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BRIEF REPORT

Antiretroviral Treatment Simplification With 2-Drug Regimens: Impact of Transmitted Drug Resistance Mutations

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The frequency of clinically relevant transmitted drug resistance mutations (DRMs) against drugs used for 2-drug regimens was 15.6%, but only 2% were not eligible for 1 or more 2-drug regimens. More than 50% of patients harboring any clinically relevant DRMs were found to be part of genetic transmission clusters.

Keywords. dolutegravir; HIV; lamivudine; molecular epidemiology; rilpivirine.

Standard-of-care antiretroviral therapy (ART) for a treatment-naïve person generally consists of 2 nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active antiretroviral drug, usually an integrase strand transfer inhibitor (INSTI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Administration of ART has significantly improved life expectancy of HIV-1-infected individuals. However, concerns have been raised regarding potential long-term toxicities developing from cumulative exposure to drugs that need to be taken for life [1]. Thus, 2-drug regimens may be preferable to induce and/or maintain viral suppression while decreasing lifetime cumulative drug exposure and potential long-term toxicities.

Promising results from studies have been published indicating successful induction and/or maintenance of viral suppression with 2-drug regimens containing the INSTI dolutegravir (DTG) [2–5]. According to the US Department of Health and Human Services guidelines, treatment simplification with 2-drug regimens containing DTG should be considered [6]. The latest version of the European AIDS Clinical Society guidelines recommend initial dual therapy with DTG plus lamivudine (3TC) for ART-naïve adult HIV-positive persons, and list a dual therapy with DTG plus rilpivirine (RPV) among switch strategies for virologically suppressed persons [7]. When considering these drugs for initial combination regimens, HIV-1-transmitted drug-resistance mutations (DRMs) become a matter of concern. To gain deeper insight into transmitted DRMs with resistance to DTG, 3TC, and RPV, this study aimed to estimate the rate of any clinically relevant transmitted DRM against 1 or more components of both of the 2-drug regimens and to reconstruct the local HIV-1 transmission network in Southeast Austria, representing an area with a population of >1 million.

METHODS

The study population included 192 ART-naïve residents of Southeast Austria with newly diagnosed HIV-1 infection from 2013 through 2018 who had initial (ie, before initiation of ART) nucleic acid amplification testing (NAT) and resistance testing performed at the Molecular Diagnostics Laboratory, Institute of Hygiene, Microbiology and Environmental Medicine, Medical University of Graz. This institute represents the only laboratory performing HIV NAT in this region, with a population of >1 million.

Demographic information and clinical data were retrospectively collected, including sex, age, date of diagnosis before the start of ART, and area of residence for all individuals. All demographic data were collected in a de-identified manner, associated with the 4-digit ZIP code of residence, and then linked to the unique HIV sequence. Conventional Sanger sequencing data of the reverse transcriptase (RT) and integrase (IN) genes of circulating RNA in plasma were uploaded to the Stanford University HIV Drug Resistance Database [8]. Screening for transmitted DRMs against DTG, 3TC, and RPV was performed according to the Stanford University Genotypic Resistance Interpretation, considering all major DRMs with high-level, intermediate, or low-level resistance to be clinically relevant [9]. Identification of these major DRMs is essential for clinicians to make clinical decisions regarding antiretroviral therapy [10]. Furthermore, the genetic transmission network was inferred based on partial pol sequences, as described recently [11]. Shared DRMs were defined as any DRM present in genetically linked individuals.

RESULTS

The majority of individuals (75.5%, 145/192) were male. The mean age of the individuals at the time of HIV diagnosis (range)

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was 39 (18–66) years. The frequency of any clinically relevant DRM against DTG, 3TC, and/or RPV at the time of diagnosis was 15.6% (30/192 patients, 13 of them with high-level, 10 with intermediate, and 7 with low-level resistance), and 2.1% (4/192) of individuals were not eligible for at least 1 of the currently suggested 2-drug regimens. When the frequency of any DRM against DTG, 3TC, and/or RPV in individuals who were diagnosed from 2013 through 2015 (16.7%; 15/90) was compared with those in individuals who were diagnosed from 2016 through 2018 (14.7%, 15/102), no difference was observed.

Of 192 individuals, 1 (0.5%) showed resistance (a combination of T66I and T97A) against DTG. Eight (4.2%) patients harbored any DRM against 3TC. Five of them had a single mutation against 3TC, whereas 3 individuals showed 2 DRMs against 3TC. The M184V DRM was observed in all 8 individuals, the K65R DRM was additionally observed in 2 individuals, and the L74V DRM was additionally observed in another individual. In 25 (13.0%) individuals, any DRM against RPV was detected. Twenty-three of them had a single mutation, whereas 2 individuals showed 2 DRMs against RPV. The E138A DRM was most frequently observed (n = 15), followed by the K101E DRM (n = 4), the K101P DRM (n = 4), the Y181C DRM (n = 3), and the H221Y DRM (n = 1).

Of 30 individuals with any clinically relevant DRM against DTG, 3TC, and/or RPV, 26 (86.7%) patients harbored DRMs against 1 drug class (INSTI, NRTI, or NNRTI), and 4 (13.3%)

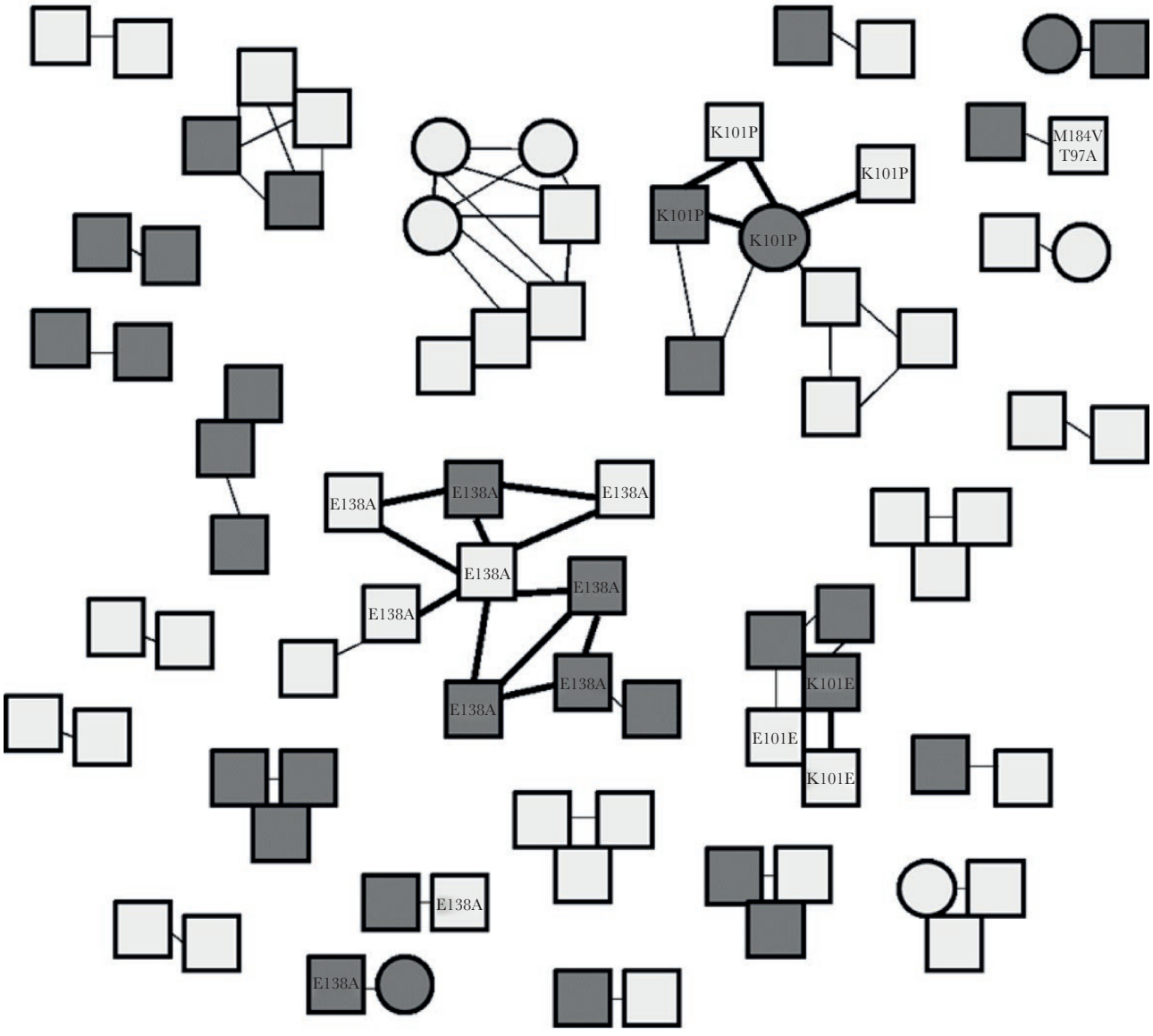

Figure 1. Transmission network analysis: 82 genetically linked individuals forming 26 clusters. Dark gray circles and squares, antiretroviral therapy (ART)–naïve residents of Southeast Austria with newly diagnosed HIV-1 infection 2013 through 2015; light gray circles (females) and squares (males), ART-naïve residents of Southeast Austria with newly diagnosed HIV-1 infection 2016 through 2018; bold lines, shared drug resistance mutations.

individuals harbored 2 or 3 DRMs against 2 drug classes (INSTI plus NRTI or NRTI plus NNRTI). There were no individuals observed who had more than 3 DRMs or DRMs against more than 2 drug classes throughout the study period.

Transmission network analysis found 82/192 (42.7%) genetically linked individuals, forming 26 clusters ranging in size from 2 to 10 (Figure 1). Of the 30 patients harboring any DRM against DTG, 3TC, and/or RPV, 18 (60%) were members of 6 different clusters. Of those, 15/18 (83.3%) were shared by HIV genetically linked partners. The frequency of relevant DRMs was significantly higher among clustering vs nonclustering individuals (18/82, 22%, vs 12/110, 10.9%; $P = 0.045$, 2-tailed Fisher exact test). When the frequency of clinically relevant resistance in clustering individuals who were diagnosed from 2013 through 2015 (23.5%, 8/34) was compared with that in individuals who were diagnosed from 2016 through 2018 (20.8%, 10/48), no significant change was observed.

DISCUSSION

Several concerns including long-term toxicity, drug–drug interactions, and aging and/or comorbidity have been raised regarding exposure to drugs that need to be taken for life. As a result new regimens have been recommended for the treatment of HIV-1 infection in adults with no known resistance to any individual component.

In this study, the rate of any clinically relevant DRM against 1 or more components of both of the 2-drug regimens was almost 16%. Only 1 (0.5%) individual showed a high-level resistance (a combination of T66I and T97A) against DTG according to the Stanford University Genotypic Resistance Interpretation. The T97A DRM alone has little to no effect on DTG susceptibility; however, in combination with another INSTI resistance mutation, susceptibility is reduced markedly [11]. Of 192 patients, 8 (4.2%) had M184V detected, a DRM against 3TC. The substitution M184V confers high-level resistance to 3TC. In this cohort, pre-exposure prophylaxis (PrEP) use was not a factor for having 3TC resistance because PrEP was started at the end of 2018. Two DRMs to M184V were additionally observed. Both combinations, K65R plus M184V and L74V plus M184V, have been reported to be highly clinically relevant, with the latter occurring most commonly in patients receiving 3TC [13]. Of 192 individuals, 25 (13.0%) showed a DRM against RPV, with the E138A/K DRMs occurring most frequently. The notably high rate of transmitted E138A/K DRMs may be explained by frequent use of RPV for ART regimens in Austria. According to the current version of the Stanford University HIV Drug Resistance Database, the E138A/K DRMs have been classified as low-level resistance. The K101E/P DRM, which reduces RPV susceptibility significantly, was found in 8 individuals, with 1 showing the K101E DRM in combination with the E138A DRM, which also may reduce susceptibility markedly [14]. The Y181C DRM was observed in 3 individuals, once in combination with the H221Y DRM, which is clinically relevant for ART [15]. In this study, the vast majority of patients harbored DRMs against 1 drug class; the only combination INSTI plus NRTI showed DRMs against DTG and RPV, resulting in an overall frequency of resistance against DTG/RPV of 13.0%, in contrast to DTG/3TC of 4.7%.

Of 82 genetically linked patients, the frequency of DRMs in clustering individuals was found to be significantly higher than that in nonclustering individuals. Of 26 clusters, 6 (23.1%) included individuals (n = 29) with clinically relevant DRMs against DTG, 3TC, and/or RPV. Of these 29 individuals, 15 (51.7%) carried shared DRMs, indicating possible transmission of the DRM within the genetic transmission network.

The limitations of the study include its single-center design and that results need to be validated in other geographic areas with different ART prescribing patterns. Also, our study was underpowered to evaluate specific risk factors for TDR such as race, age, and sexual orientation [16]. Future larger studies are needed to investigate whether the same risk factors are drivers of TDRM in Europe.

In summary, 16% of the overall population studied showed any clinically relevant DRM against DTG, 3TC, and/or RPV before initiating ART. However, only 2% were not eligible for at least 1 of the currently suggested 2-drug regimens, indicating that it may be safe to initiate these 2-drug ART regimens, whereas the results of antiretroviral drug resistance testing are still pending. The prevalence of the DRMs investigated was significantly higher in clustering individuals when compared with nonclustering individuals. Within clusters, the majority of DRMs were shared DRMs, indicating an elevated risk of transmission of resistant HIV-1 strains for patients entering these local clusters. Longitudinal studies investigating the spread of DRMs against DTG, 3TC, and/or RPV in larger populations in other geographical areas are suggested.

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Author contributions. H.H.K., E.S., and M.H. designed the study. H.H.K., E.S., A.B., S.R.M., A.S.B., A.C., and M.H. analyzed and interpreted the data. H.H.K., E.S., S.R.M., C.G.-H., A.C., and M.H. provided the data and contributed critically important ideas on how to interpret the data. H.H.K., E.S., and M.H. drafted the primary draft of the manuscript. H.H.K., E.S., C.G.-H., B.I.S., and M.H. revised the manuscript critically for important intellectual content. All authors revised and approved the final version of the manuscript.

Availability of data and materials. The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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