HIV-1 drug resistance in people on dolutegravir-based ART: A collaborative cohort analysis

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Summary

Background: The widespread use of the integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) in first- and second-line antiretroviral therapy (ART) may facilitate emerging resistance. The DTG RESIST study combined data from HIV cohorts to examine patterns of drug resistance mutations (DRMs) and identify risk factors for DTG resistance.

Methods: We included cohorts with INSTI resistance data from two collaborations (ART Cohort Collaboration, International epidemiology Databases to Evaluate AIDS in Southern Africa), and the UK Collaborative HIV Cohort. Eight cohorts from Canada, France, Germany, Italy, the Netherlands, Switzerland, South Africa, and the UK contributed data on individuals who were viraemic on DTG-based ART and underwent genotypic resistance testing. Individuals with unknown DTG initiation date were excluded. Resistance levels were categorised using the Stanford algorithm. We identified risk factors for resistance using mixed-effects ordinal logistic regression models.

Findings: We included 599 people with genotypic resistance testing on DTG-based ART between 2013 and 2022. Most had HIV-1 subtype B (N=351, 58·6%), a third had been exposed to first-generation INSTIs (N=193, 32·2%); 70 (11·7%) were on DTG dual therapy, and 18 (3·0%) on DTG monotherapy. INSTI DRMs were detected in 86 (14·4%) individuals; 20 (3·3%) had more than one mutation. Most (N=563, 94·0%) were susceptible to DTG, 7 (1·2%) had potential-low, 6 (1·0%) low, 17 (2·8%) intermediate and 6 (1·0%) high-level DTG resistance. The risk of DTG resistance was higher on DTG monotherapy (adjusted odds ratio (aOR) 34·1, 95% CI 9·93 to 117) and DTG lamivudine dual therapy (aOR 9·21, 95% CI 2·20 to 38·6) compared to combination ART, and in the presence of potential-low/low (aOR 5·23, 95% CI 1·32 to 20·7) or intermediate/high-level (aOR 13·4, 95% CI 4·55 to 39·7) nucleoside reverse transcriptase inhibitors (NRTI) resistance.

Interpretation: Among people experiencing viraemia on DTG-based ART, INSTI DRMs and DTG resistance were rare. NRTI resistance substantially increased the risk for DTG resistance, which is of concern, notably in resource-limited settings. Monitoring is important to prevent resistance at the individual and population level and ensure the long-term sustainability of ART.

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Research in context

Evidence before this study

We searched SCOPUS on 20 March 2023 for all publications from inception using the terms "dolutegravir" or "DTG", "resistant" or "resistance", and "HIV". The available evidence on resistance evolution in people living with HIV (PLHIV) with virological failure on DTG-based ART is limited. Most studies assessed the efficacy of DTG-based regimens in clinical studies. They reported drug resistance in individuals experiencing virological failure as a secondary objective or reported single or multiple cases of individuals developing resistance on DTG-based ART. Clinical trials such as the NADIA trial showed high viral suppression even in people with NRTI resistance. Consequently, previous analyses included only a few people experiencing failure on DTG; the SINGLE trial with 39 people with virologic failure on DTG was the largest. The highest number of individuals with DTG resistance was nine study participants in the NADIA trial. There is evidence that DTG resistance in PLHIV on a DTG monotherapy may be more likely, and studies suggest that HIV-1 subtype and mutations acquired during a first-generation INSTI-based regimen might affect the risk of DTG resistance.

Added value of this study

To our knowledge, DTG RESIST is the first study systematically investigating resistance in PLHIV experiencing viraemia on DTG-based ART using a multi-cohort collaboration design reflecting real-world routine care. We collected genotypic resistance tests and clinical data from eight observational HIV cohorts. This resulted in a large dataset of PLHIV experiencing viraemia on a DTG regimen (599 individuals). It allowed a robust assessment of drug resistance mutations and risk factors for DTG resistance. Cross-resistance of first-generation INSTIs does not appear to explain the mutation patterns in PLHIV who experience virological failure on DTG-based ART regimens. PLHIV who received DTG monotherapy or DTG lamivudine dual therapy and those infected with non-B subtypes were more likely to develop resistance. Resistance to NRTIs was a major risk factor for DTG resistance, indicating that PLHIV receiving functional monotherapy are more likely to develop DTG resistance.

Implications of all the available evidence

HIV-1 drug resistance is a significant threat to the sustainability of current and future antiretroviral therapy for combating the ongoing HIV-1 pandemic. Our collaborative analysis shows that cases of DTG resistance are rare at present but not negligible. Given the global DTG roll-out, this might lead to increased frequencies and transmission of DTG resistance, particularly in PLHIV with resistance to NRTIs. While the evidence regarding subtype differences is tentative, it indicates that non-B subtypes,

which are most relevant for the global roll-out of DTG, might be associated with an increased risk of resistance.

Introduction

The integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) was approved in 2013 in the United States and shortly afterwards in the European Union to treat HIV-1. In 2019, the WHO recommended DTG as the preferred drug for first-line and second-line antiretroviral therapy (ART) in all populations, including pregnant women and those of childbearing age. Since then, DTG-based ART was rolled out globally,[1] with about 100 countries including DTG in their treatment guidelines by mid 2020.[2]

DTG has a high genetic barrier to resistance,[3,4] and relatively few people living with HIV (PLHIV) are so far known to have developed resistance.[5–7] The mutations leading to DTG resistance may differ between HIV-1 subtypes. In PLHIV without prior exposure to INSTI-based ART, DTG resistance is mainly associated with the Arg263Lys mutation,[8,9] which was observed in three cases of DTG resistance in the NADIA trial.[10] The Asn155His mutation was present in two individuals with subtype A and C in the SAILING trial,[11] while the Gly118Arg mutation appears to be facilitated by a natural polymorphism in subtype C.[12] In a recent study in Ethiopia, the Gln148His/Lys/Arg mutation was found to be less prevalent in subtype C.[13] Pre-existing mutations, such as those acquired during a first-generation INSTI regimen, may directly confer resistance to DTG or facilitate the accumulation of additional mutations.[14,15]

The risk factors and the mutational patterns that confer resistance to DTG in vivo are less well established than for older antiretroviral drugs.[16] The widespread use of DTG in resource-limited settings, where ART regimens are highly standardised, drugs are recycled, access to adherence support, viral load and resistance testing is limited, and the risk for drug stock-outs is higher, may facilitate the emergence of resistance. In the DTG RESIST study, we combined data from European, North American, and South African cohorts to identify risk factors for DTG resistance and examine the patterns of resistance mutations across different HIV-1 subtypes.

Methods

Study design and population

The DTG RESIST project was discussed in two HIV cohort collaborations: the ART Cohort Collaboration (ART-CC)[17] and the International epidemiology Databases to Evaluate AIDS (IeDEA)[18] in Southern Africa. Six of the 21 ART-CC cohorts participated: The Agence Nationale de la Recherche sur le SIDA et les hépatites virales (ANRS CO3), Aquitaine Cohort, the AIDS Therapy Evaluation in the Netherlands cohort (ATHENA), the Köln/Bonn Cohort (CBC), Germany, the Italian Cohort of Antiretroviral-Naïve Patients (ICONA), the South Alberta Clinic Cohort (SAC), Canada, and the Swiss HIV Cohort Study (SHCS). The main reason for the non-participation of the other cohorts was the lack of access to

resistance data. The UK Collaborative HIV Cohort (UK CHIC) Study and linked UK HIV Drug Resistance Database (UKHDRD), although not formally part of the ART-CC collaboration, also joined. In IeDEA Southern Africa, the South African Aid for AIDS (AfA) cohort was the only cohort with access to INSTI resistance data. The clinical data were provided by the data centres of the two cohort collaborations, ART-CC and IeDEA, and the genotypic data by the cohorts. Genotypic data were the GRT consensus nucleotide sequences. There were two exceptions: AfA provided a list of mutations, and Aquitaine provided the Stanford resistance algorithm output. UK CHIC provided all data directly to the DTG RESIST study team. The appendix provides further details (p 2).

We included participants who underwent genotypic resistance testing from plasma HIV-1 RNA covering the integrase gene between two weeks after starting and up to two months after stopping any DTG-based regimen. The latest test was considered in the case of multiple genotypic resistance tests. Participants with unknown dates of initiation of DTG-based ART were excluded. The analysis of risk factors for DTG resistance was restricted to individuals with at least one year of follow-up, ensuring the availability of viral load data and assessment of viral load testing frequency.

The Human Research Ethics Committee of the University of Cape Town and the Cantonal Ethics Committee of the Canton of Bern granted permission to analyse these data.

Procedures

We determined HIV-1 subtypes from the integrase gene using COMET (COntext-based Modeling for Expeditious Typing)[19] and REGA.[20] If REGA and COMET output differed, the subtype with higher support was assigned. As nucleotide sequences were not available for AfA, we used subtype information from the cohort based on reverse transcriptase (RT) and protease. For Aquitaine, information on subtype was used where available and otherwise considered unknown. The Aquitaine subtypes were characterised locally using Blast analysis on Smartgene HIV module on at least two genes. In the analysis, we grouped HIV-1 subtypes other than the four most common subtypes in the study population (B, C, A, G) as 'other' (F, AD, AE, D, 06_CPX, 18_CPX, unknown) (appendix p 3).

Individuals prescribed raltegravir or elvitegravir before starting the DTG-based regimen were considered exposed to first-generation INSTIs. Viral load testing frequency was calculated for individuals with more than one year of follow-up before the Genotypic Resistance Test (GRT). We quantified HIV-1 viral load as the area under the curve (AUC) of the $\log_{10}$-transformed viral load measurements from DTG initiation to the GRT sample date. To account for differences in detection limits, we set any viral load measurement below 50 to 0 copies per mL. For individuals who initiated ART with the DTG-based regimen, we excluded viral loads at ART initiation by setting measurements

within the first 180 days from the first HIV-1 RNA measurement to 0. Time on DTG-based ART was calculated in years from DTG initiation to GRT. The ART regimen at GRT was the regimen an individual took 14 days before the test. If available, GRT results from earlier time points were used to assess prior NRTI resistance. We defined monotherapy as ART consisting of DTG only. DTG dual therapy was defined as DTG combined with a second antiretroviral drug. DTG-based regimens comprised of DTG and two or more antiretroviral drugs were considered triple or intensified regimens, respectively.

Outcomes

We defined two HIV drug resistance outcomes: the level of resistance to DTG and the presence of known drug resistance mutations (DRMs). The Stanford HIV Database version 9·0 and the Stanford HIVdb algorithm[21] were used to categorise drug resistance levels as susceptible (score below 10), potential low (10-14), low (15-29), intermediate (30-59) or high ($\geq$60). We defined INSTI-DRMs[22] as all mutations associated with INSTIs by the Stanford HIVdb algorithm, including major and accessory mutations. We used the same approach to assess resistance to all other antiretroviral drugs, whereby drug resistance to tenofovir alafenamide (not covered by the Stanford algorithm) was considered equal to tenofovir disoproxil fumarate resistance. Resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) was calculated as the median of the scores for efavirenz, etravirine, nevirapine, and rilpivirine. Finally, we calculated resistance to nucleoside reverse transcriptase inhibitors (NRTIs) as the median of abacavir, zidovudine, emtricitabine/lamivudine, and tenofovir disoproxil fumarate scores. We used alternative definitions in sensitivity analyses.

Statistical analysis

We used descriptive statistics to present the characteristics of the study population and the different INSTI drug-resistance mutations. A negative binomial generalised linear model, adjusting for HIV-1 subtype, exposure to first-generation INSTIs, and sex, was used to analyse the number of major and accessory INSTI drug-resistance mutations. We used ordinal logistic regression to identify risk factors for developing resistance, including cohort as a random effect. We considered variables based on availability and clinical relevance. We included sex, age at initiation and time on the DTG-based regimen, HIV-1 subtype, type of ART (combination ART based on three drugs or more, DTG lamivudine dual therapy, other DTG dual therapy, or monotherapy), exposure to first-generation INSTIs, HIV-1 viral load, viral load testing frequency, and resistance to NRTIs. If the sequencing did not cover the RT, the missing data was included as a separate category. All analyses were performed in R, version 4·0·5.

We performed several sensitivity analyses. First, we replaced the NRTI resistance variable with the presence or absence of the Met184Val/Ile mutation (sensitivity analysis S1). Further, we performed

logistic regression using the same covariables as in the main risk factor analysis, using susceptible versus any DTG resistance as the outcome (S2). We also considered DTG resistance according to the WHO definition, whereby potential low is considered susceptible (S3). We repeated the risk factor analyses excluding study participants where RT was not sequenced (S4). Given the widespread use of tenofovir disoproxil fumarate-lamivudine-dolutegravir (TLD), we restricted the analysis of NRTIs to tenofovir disoproxil fumarate and lamivudine, using the higher resistance level of the two to quantify NRTI resistance (S5). In the subset of people on a DTG + 2 NRTI regimen, we calculated NRTI resistance specific to the two NRTIs used in each participant (S6). The main analysis could not assess whether NRTI and NNRTI resistance mutations pre-existed or were acquired on DTG. Sensitivity analysis S7 restricted the study population to participants with available GRTs before experiencing viraemia on the DTG-containing regimen.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 599 people met the eligibility criteria and were included in the analysis of mutations conferring resistance to DTG; 540 (90%) had more than one year of follow-up since starting the DTG-based regimen and were included in the analysis of risk factors for DTG resistance. Table S3 and table S4 (appendix p. 4 and p. 5) show the number of participants included in the risk factor analysis by presence or absence of INSTI DRMs, and by DTG resistance levels, respectively.

The study participants included in the two analyses – mutations conferring DTG resistance and risk factors for DTG resistance – were similar (**Table *1***): most participants were men living with HIV-1 subtype B who were on combination ART with three or more antiretroviral drugs (see appendix p 3 for details on ART regimens). The median year of starting DTG was 2016. People had been on DTG for a median of 1·4 years at the time of genotypic resistance testing, and the median AUC of $\log_{10}$ viral load (copies per mL) accumulated during this period was 3·6. The first GRT was performed on 22. May 2013, and the last on 20. December 2021. About a third of participants had previously been exposed to first-generation INSTIs; most were exposed to raltegravir (142/193), followed by elvitegravir (38/193), and both elvitegravir and raltegravir (13/193). A total of 129 people did not have a CD4 measurement within a year of the GRT, ten did not have any recorded HIV-1 RNA measurements before the GRT, and in 62 people sequencing did not cover RT.

At least one major or accessory INSTI DRM was found in 86 (14%) of the 599 study participants; 20 (3%) had more than one mutation (appendix p 6-7). The proportion of study participants with any INSTI DRM was similar between first-generation INSTI exposed and unexposed individuals (28 out of 86 (33%) and 165 out of 513 (32%), respectively). Most (563; 94%) study participants were fully susceptible to DTG, with potential low, low, intermediate, and high levels of DTG resistance being observed in 7 (1%), 6 (1%), 17 (2%) and 6 (1%), respectively (**Figure *1***).

The most common major INSTI DRM was Arg263Lys (N = 10), which only once occurred with another major INSTI DRM (appendix p 6). Other common major mutations included Gly140Lys/Arg/Ser (N = 9), Asn155His (N = 9), Gln148His/Arg (N = 6), and Glu138Lys (N = 7). The Gly118Arg, which has the strongest impact on susceptibility to DTG, was only observed three times. Among accessory DRMs, Glu157Gln (N = 23) and Thr97Ala (N = 18) were the most common. The distribution of INSTI resistance mutations was similar in people previously exposed to first-generation INSTIs and those not exposed (**Figure *2***). There was no statistically significant association of specific DRMs with first-generation INSTI experience. For HIV-1 subtype, we found a significant association after adjusting for multiple testing for the accessory INSTI DRM Thr97Ala (adjusted p-value = 0·015, see appendix p 8). This DRM occurred in 6 of 54 (11%) people with HIV-1 subtype A, 4 of 42 (10%) people with subtype G, 6 of 351 (2%) people with subtype B, and 0 of 69 people with HIV-1 subtype C.

The results from the negative binomial model of the number of mutations showed little evidence of a difference between HIV-1 subtypes. The total INSTI DRM count (including both accessory and major DRMs) was higher in first-generation INSTI-exposed people (adjusted RR 1·59, 95% CI 0·98 to 2·59) (**Error! Reference source not found.**). This association became stronger when considering only the n umber of major INSTI DRMs (adjusted RR 2·67, 95% CI 1·25 to 5·87) (see appendix p 9 for further details).

The prevalence of predicted resistance (low, intermediate or high) to NRTIs and NNRTIs was substantially higher in the presence of DTG resistance (Table 2). Among GRTs with coverage of the RT, the prevalence of at least low-level NRTI resistance was 7% overall (39 of 530), but 32% (7 of 22) among those with DTG resistance. The corresponding figures for NNRTI resistance were 15% (82 of 530) and 50% (11 of 22).

The risk of DTG resistance was higher on DTG monotherapy compared to combination ART with three or more drugs (adjusted odds ratio [aOR] 34·09, 95% CI 9·93 to 117·01) and for DTG lamivudine dual regimen (aOR 9·21, 95% CI 2·20 to 38·55) (**Error! Reference source not found.**). The risk of resistance w as also increased in the presence of a potential low/low level of NRTI resistance (aOR 5·23, 95% CI 1·32 to 20·71) or intermediate/high level (aOR 13·44, 95% CI 4·55 to 39·68), compared to no NRTI

resistance. Non-B HIV-1 subtypes were also associated with increased resistance, particularly subtype A (aOR 3·12, 95% CI 0·84 to 11·61 compared to subtype B), but associations were not statistically significant (appendix p 10). Similarly, there was weak, statistically non-significant evidence for an association of viral load with DTG resistance (aOR 1·42, 95% CI 0·92 to 2·19 per standard deviation of the $\log_{10}$ virus load area under the curve).

The results of the risk factor analyses were similar when replacing the NRTI resistance variable with the Met184Val/Ile mutation (sensitivity analysis S1, N=540/540, appendix p 12), when analysing susceptible versus any DTG resistance as the outcome in a logistic regression (S2, N=540/540, appendix p 13), or when considering DTG resistance levels following the WHO definition, where potential low-level resistance is considered susceptible (S3, N=540/540, appendix p 14). The exclusion of 58 individuals with missing RT sequences allowed the inclusion of both NRTI and NNRTI resistance in the model. The results for NRTI resistance were similar, and intermediate/high-level NNRTI resistance was also associated with DTG resistance (adjusted OR 2·72, 95% CI 0·94 to 7·86) (S4, N=482/540, appendix p 15). Results were similar when excluding individuals on DTG monotherapy (S5, N=474/540, appendix p 16). The analysis restricted to lamivudine and tenofovir disoproxil fumarate (S6, N=540/540, appendix p 17) confirmed that DTG resistance was associated with both potential low/low and intermediate/high-level resistance to these NRTI drugs. Similarly, when restricting the analysis to people on a DTG regimen with two NRTIs, we found similar results for the specific NRTIs (S7, N=309/540, appendix p 18). Finally, in sensitivity analysis S8, we used data on pre-existing NRTI resistance and found that DTG resistance was associated with prior intermediate/high NRTI resistance (N=356/540, appendix p 19).

Discussion

In this collaborative analysis of eight large cohort studies, we identified INSTI DRMs in 86 of 599 (14%) PLHIV with a genotypic resistance test while viraemic on DTG-based ART. Resistance to DTG according to the Stanford algorithm was present in 36 (6%) individuals. DTG resistance was associated with DTG monotherapy, lamivudine DTG dual therapy, and resistance to NRTIs. Exposure to first-generation INSTI was associated both with more resistance mutations and higher levels of DTG resistance, but the association with DTG resistance was not statistically significant. A wide range of INSTI DRMs was present. The polymorphic accessory INSTI DRM Thr97Ala was detected more frequently in subtypes A and G (compared to subtypes B and C), consistent with previously reported data.[23] The major INSTI DRMs Gly140Lys/Arg/Ser and Gln148His/Arg were detected in 5 out of 6 people with high-level DTG resistance.

DTG monotherapy, DTG lamivudine dual therapy and resistance to the NRTI backbone were most strongly associated with DTG resistance in our study. The complete sequence analysis, which allowed us to distinguish between NRTI and NNRTI resistance, suggests that the association may be mediated via NRTI resistance. It was robust when considering only 3TC and TDF resistance in a sensitivity analysis. As the main analysis was cross-sectional, it did not allow determining the timing of NRTI resistance relative to DTG resistance. However, an additional analysis in people with prior resistance tests suggests that NRTI resistance may often have predated DTG resistance. These results suggest that resistance to NRTI backbone drugs from previous regimens may have promoted the emergence of DTG resistance. However, its also possible that prior NRTI resistance reflects adherence issues, which may facilitate the emergence of DTG resistance.

The results from our study align with previous studies[10,24,25] that showed associations of DTG resistance with DTG monotherapy or NRTI resistance. By contrast, the NADIA trial found no evidence that resistance to NRTIs affects the effectiveness of DTG-based ART.[10] The NADIA trial does not, however, contradict the results of our study because outcomes differed: NADIA examined the risk of virological failure, whereas our study focused on the risk of DTG resistance among PLHIV tested for drug resistance while on DTG-based ART. Resistance to NRTIs may not impact treatment failure risk but still increase the chances of acquiring resistance in case of failure. Research on other drug classes[26] indicates that drug regimens with high and low genetic barriers can have similar failure rates but different probabilities of acquiring resistance.

Our study contributes important new information on DTG resistance in PLHIV receiving different DTG-based ART regimens by examining risk factors for DTG resistance in real-world cohort data from different settings. The cohort collaboration resulted in a large dataset of GRT results in people who experienced viraemia on DTG. Our results are central to informing HIV treatment and monitoring policies in the context of the continued expansion of DTG-based treatment regimens. The pooling of data from diverse routine clinical cohorts also has limitations. The participating cohorts include PLHIV in routine care but practices regarding when and for whom GRT is done will differ between cohorts. Further, the personalised approach to ART and HIV care in the European settings will not be generalisable to other settings, particularly to low- and middle-income countries. In our regression models, we accounted for this heterogeneity between cohorts by including cohort as a random effect, but confounding by cohort may still have affected our results. Furthermore, GRT before starting or switching ART may have prevented some individuals from receiving DTG, thus introducing selection bias. However, pre-treatment resistance to DTG was unlikely during the study period.[27]

A further limitation of our study is the dominance of HIV-1 subtype B, which was expected considering that our study population is comprised mainly of PLHIV from European countries, where subtype B predominates. More data from people with non-B subtypes are needed. The prospective arm of DTG RESIST is ongoing within the framework of the International epidemiology Databases to Evaluate AIDS (IeDEA):[18] individuals experiencing virologic failure on DTG-based ART are prospectively enrolled in around forty sites across sub-Saharan Africa, South America, and Asia. Furthermore, the WHO plans to launch sentinel surveys of acquired HIV resistance to DTG among people receiving DTG-based ART.[28] We could not assess adherence or drug interactions with rifampicin, which may influence the emergence of DTG resistance.[29] Adherence and rifampicin use were not recorded consistently and comparably in the participating cohorts. In our study population, the DTG-based regimens were too heterogenous to investigate DTG resistance outcomes of specific regimens and treatment histories. Lastly, there is growing evidence that mutations outside integrase may confer DTG resistance[30–32]. Our study was based on pol sequences, which did not allow us to investigate the effects of these mutations.

The associations we found with DTG resistance, resistance to NRTI backbone drugs, and trends for HIV-1 subtype and unsuppressed virus load have important implications for ensuring the long-term sustainability of ART. While overall INSTI resistance was rare in our population, and while the low risk of virological failure will further reduce the incidence of resistance among people treated with DTG, DTG resistance is still a concern. Firstly, the duration of DTG therapy and the duration of viraemia whilst receiving DTG was relatively short in our population: the median time on DTG was less than two years, and drug resistance might emerge more frequently in settings where individuals remain viraemic for a longer time on DTG regimens. This could happen in resource-limited settings where guidelines recommend not switching from DTG-based therapy unless multiple viral loads >1000 copies per mL have been documented and where delays in regimen switching are common.[33] Secondly, the strong association of DTG resistance with NRTI resistance suggests that the risk of resistance might be higher in people with previous failure on NNRTI-based first-line therapy, among whom the prevalence of NRTI resistance is much higher than in our study population. The WHO guidelines recommend DTG in 1st-, 2nd- and 3rd-line ART. This multiplicity of roles combined with the recycling of drugs and limited access to viral load and drug resistance testing will facilitate the emergence of DTG resistance. Finally, even a relatively low level of acquired DTG resistance in the millions of people receiving DTG-based ART could lead to rising levels of transmitted INSTI resistance, which could negatively affect both treatment and prevention.

In conclusion, our study underlines the importance of resistance testing, especially in treatment-experienced people. Although rare, DTG resistance can develop in people who experience viraemia

on a DTG-containing ART regimen. Monitoring the emergence of such resistance is important to prevent resistance at the individual and the population level and to ensure the long-term sustainability of ART.

Figures & tables

Table 1: Demographics and clinical characteristics in the study population. People with virological failure on DTG-based ART with available genotypic resistance tests from eight observational HIV cohorts were included in the study. Study participants where clinical data was available for at least one year were considered for analysing risk factors for DTG resistance.

Numbers (%) and medians [interquartile range] are shown.

* Other subtypes are comprised as follows: For the analysis of resistance conferring mutations - Unknown, N=28 (4.7%); F, N=19 (3.2%); AE, N=10 (1.7%); D, N=10 (1.7%); 06_CPX, N=6 (1%); AG, N=4 (0.7%); 18_CPX, N=2 (0.3%); NA, N=2 (0.3%); AD, N=1 (0.2%); and H, N=1 (0.2%). For the analysis of risk factors for DTG resistance - Unknown, N=25 (4.6%); F, N=15 (2.8%); D, N=10 (1.9%); AE, N=7 (1.3%); 06_CPX, N=5 (0.9%); AG, N=4 (0.7%); NA, N=2 (0.4%); 18_CPX, N=1 (0.2%); AD, N=1 (0.2%); and H, N=1 (0.2%).

Abbreviations: ATHENA, the AIDS Therapy Evaluation in the Netherlands cohort; Aquitaine, Agence Nationale de la Recherche sur le SIDA et les hépatites virales (ANRS) CO3 Aquitaine Cohort; ICONA, Italian Cohort of Antiretroviral-Naïve Patients; CBC, Cologne/Bonn Cohort, Germany; SHCS, Swiss HIV Cohort Study; SAC, South Alberta Clinic Cohort, Canada; AfA, Aid for AIDS, South Africa; UK CHIC/UKHDRD, UK Collaborative HIV Cohort (UK CHIC) Study/ UK HIV Drug Resistance Database.

Figure 1: Prevalence of DTG resistance and INSTI DRMs. Genotypic resistance tests of 599 people with genotypic resistance testing on DTG-based ART were analysed using the Stanford resistance algorithm to determine INSTI DRMs and resistance level to DTG. Both major and accessory INSTI DRMs were considered for the number of INSTI DRMs. People with no INSTI DRMs (N = 86, 85.6%), and who are susceptible to DTG (N = 563, 94%) are not displayed.

Figure 2: INSTI drug resistance mutations found in 599 people experiencing viraemia on a DTG-based regimen. Drug resistance mutations were classified as major and accessory according to the Stanford resistance database[22]. Bars are coloured by previous history of first-generation INSTIs (raltegravir, elvitegravir).

Figure 3: Rate ratio for number of INSTI DRMs. A negative binomial generalised linear model was fit to the number of major and accessory INSTI DRMs in 599 people with viraemia on DTG-based ART. The plot shows uni- and multivariable point estimates and 95% confidence intervals of rate ratios.

Table 2: Resistance levels to DTG, non-nucleoside reverse transcriptase inhibitors and nucleotide reverse transcriptase inhibitors. Number and percentage of people with corresponding drug resistance levels are given for the entire study population. NRTI resistance level is based on median resistance score to ABC, AZT, XTC and TDF/TAF. NNRTI resistance level is based on median resistance score to EFV, ETR, NVP, and RPV.

Figure 4: Odds ratios for DTG resistance levels with 95% confidence intervals from uni- and multivariable ordinal logistic models for genotypic DTG resistance. Cohorts were included as random effect. DTG resistance levels in people with viraemia on DTG-based ART were assessed using the Stanford resistance algorithm.

Authors' contributions

Conceptualisation (HFG, JACS, RL, ME, RK), Data curation (TL, SH, SI, HO), Methodology (TL, CS, RK, ME, JACS), Formal analysis & Validation (TL, RK), Investigation (TL, SH, SI), Project administration (SH, SI), Resources (HO, KK, JM, AvS, MS, AAM, JG, CS, GM), Software (TL, KK), Supervision (HFG, JACS, RL, ME, RK), Visualisation (TL), Writing – original draft (TL, RL, ME, RK), Writing – review & editing (All authors).

TL and RDK had directly accessed and verified the underlying data reported in the manuscript. ME, TL and RDK had full access to the data, other authors had access to the data from their cohort, but not to the data from the other cohorts. ME had the final responsibility for the decision to submit for publication.

Declaration of interests

SMI reports grant funding from NIH NIAAA for the work of ART-CC (payment to institution). AvS reports funding from the Dutch Ministry of Health, Welfare and Sport for the maintenance of the ATHENA database, and grant funding from the European Centre for Disease Prevention and Control (ECDC) (payment to institution). MJG reports honoraria as Ad Hoc member of HIV National Advisory Board from Merck, Gilead Sciences, and ViiV, and a leadership position as Medical Director S Alberta HIV clinic. CAS has received funding from Gilead Sciences, ViiV Healthcare and Janssen-Cilag for membership of Data Safety and Monitoring Committees, Advisory Committees and for preparation of educational material. HFG has received personal fees from Merck, Gilead Sciences, ViiV, GSK, Janssen, Johnson and Johnson and Novartis, as an advisor/consultant or for DSMB membership and has received a travel grant from Gilead. JACS reports funding for research in this publication from NIH NIAAA (payment to institution), UK NIHR (payment to institution), and the University of Bern (payment to institution). RL reports support for research in this publication by the National Institute of Allergy & Infectious Diseases of the National Institutes of Health under award number R01AI152772, and support from the National Institute of Allergy & Infectious Diseases of the National Institutes of Health under award number R01AI167699 for a separate project pertaining to HIV treatment strategies. ME reports funding for research in this publication from the Swiss National Science Foundation (32FP30-18949) and the National Institutes of Health (Cooperative Agreement AI069924 and R01 AI152772-01). RK reports funding for research in this publication from the Swiss National Science Foundation and the National Institute of Allergy & Infectious Diseases of the National Institutes of Health, and reports grant funding from Gilead Sciences. All other authors declare no competing interest.

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Data sharing statement

Study data will not be publicly available. Data can be made available to interested researchers. Deidentified participant data and a data dictionary can be made available and shared under a data transfer agreement. Requests for access to DTG RESIST data should be sent to matthias.egger@unibe.ch. Nucleotide sequences are available on GenBank for the cohorts where local regulations allowed data sharing (see table S1, appendix p. 2)

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Table 3: Demographics and clinical characteristics in the study population. People with virological failure on DTG-based ART with available genotypic resistance tests from eight observational HIV cohorts were included in the study. Study participants where clinical data was available for at least one year were considered for analysing risk factors for DTG resistance.

	Analysis of resistance conferring mutations (N=599)	**Analysis of risk factors for DTG resistance** (N=540)
Sex		
Female	187 (31.2%)	175 (32.4%)
Male	412 (68.8%)	365 (67.6%)
Age at DTG Initiation (years)	44 [36 - 52]	45 [37 - 52]
HIV Subtype		
B	351 (58.6%)	316 (58.5%)
C	69 (11.5%)	63 (11.7%)
A	54 (9.0%)	51 (9.4%)
G	42 (7.0%)	39 (7.2%)
Other*	83 (13.9%)	71 (13.1%)
ART regimen at DTG initiation		
Combination therapy with ≥3 ARVs	511 (85.3%)	455 (84.3%)
Dual therapy (DTG & other)	51 (8.5%)	50 (9.3%)
Dual therapy (DTG & Lamivudine)	19 (3.2%)	17 (3.1%)
Monotherapy	18 (3.0%)	18 (3.3%)
ART duration at DTG initiation (years)	6.7 [0.95 - 14]	7.9 [2.4 - 15]
Missing	4 (0.7%)	4 (0.7%)
Year of DTG initiation	2016 [2015 - 2017]	2016 [2015 - 2017]
Year of genotypic resistance test	2018 [2017 - 2019]	2018 [2017 - 2019]
Availability of additional (prior) GRTs		
Yes	395 (65.9%)	356 (65.9%)
No	204 (34.1%)	184 (34.1%)
DTG-regimen initiation		
Switch to DTG-based ART	486 (81.1%)	470 (87.0%)
Initiation on DTG-based ART	113 (18.9%)	70 (13.0%)
Duration on DTG-based ART at GRT (years)	1.4 [0.58 - 2.7]	1.6 [0.67 - 2.8]
Exposure to first generation INSTI		
Yes	193 (32.2%)	184 (34.1%)
No	406 (67.8%)	356 (65.9%)
CD4 count at GRT (cells per µL)	412 [213 - 674]	433 [218 - 681]
Missing	129 (21.5%)	115 (21.3%)
Viral load AUC (of log10 copies per ml during DTG based ART)	3.6 [2.2 - 5.0]	3.6 [2.3 - 4.9]
Missing	10 (1.7%)	0 (0%)
No. of HIV tests per year	3.0 [2.0 - 4.3]	3.3 [2.3 - 4.3]
Missing	20 (3.3%)	0 (0%)
Cohort		
AfA	9 (1.5%)	9 (1.7%)
Aquitaine	64 (10.7%)	59 (10.9%)
ATHENA	66 (11.0%)	64 (11.9%)

CBC	89 (14.9%)	76 (14.1%)
ICONA	8 (1.3%)	5 (0.9%)
SAC	92 (15.4%)	87 (16.1%)
SHCS	118 (19.7%)	108 (20.0%)
UK CHIC/UKHDRD	153 (25.5%)	132 (24.4%)

Numbers (%) and medians [interquartile range] are shown.

* Other subtypes are comprised as follows: For the analysis of resistance conferring mutations - Unknown, N=28 (4.7%); F, N=19 (3.2%); AE, N=10 (1.7%); D, N=10 (1.7%); 06_CPX, N=6 (1%); AG, N=4 (0.7%); 18_CPX, N=2 (0.3%); NA, N=2 (0.3%); AD, N=1 (0.2%); and H, N=1 (0.2%). For the analysis of risk factors for DTG resistance - Unknown, N=25 (4.6%); F, N=15 (2.8%); D, N=10 (1.9%); AE, N=7 (1.3%); 06_CPX, N=5 (0.9%); AG, N=4 (0.7%); NA, N=2 (0.4%); 18_CPX, N=1 (0.2%); AD, N=1 (0.2%); and H, N=1 (0.2%).

Abbreviations: ATHENA, the AIDS Therapy Evaluation in the Netherlands cohort; Aquitaine, Agence Nationale de la Recherche sur le SIDA et les hépatites virales (ANRS) CO3 Aquitaine Cohort; ICONA, Italian Cohort of Antiretroviral-Naïve Patients; CBC, Cologne/Bonn Cohort, Germany; SHCS, Swiss HIV Cohort Study; SAC, South Alberta Clinic Cohort, Canada; AfA, Aid for AIDS, South Africa; UK CHIC/UKHDRD, UK Collaborative HIV Cohort (UK CHIC) Study/ UK HIV Drug Resistance Database.

Figure 1

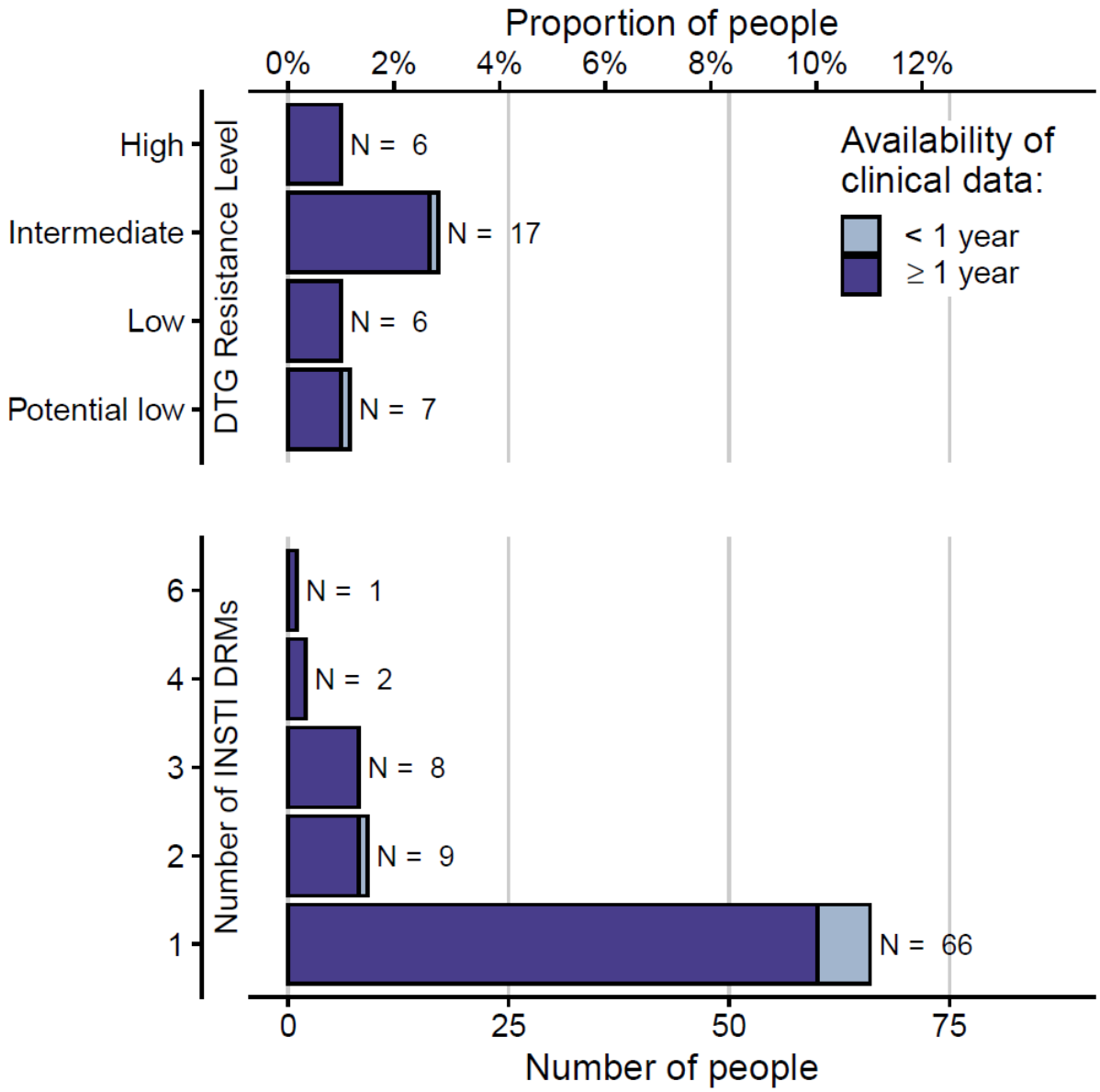

Proportion of people
0%
2%
4%
6%
8%
10%
12%
DTG Resistance Level
High
Intermediate
Low
Potential low
N = 6
N = 17
N = 6
N = 7
Availability of clinical data:
< 1 year
≥ 1 year
Number of INSTI DRMs
6
4
3
2
1
N = 1
N = 2
N = 8
N = 9
N = 66
0
25
50
75
Number of people

Figure 2

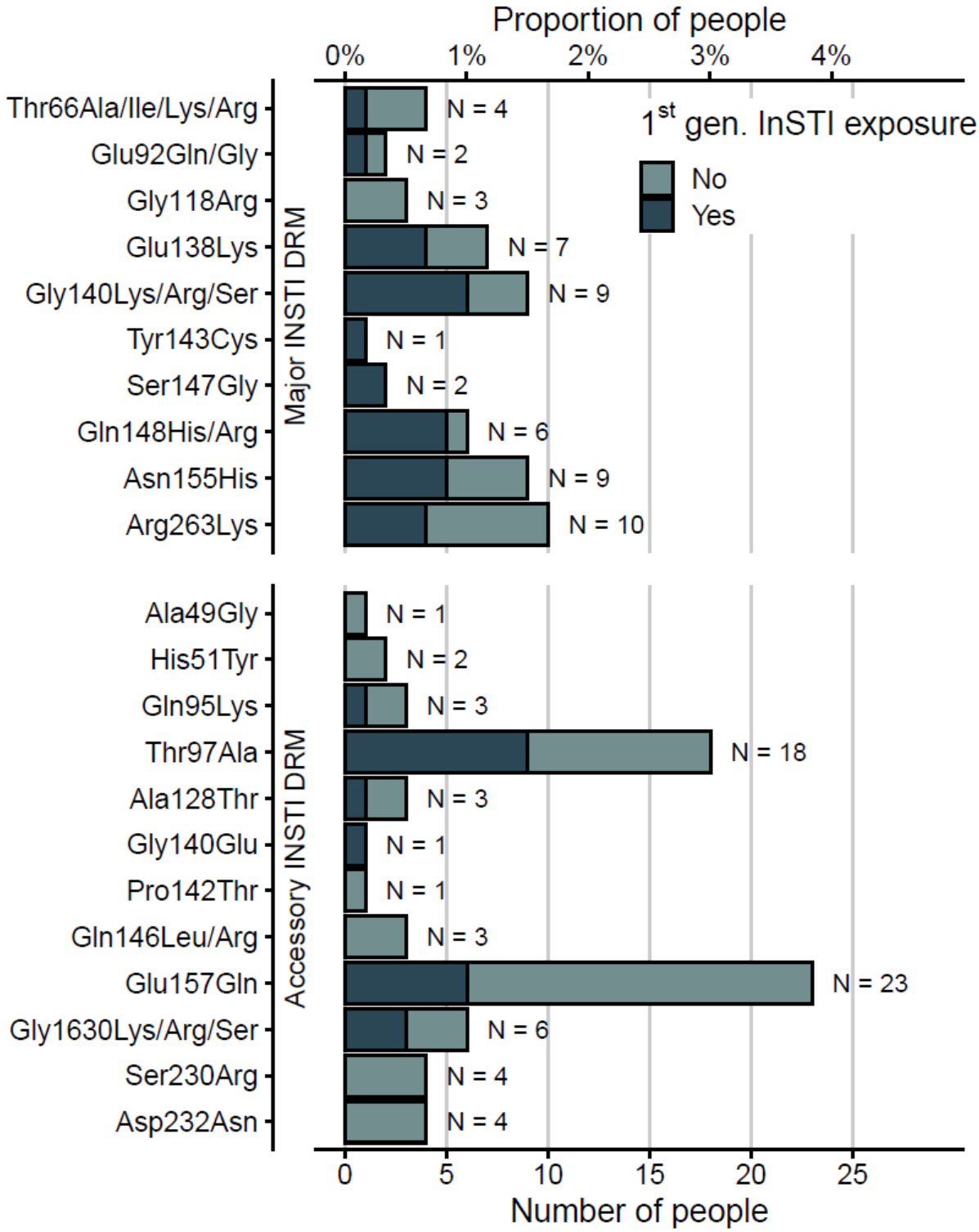

Proportion of people
0%
1%
2%
3%
4%
1st gen. InSTI exposure
No
Yes
Major INSTI DRM
Thr66Ala/Ile/Lys/Arg
Glu92Gln/Gly
Gly118Arg
Glu138Lys
Gly140Lys/Arg/Ser
Tyr143Cys
Ser147Gly
Gln148His/Arg
Asn155His
Arg263Lys
N = 4
N = 2
N = 3
N = 7
N = 9
N = 1
N = 2
N = 6
N = 9
N = 10
Accessory INSTI DRM
Ala49Gly
His51Tyr
Gln95Lys
Thr97Ala
Ala128Thr
Gly140Glu
Pro142Thr
Gln146Leu/Arg
Glu157Gln
Gly1630Lys/Arg/Ser
Ser230Arg
Asp232Asn
N = 1
N = 2
N = 3
N = 18
N = 3
N = 1
N = 1
N = 3
N = 23
N = 6
N = 4
N = 4
0
5
10
15
20
25
Number of people

Figure 3

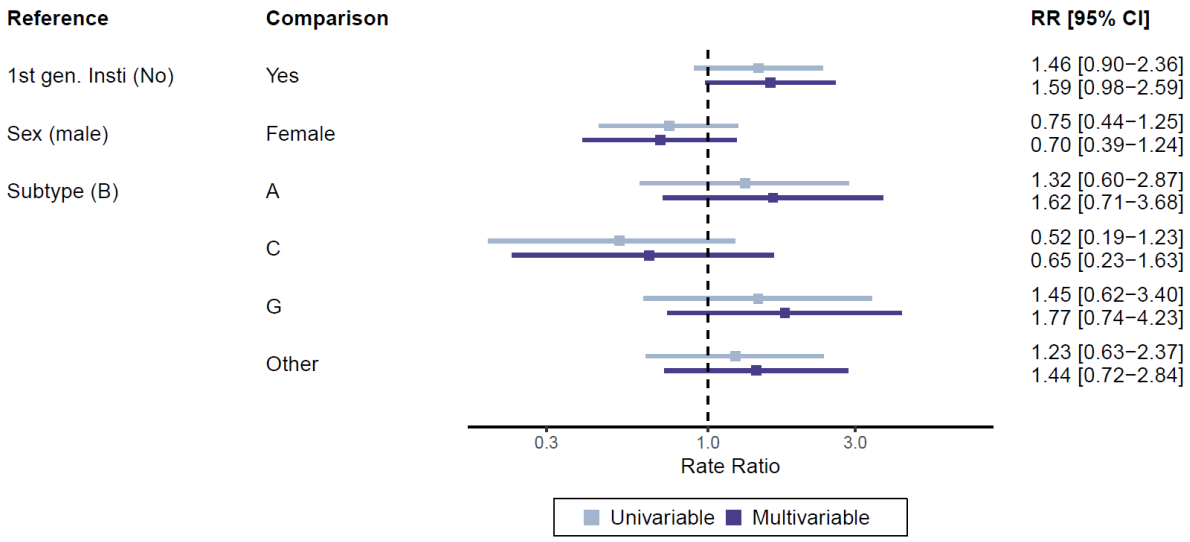
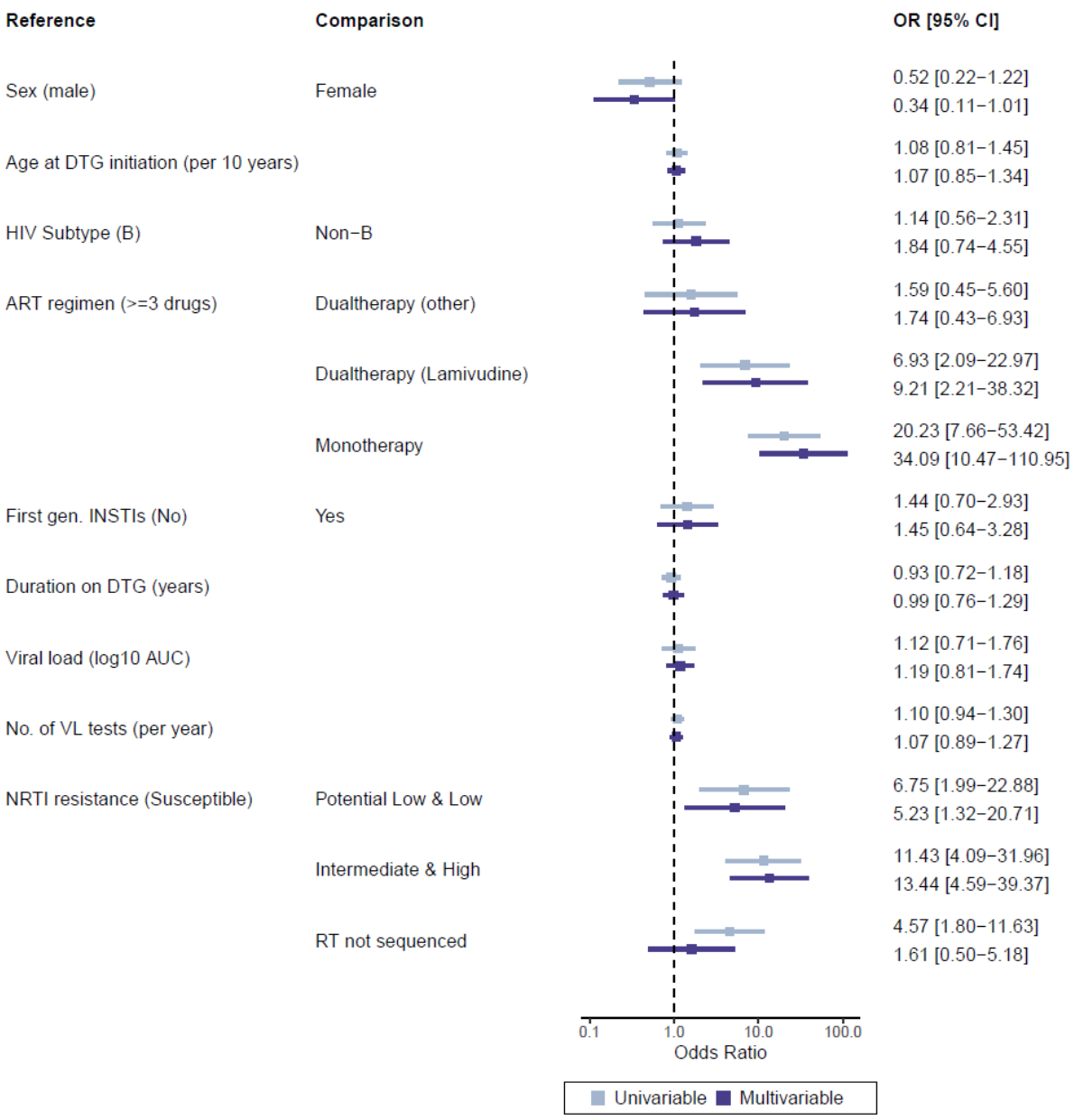

Reference
Comparison
RR [95% CI]
1st gen. Insti (No)
Yes
1.46 [0.90−2.36]
1.59 [0.98−2.59]
Sex (male)
Female
0.75 [0.44−1.25]
0.70 [0.39−1.24]
Subtype (B)
A
1.32 [0.60−2.87]
1.62 [0.71−3.68]
C
0.52 [0.19−1.23]
0.65 [0.23−1.63]
G
1.45 [0.62−3.40]
1.77 [0.74−4.23]
Other
1.23 [0.63−2.37]
1.44 [0.72−2.84]
0.3
1.0
3.0
Rate Ratio
Univariable
Multivariable

Table 4: Resistance levels to DTG, non-nucleoside reverse transcriptase inhibitors and nucleotide reverse transcriptase inhibitors. Number and percentage of people with corresponding drug resistance levels are given for the entire study population. NRTI resistance level is based on median resistance score to ABC, AZT, XTC and TDF/TAF. NNRTI resistance level is based on median resistance score to EFV, ETR, NVP, and RPV.

	DTG resistance level	
	Susceptible & Potential Low (N=570)	**Low, Intermediate, High** (N=29)
NRTI resistance level		
Susceptible	467 (81.9%)	13 (44.8%)
Potential low	9 (1.6%)	2 (6.9%)
Low	10 (1.8%)	1 (3.4%)
Intermediate	9 (1.6%)	2 (6.9%)
High	13 (2.3%)	4 (13.8%)
RT not covered in GRT	62 (10.9%)	7 (24.1%)
NNRTI resistance level		
Susceptible	414 (72.6%)	11 (37.9%)
Potential low	23 (4.0%)	0 (0%)
Low	18 (3.2%)	0 (0%)
Intermediate	34 (6.0%)	4 (13.8%)
High	19 (3.3%)	7 (24.1%)
RT not covered in GRT	62 (10.9%)	7 (24.1%)

Figure 4


Reference
Comparison
OR [95% CI]
Sex (male)
Female
0.52 [0.22−1.22]
0.34 [0.11−1.01]
Age at DTG initiation (per 10 years)
1.08 [0.81−1.45]
1.07 [0.85−1.34]
HIV Subtype (B)
Non−B
1.14 [0.56−2.31]
1.84 [0.74−4.55]
ART regimen (>=3 drugs)
Dualtherapy (other)
1.59 [0.45−5.60]
1.74 [0.43−6.93]
Dualtherapy (Lamivudine)
6.93 [2.09−22.97]
9.21 [2.21−38.32]
Monotherapy
20.23 [7.66−53.42]
34.09 [10.47−110.95]
First gen. INSTIs (No)
Yes
1.44 [0.70−2.93]
1.45 [0.64−3.28]
Duration on DTG (years)
0.93 [0.72−1.18]
0.99 [0.76−1.29]
Viral load (log10 AUC)
1.12 [0.71−1.76]
1.19 [0.81−1.74]
No. of VL tests (per year)
1.10 [0.94−1.30]
1.07 [0.89−1.27]
NRTI resistance (Susceptible)
Potential Low & Low
6.75 [1.99−22.88]
5.23 [1.32−20.71]
Intermediate & High
11.43 [4.09−31.96]
13.44 [4.59−39.37]
RT not sequenced
4.57 [1.80−11.63]
1.61 [0.50−5.18]
0.1
1.0
10.0
100.0
Odds Ratio
Univariable
Multivariable