HIV subtype B versus non-B subtypes (OR, 3.3; 95% CI, 1.7–6.4; $P = .001$).

The results were similar when we restricted the analysis to recently infected patients. No major mutation was detected in 303 samples. Minor mutations tended to be more common in subtype non-B infections (4 of 92 samples [4.4%]) as compared to subtype B infections (3 of 211 samples [1.4%]; $P = .205$).

Potential Reasons for the Low Prevalence of Transmission
The prevalence of transmitted INSTI mutations remained low, although the number of patients receiving INSTI was increasing, from 259 in 2008 to 2180 in 2014 (Supplementary Appendix 2). The low prevalence may be explained by the low number of patients who were potential transmitters of INSTI resistance. Between 2008 and 2014, 85 patients experienced a treatment failure on ART including INSTIs in the entire SHCS database. Of these, 56 (61%) changed treatment after a median of 49 days (interquartile range, 15–167 days) following treatment failure, and a large proportion of these patients reached viral suppression (<50 HIV-1 RNA copies/mL) later (42 of 47 patients [89%] with a measurement).

GRTs were performed in 54 of 85 patients (64%) who experienced a treatment failure on INSTI treatments. In 26 (48%), GRTs INSTI mutations were found. The following major mutations were most commonly detected: N155H (in 18 [33%]), Q148H (in 4 [7%]), Y143C (in 4 [7%]), and Y143R (in 3 [6%]). In addition, 13 GRTs with drug-resistant viruses were performed on samples from patients who had detectable viral load while receiving ART containing INSTI but did not fulfill our criteria for nonresponse to treatment. However, the majority of patients ever detected with a major INSTI resistance mutation were successfully treated (HIV-1 RNA load, <50 copies/mL) at the last study visit (23 of 40 [58%]), died (4 of 40 [10%]), or stopped participating in the SHCS (8 of 40 [20%]). Our findings reveal that only a very small number of patients are known to be potential transmitters of INSTI resistance mutations.

Comparison to the Introduction of Other Drug Classes
The transmission of drug resistance mutations against other drug classes was higher in the years following introduction [2]. An explanation for the difference is that the number of patients who did not respond to a treatment containing the other drug class was higher as compared to the number of patients who did not respond during INSTI treatments (Supplementary Appendix 2). As mentioned above, in the first 7 years after the introduction of
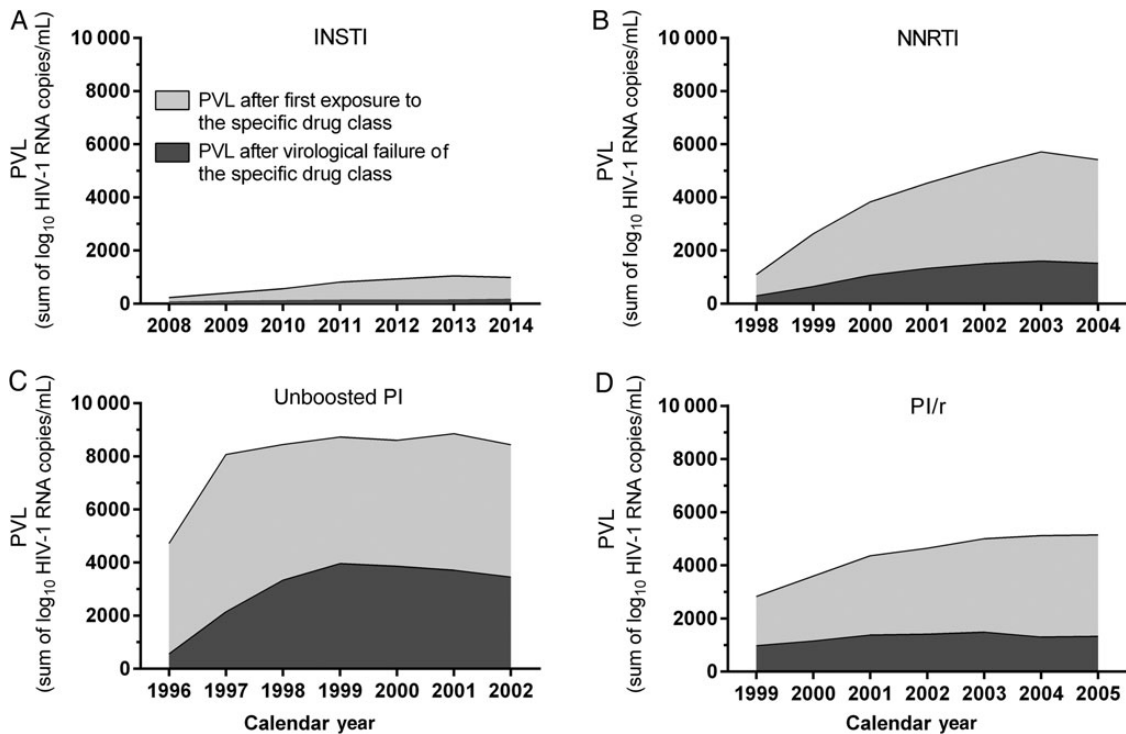
Figure 1. *A–D*, Population viral load (PVL) of patients treated with integrase strand transfer inhibitor (INSTIs; *A*), nonnucleoside reverse transcriptase inhibitors (NNRTIs; *B*), unboostsed protease inhibitors (PIs; *C*), and ritonavir-boosted PI (PI/r; *D*) in the 7 years after introduction of each drug class. The areas represent the PVL after first exposure to the specific drug class (light gray) and the PVL after virological failure of the specific drug class (dark gray). Abbreviation: HIV-1, human immunodeficiency virus type 1.

INSTIs, only 85 of 2751 patients receiving INSTIs experienced a virological failure. In the 7 years after the introduction of unboosted PIs, PI/r, and NNRTIs, 18.2 times (1543 of 5923), 5.7 times (482 of 5332), and 7.2 times (609 of 4347) more patients did not respond to the respective ART. The median PVL after first exposure to INSTIs, after treatment failure during INSTI receipt, and after detection of INSTI resistance in the 7 years after introduction of the first INSTI was much lower, compared with the median PVL after introduction of other drug classes (Figure 1 and Supplementary Appendix 3 and 4).

DISCUSSION

Seven years after introduction of INSTIs in Switzerland, no transmission of major INSTI resistance mutations was detected by our study. The major reason for this unexpected absence of INSTI transmission is most likely the very low transmission potential in the SHCS. Treatment-naive patients had no transmission potential of INSTI resistance because of lacking INSTI resistance mutations, and the number of treatment failures during INSTI receipt remained remarkably low. Thus, the PVL of patients who experienced a virological failure during INSTI receipt or who carried viruses with INSTI resistance mutations was very low. To put these findings in a historical context was even more impressive. The transmission potential of resistance

mutations remained very low after the introduction of INSTI as compared to the time after introduction of PIs and NNRTIs.

Despite these very encouraging and unexpected findings, the transmission of INSTI resistance most likely cannot be avoided in the long run [6, 7]. Boyd et al postulated that it is only a matter of time until the prevalence of transmitted drug resistance affecting INSTIs is reaching higher levels. However, we demonstrated that the transmission of drug resistance affecting a new class can be minimized. The Swiss setting cannot be compared to other settings (eg, those with limited access to viral load monitoring or no available second-line and third-line therapies). In these settings, patients may continue to receive failing regimens and may accumulate more drug resistance mutations. These patients have a high transmission potential and might also accumulate secondary mutations. Such strains might be transmitted and fixed in the population and might lead to major public health issues in the future [2].

Minor mutations were more frequently seen in non-B subtype infections, but they probably do not have an impact on the treatment outcome, as has been shown for minor PI mutations [11, 12]. The sample size was too small to analyze specific pattern among non-B subtypes.

To our knowledge, this is the largest study to assess the transmission of INSTI resistance in a highly representative population. Owing to the similar history of drug approval and

treatment guidelines, our finding most likely also reflects the situation in other resource-rich settings.

Our study is limited by the fact that not all patients who experienced virological failure during INSTI receipt had a GRT performed. This was partially due to the fact that drugs were switched at low viral loads, making resistance testing less successful [13]. Viral load measurements and genotypic drug resistance testing have been routinely integrated in clinical care in Switzerland since 1997 and 2002, respectively, and therefore the PVL, number of failures, and number of mutations might be slightly underestimated. But these issues do not alter our conclusions.

To summarize, our study demonstrated that the transmission potential of drug resistance against a new drug class can be minimized in a setting coming very close to the World Health Organization target 90-90-90 [14, 15]. Nevertheless, it might only be a matter of time until the prevalence of transmitted drug resistance affecting INSTI reaches notable levels. Of particular importance will be to investigate the effect of decreasing monitoring frequency that is proposed and performed in some countries. This may lead to delayed detection of treatment failures with subsequent emergence of resistance and a higher PVL of nonresponding patients. From a global health perspective, it is important that the transmission potential in other settings can be minimized in a similar way.

STUDY GROUP MEMBERS

The members of the SHCS are V. Aubert, M. Battegay, E. Bernasconi, J. Böni, D. L. Braun, H. C. Bucher, C. Burton-Jeangros, A. Calmy, M. Cavassini, G. Dollenmaier, M. Egger, L. Elzi, J. Fehr, J. Fellay, H. Furrer (chairman of the Clinical and Laboratory Committee), C. A. Fux, M. Gorgievski, H. Günthard (president of the SHCS), D. Haerry (deputy of the Positive Council), B. Hasse, H. H. Hirsch, M. Hoffmann, I. Hösli, C. Kahlert, L. Kaiser, O. Keiser, T. Klimkait, R. Kouyos, H. Kovari, B. Ledergerber, G. Martinetti, B. Martinez de Tejada, C. Marzolini, K. Metzner, N. Müller, D. Nadal, D. Nicca, G. Pantaleo, A. Rauch (chairman of the Scientific Board), S. Regenass, C. Rudin (chairman of the Mother and Child Substudy), F. Schöni-Affolter (head of the data center), P. Schmid, R. Speck, M. Stöckle, P. Tarr, A. Trkola, P. Vernazza, R. Weber, and S. Yerly.

Notes

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