Predictors of treatment-emergent resistance to dolutegravir

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Integrase strand transfer inhibitor (INSTI)-based regimens became a first-line treatment for HIV worldwide in 2018, with 93% of people with HIV who are on antiretroviral therapy (ART) estimated to be taking dolutegravir-based regimens as of 2023. Since the genetic barrier to resistance of dolutegravir is not impenetrable, rising rates of dolutegravir resistance among those with virological failure on this drug regimen have been reported. Risk factors for dolutegravir resistance include treatment experience, having background resistance to the nucleoside reverse transcriptase inhibitors in the regimen, switching to tenofovir, lamivudine, and dolutegravir when viraemic on a former regimen, previous experience with first-generation INSTIs, and being on dolutegravir monotherapy or dual therapy, with rates higher in children than in adults. HIV drug resistance does not emerge if selective drug pressure is not present, so some exposure to the ART regimen with virological failure is associated with higher rates of resistance than complete non-adherence. Detectable objective metrics of adherence (eg, ART drug concentrations in urine, plasma, dried blood spots, and hair) have been associated with high levels of viral resistance and can be used to triage who needs resistance testing the most.

Lancet HIV 2025

Published Online June 19, 2025 https://doi.org/10.1016/S2352-3018(25)00127-4

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Introduction

In 2018, one of the most notable changes in the modern era of antiretroviral therapy (ART) began with the recommendation of tenofovir, lamivudine, and dolutegravir as the preferred ART regimen for most people with HIV worldwide. In addition to people with HIV who are newly initiating ART, over 20 million treatment-experienced people with HIV have now been transitioned from non-nucleoside reverse transcriptase inhibitor (NNRTI)-based and protease inhibitor (PI)-based regimens to a tenofovir, lamivudine, and dolutegravir regimen. By 2023, 93% of all people with HIV in low-income and middle-income countries were estimated to be taking dolutegravir-based regimens.[1]

The recommendation for tenofovir, lamivudine, and dolutegravir as the preferred ART regimen was a result of multiple factors, including tolerability, lower costs, potency, and, notably, the high genetic barrier to resistance to dolutegravir as compared with NNRTIs. Given this high genetic barrier to resistance, inadequate adherence to this regimen is the most likely cause of virological failure, as shown in large observational cohort studies.[2,3] Still, no antiretroviral agent is impervious to resistance, particularly in the setting of inadequate adherence, and, since the widespread introduction of tenofovir, lamivudine, and dolutegravir, data on dolutegravir resistance have started to emerge from research studies and national ART programmes.[4–6] However, these emerging reports reveal a wide range of prevalence estimates for dolutegravir resistance, highlighting the challenges in interpreting prevalence estimates for drug resistance from studies using different methodologies and including heterogeneous populations with diverse HIV treatment histories.

Risk factors for the emergence of dolutegravir resistance

Importantly, data show that the prevalence of treatment-emergent dolutegravir resistance varies depending on the presence of key risk factors (figure). In a scoping review of clinical trials, the median prevalence of dolutegravir resistance was 0% among people who did not reach viral suppression and were previously ART naive (IQR 0–0% for those started on a three-drug regimen; IQR 0–0·6% for those started on a two-drug regimen) or had viral suppression before receipt of a two-drug or three-drug dolutegravir-containing regimen (IQR 0–0%).[5] However, among people with HIV who were treatment experienced and did not have viral suppression before receipt of a three-drug dolutegravir-containing regimen, the median prevalence of dolutegravir resistance was higher at 1·5% (IQR 0·5–3·6).[5] These data highlight previous ART experience as an important risk factor for treatment-emergent resistance to dolutegravir, which has been reinforced by the country surveillance data presented in the 2024 WHO HIV drug resistance report, and data from the DTG RESIST study and the VICONEL cohort from Lesotho.[6–8] The prevalence of dolutegravir resistance among people with viraemia on dolutegravir-containing regimens in the WHO report was highest in Mozambique (19·6%), where the survey was conducted exclusively among ART-experienced people with HIV who were switched to tenofovir, lamivudine, and dolutegravir and had confirmed virological failure following an adherence intervention. In comparison, there were lower overall prevalence estimates in Malawi (8·6%), Uganda (3·9%), and Ukraine (6·6%), which included all people with HIV with viraemia on dolutegravir-containing regimens.[6] In a recent update from the DTG RESIST study, which presented data from seven African countries, all participants who were found to have major dolutegravir resistance mutations were ART experienced (n=28).[7]

Among those who are treatment experienced, there are additional factors that increase the risk of treatment-emergent resistance to dolutegravir. Although the NADIA trial provided reassurance that tenofovir, lamivudine, and dolutegravir remains highly effective in individuals with nucleoside or nucleotide reverse transcriptase inhibitor (NRTI) resistance,[9] the DTG RESIST study showed that

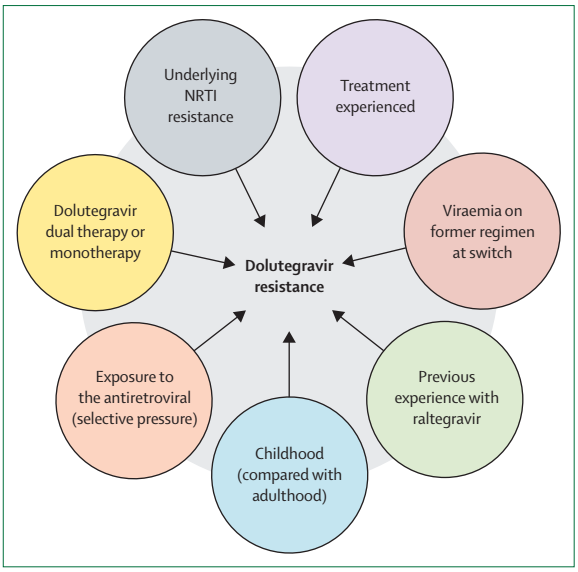

Figure: **Risk factors for the development of dolutegravir resistance on tenofovir, lamivudine, and dolutegravir**
NRTI=nucleoside or nucleotide reverse transcriptase inhibitor.

development of virological failure on dolutegravir-containing regimens with background NRTI resistance is associated with emergent resistance to dolutegravir.[4] Similarly, data from the VICONEL cohort in Lesotho showed that, among individuals with dolutegravir resistance and available genotypic resistance data from before initiation of dolutegravir, all had pre-existing resistance to NRTIs, thus supporting concerns regarding the potential for emergence of resistance in individuals who have virological failure while receiving functional monotherapy.[8] In addition, viraemia on a regimen before transition to tenofovir, lamivudine, and dolutegravir has been shown to predict virological failure on this regimen,[2,10] along with emergent dolutegravir resistance.[8] Dolutegravir resistance is also more common among individuals with treatment experience on early generation integrase strand transfer inhibitors,[11–13] probably due to accumulation of drug resistance mutations that confer cross-resistance to dolutegravir; integrase resistance profiles for these individuals might also differ from those without this previous experience.[13] Dolutegravir resistance has also been identified more commonly among children than adults, as children with HIV harbour many of the aforementioned risk factors due to exposure to multiple regimens and years of treatment experience. In a recent cross-sectional survey from Uganda, 6·6% of children versus 3·9% of adults with viraemia on dolutegravir-containing regimens had resistance to dolutegravir,[6] with a similar trend noted in a survey from Tanzania.[14]

No antiretroviral has an impermeable genetic barrier to resistance when administered unsupported. Consequently, dolutegravir monotherapy was the strongest risk factor for emerging dolutegravir resistance in the multicountry DTG RESIST study, with the use of dolutegravir with lamivudine as dual therapy being another strong risk factor for dolutegravir resistance.[4]

Finally, other risk factors for dolutegravir resistance might emerge as more data become available. Data from the DTG RESIST study suggest that dolutegravir resistance might be more frequent among non-B HIV-1 subtypes, although this relationship was not statistically significant.[4] A case series reporting characteristics of individuals with dolutegravir resistance suggested additional potential risk factors that warrant consideration, although not in the context of a statistical analysis. These included drug interactions (which are also cited as a concern in many HIV management guidelines), concurrent opportunistic infections, and a pretreatment viral load of more than 100 000 copies per mL.[15] In addition, recent evidence suggests that non-canonical mutations in the HIV genome outside integrase might contribute to dolutegravir resistance.[16]

Exploring the correlation between surrogates of adherence and resistance

It is also important to consider drug selection pressure as a key risk factor for dolutegravir resistance. Indeed, without any exposure to ART, resistance mutations are unlikely to develop.[3,17] Thus, individuals with complete non-adherence to a regimen should be able to achieve viral resuppression on the same regimen with improved adherence. Conversely, variable adherence to ART results in drug exposure in the setting of ongoing viral replication, creating potential for selection of drug-resistant variants. Therefore, gaining insight into an individual's ART adherence through measurement of ART drug concentrations (as an indicator of selection pressure) might help to further stratify resistance risk among people with virological failure. Available technologies include evaluation of ART drug concentrations from a range of biomatrices including plasma, dried blood spots, hair, and urine.[18] Although measurement of drug concentrations from hair and dried blood spots provides adherence data over the longest time horizon (weeks to months), these technologies are not yet available for point-of-care or near point-of-care assessments to inform real-time clinical decision making, nor are assays that detect ART in urine over a short timeframe (days).[18]

Several proof-of-concept studies using each of these modalities among individuals with virological failure on NNRTI-containing and PI-containing regimens have contributed important data showing the promise of drug-level testing as a mechanism of stratifying HIV drug resistance risk (table).[19–28] In studies evaluating amounts of the older PI, indinavir, in hair, drug concentrations were significantly higher in those with virological failure who had PI resistance mutations than in those without PI resistance mutations,[21] and the number of mutations was inversely correlated with drug

	Objective adherence metric	Prediction of HIV drug resistance
Hermans et al (2020)[19]	Protease inhibitor concentrations in plasma (measured via LCMS)	Detectable protease inhibitor concentrations accurately identified those at highest risk of resistance
Ferré et al (2023)[20]	Antiretroviral drug concentrations in plasma (measured via LCMS)	Use of resistance testing only for individuals with both viraemia and detectable drug concentrations enhanced efficiency of resistance testing
Bernard et al (2002)[21]	Indinavir concentrations in hair (measured via LCMS)	Intermediate concentrations of indinavir in hair associated with resistance
Castillo-Mancilla et al (2021);[22] Singh et al (2023)[23]	Tenofovir disoproxil fumarate concentrations in dried blood spots (measured via LCMS)	Concentrations showed stepwise inverse relationship with resistance (mid-range cumulative adherence to ART selected for resistance)
McCluskey et al (2023)[24]	Urine tenofovir assay (POC antibody-based assay)	Positive predictive value of a detectable urine tenofovir assay for resistance to NNRTIs or NRTIs (91% in those experiencing NNRTI-based ART failure)
Jennings et al (2022)[25]	Urine tenofovir assay (POC antibody-based assay)	Detectable urine tenofovir with 100% sensitivity for NNRTI and NRTI resistance for those experiencing NNRTI-based ART failure
Hermans et al (2023)[26]	Urine tenofovir assay (POC antibody-based assay)	Detectable urine tenofovir during viral rebound predicted NRTI resistance on either efavirenz-based or dolutegravir-based ART with tenofovir disoproxil fumarate or tenofovir alafenamide (83% sensitivity)*
Steegen et al (2025);[27] Coetser et al (2025)[28]	Dolutegravir plasma level	Undetectable plasma dolutegravir is a strong predictor for the absence of dolutegravir resistance (negative predictive values of 97·7% and 94·2%)

ART=antiretroviral therapy. LCMS=liquid chromatography–mass spectrometry. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside or nucleotide reverse transcriptase inhibitor. POC=point-of-care. *Only NRTI resistance mutations reported.

Table: **Studies showing the predictive value of an objective adherence metric for HIV drug resistance in participants experiencing ART failure**

concentrations.[29] In a more recent study evaluating the utility of plasma lopinavir quantification, undetectable lopinavir concentrations had a negative predictive value of 95% to predict the presence of major PI resistance mutations; non-adherence, therefore, was associated with a much lower risk of resistance than some adherence.[19] Similarly, a study in Togo among a population of people with HIV on NNRTI-containing regimens suggested that quantification of antiretrovirals from plasma, when added to viral load testing, could be used to enhance the efficacy and cost-efficiency of resistance tests.[20] In addition, studies have shown the utility of tenofovir diphosphate concentrations in dried blood spots[22,23] and, importantly, point-of-care urine tenofovir assays[24–26] to stratify resistance risk among people with HIV experiencing failure of NNRTI-containing regimens.

Finally, in two recent studies examining the association between dolutegravir plasma concentrations and resistance, undetectable plasma dolutegravir was a strong predictor for the absence of dolutegravir resistance (negative predictive values of 97·7% and 94·2%).[27,28] However, additional studies are needed in people with HIV with virological failure on dolutegravir-based regimens with objective metrics of adherence, including the urine tenofovir assay, which has never been examined to predict dolutegravir resistance on tenofovir, lamivudine, and dolutegravir. Given the increase in dolutegravir resistance seen among populations with virological failure in the past 6 years, a systematic examination is needed to evaluate the potential of these technologies as a screening tool to establish when resistance testing should be performed.

Role of cataloguing risk factors for dolutegravir resistance to triage resistance testing

Currently, genotypic resistance testing is not universally recommended or available as part of the management of virological failure on tenofovir, lamivudine, and dolutegravir in many low-income and middle-income settings due to costs, resource constraints, and a paucity of data to guide policy. Therefore, as policy decisions evolve on the management of virological failure for people with HIV on tenofovir, lamivudine, and dolutegravir, it is essential to better understand who would benefit most from genotypic resistance testing and a subsequent switch to more complex regimens. In this current era of interruptions in ART supply due to global health funding cuts,[30] the emergence of dolutegravir resistance might accelerate. Cataloguing the various risk factors summarised here for dolutegravir resistance in a patient with HIV with virological failure on tenofovir, lamivudine, and dolutegravir can help to identify who might qualify for resistance testing in resource-limited settings.

Conclusion

6 years into the roll-out of tenofovir, lamivudine, and dolutegravir, with high uptake of this combination in low-income and middle-income countries as of 2023,[1] dolutegravir resistance is starting to emerge, but not evenly. Risk factors for the emergence of dolutegravir resistance, such as previous treatment experience, underlying NRTI resistance, dolutegravir monotherapy or dual therapy, viraemia when switching to tenofovir, lamivudine, and dolutegravir, previous experience with earlier generation integrase strand transfer inhibitors, childhood, and selective pressure from (inadequate)

exposure to the drug, have now been identified and summarised in this Viewpoint. Cataloguing these risk factors can inform clinicians and policy makers in more precisely identifying which individuals with virological failure on tenofovir, lamivudine, and dolutegravir are most in need of resistance testing or regimen switch. By improving our understanding, the aim is to maintain the durability of tenofovir, lamivudine, and dolutegravir for first-line and second-line therapy worldwide, thereby advancing both HIV treatment and prevention goals.

Contributors

MG conceived of the Viewpoint. SMM and MG performed the literature review, and drafted and edited the Viewpoint for submission.

Declaration of interests

SMM has served as a co-investigator on investigator-initiated grants paid to her institution from Merck and ViiV Healthcare, neither of which have any involvement with this Viewpoint. MG's Hair Analytical Laboratory co-owns the patent on the antibody directed against tenofovir with Abbott Laboratories.

Acknowledgments

This work was supported by funding from the National Institutes of Health (R37AI098472 to MG, R01AI143340 to MG, and R01AI167699 to SMM). The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

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