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Checking the Status: The Evolutionary Explanations and Drug Resistance Prevalence to Dolutegravir for HIV Treatment (A Review)

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Drug treatment advancements for HIV have dramatically advanced since the virus' identification in the early 1980s. Integrase strand transfer inhibitors (INSTIs) are one of the seven HIV treatment drug classes currently utilized to create an undetectable viral count in blood samples of people living with HIV (PLWH). First-generation INSTIs are documented with low barriers of genetic resistance, which indicates that the number of mutations to lead to a drug-resistant mutation is low. The introduction of dolutegravir, a second-generation INSTI, shows a higher barrier of genetic resistance that reduces drug-resistant mutations to INSTIs and increases the overall effectiveness of this class of HIV treatment. PLWH can be categorized based on whether they received treatment previously/currently or have never received treatment. Therapy-naive and previously treated (successfully or unsuccessfully) patients for HIV report different rates of drug-resistant mutations compared to actual resistance to dolutegravir, 0.4–31% and 0.1–67.2%, respectively. Evolutionary considerations of genetic resistance, including epistatic interactions and point mutations, suggest both non-polymorphic and polymorphic mutations for these drug-resistant mutations. An incomplete understanding of how evolutionary factors contribute to HIV drug resistance highlights the importance of conducting further research. This research may help improve the efficacy of second-generation INSTIs in future treatment options for PLWH. This review describes the landscape of existing research on drug resistance prevalence for dolutegravir and possible evolutionary explanations on how these mutations arise in the first place, leading to implications in developing more robust treatment modalities.

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Background

The human immunodeficiency virus (HIV) is a prominent retrovirus identified in 1983 that has no cure, yet it can be readily treated with the right combination antiviral therapy (cART) (Greene, 2007). At the end of 2021, the World Health Organization (WHO) estimated that 38.4 million people around the globe are living with HIV (WHO, 2022). UNAIDS set Ambition 2030 targets to end the ongoing HIV epidemic: (1) 95% of people living with HIV (PLWH) know their status; (2) 95% of people who know their status are receiving treatment; (3) 95% of those receiving treatment are virally suppressed (Ehrenkranz et al., 2021). PLWH who are virally suppressed reach a level of virus in the body that cannot be detected by laboratory tests. At these levels, HIV cannot be transmitted to other individuals, highlighting relevant campaigns such as undetectable equals untransmittable (U=U) and treatment as prevention.

HIV is a very mutable virus (Yeo et al., 2020). Viral mutations in the body and during seroconversions to infection increase due to error-prone replication cycles. Therefore, the HIV virus can develop drug-resistant mutations, decreasing the effectiveness of these medications in high active antiretroviral therapy (HAART) regimens. The strain of HIV in PLWH can be naturally resistant to certain drugs due to certain mutations in the virus or due to the development of acquired resistance over time in PLWH. In addition, there is evidence to suggest that people who inconsistently adhere to their medication can see increased rates of drug-resistant strains of HIV (Chen, Chen, & Kalichman, 2017). When PLWH and HIV providers encounter drug resistance, the range of medications to treat an HIV diagnosis may become limited, impacting the health outcomes of PLWH.

Dolutegravir is a second-generation integrase strand transfer inhibitor (INSTI) approved by the US Federal Drug Administration (FDA) in 2013 to treat HIV (Kandel & Walmsley, 2015). As it entered the global state, many HIV providers and public health officials promoted its potential to be a more effective medication than existing first-generation INSTIs, which are well-tolerated, are easy to take, and have decreased drug-drug interactions (Rhee et al., 2019). Furthermore, the greatest factor for dolutegravir's success is its higher barrier to genetic resistance compared to first-generation INSTIs like raltegravir, reducing the chance of an individual needing to switch treatment regimen throughout their lifetime. Even with dolutegravir's increased barrier to resistance, there is currently little understanding of the population-level prevalence of dolutegravir drug resistance and how drug resistance arises.

Drug Resistance Prevalence

Drug resistance is broadly outlined as the reduction in effectiveness of medications in treating a disease or conditions with prime examples coming from the fields of antimicrobial resistance in antibiotics and cancer medicine (Habboush & Guzman, 2022). PLWH can be categorized into two treatment categories: (1) therapy-naive patients and (2) previously treated patients (Colombo, Di Matteo, & Maggiolo, 2013; Tseng, Seet, & Phillips, 2015). Both therapy-naive and previously treated patients are individuals who have seroconverted, meaning the body has responded to HIV by creating antibodies. Importantly, therapy-naive patients contain a level of the virus in the body that is detectable for treatment response yet have never received treatment for HIV. Previously treated patients for HIV are individuals enrolled in previously successful or unsuccessful treatment regimens.

Research suggests that the rate of drug resistance for INSTIs in therapy-naive patients is 3.82%, while HIV in previously treated patients is resistant at 11% (Fan et al., 2022; Kamelian et al., 2019). For therapy-naive patients, the genotypes of the individual's virus were screened for resistance-associated mutations (RAMs), which may suggest an individual's inherent resistance to INSTIs. RAMs can be major or accessory. Major RAMs (Y143R/C/D/G and P145S) are shown to create actual drug resistance. Accessory RAMS (G140E, E157Q, and G163R) can, in combination and over time, lead to actual drug resistance. Among samples of therapy-naive patients in Cameroon, Mikaski et al. reported 5.4% major RAMs and 8.1% accessory RAMs (Mikasi et al., 2020). It is important to note that these samples were conducted for all INSTI mutations, not dolutegravir specifically. Áy et al. (2021) collected data on therapy-naive patients, which report different percentages of mutations, including 1 out of 249 (0.4%) to have major RAMs and 31% accessory RAMs. These dramatically different percentages may reflect population or geographically distinct prevalence of major and accessory RAMs associated with dolutegravir. These samples identify the critical role drug resistance screening plays in the larger rollout of dolutegravir and emphasize the research that must be conducted to pre-screening efforts.

There is markedly more research for drug resistance among previously treated patients. First-generation INSTIs have shown a plethora of drug resistance mutations leading to the increased failure of treatment regimens for HIV (Anstett et al., 2017). Data collected for drug resistance to dolutegravir are separated into two main outcomes for PLWH: (1) potential resistance from possible future mutations that can reduce the effectiveness of dolutegravir and (2) inherent resistance from existing mutations to dolutegravir in a specific HIV strain. Importantly, previously treated patients can be categorized based on their success or failure of previous treatment regimens. The range of actual resistance in PLWH was from 0.1–0.7% to 21.9% among those who are currently successfully virally suppressed under

Source	Patient Population	Geographic Population	Actual Resistance	Potential Resistance
Kamelian et al., 2019	HAART-treated individuals	British Columbia, Canada	0.1–0.7% (1 to 7 per 1000)	–
Van Oosterhout et al., 2022	First-generation INSTI regimen failure	Malawi	29.6% (8 out of 27)	–
Fourati et al., 2015	First-generation INSTI regimen failure	France	13.9%	64%
Engone-Ondo et al., 2021	HAART-treated individuals; First-generation INSTI regimen failure	Semi-rural Gabon	21.9%; 67.2%	84.6% (among patients who failed first-generation INSTI regimen)

Table 1: Description of Actual and Potential Resistance from Current Literature Categorized by Patient and Geographic Populations

HAART (Kamelian et al., 2019; Engone-Ondo et al., 2021). These percentages greatly increased for PLWH who had previously or are currently failing first-generation INSTI treatment regimens, ranging from 29.6% to 67.2% showing resistance to dolutegravir (van Oosterhout et al., 2022; Engone-Ondo et al., 2021). Critically, 64–84.6% of HIV sequences screened show potential drug resistance mutations to dolutegravir among those who previously or are currently failing first-generation INSTIs (Fourati et al., 2015; Engone-Ondo et al., 2021). Saladini et al. (2012) reported that 59.8% of samples collected from previously treated patients harbored at least one of the resistance mutations for first- or second-generation INSTIs. Table 1 consolidates the patient and geographic population with the actual and potential resistance described in the source paper. Nonetheless, this does not indicate actual resistance, nor does it show treatment regimen failure for dolutegravir for PLWH.

Evolutionary Explanation to Drug Resistance

HIV Drug Evasion

Drug resistance among HIV strains in PLWH can vary in their categorizations, including transmitted, acquired, or multi-class drug resistance (Pennings, 2013).

Transmitted drug resistance indicates a viral strain that, when transmitted to another host, already contains drug-resistant mutations, while acquired drug resistance explains how an individual's strain of HIV can mutate over time to confer drug-resistant mutations. Multi-class drug resistance describes strains of HIV that confer multiple mutations that evade more than one of the seven drug classes that target HIV. There is a stark geographic and socioeconomic influence of transmitted drug resistance, where the standard for patients in higher-income countries is to screen for genetic resistance before treatment begins. By conducting genetic screening, a provider can readily assess the feasibility of PLWH to receive some treatment over others. Acquired drug resistance appears to increase over time for a treated patient, indicating that although not all patients over time will develop resistance, a small subset of the population will develop drug resistance HIV virus strains. This type of resistance is notable for potential dolutegravir candidates who may have previously failed a first-generation INSTI in the same drug class. cART requires drugs from multiple classes, and when PLWH are limited in access to multiple drug classes, the course of treatment over a lifetime may become limited, creating future problems for maintaining viral suppression. Research suggests that drugs targeting viruses like HIV may have imperfect tissue penetrations and result in spatial monotherapy (Moreno-Gamez et al., 2015). These implications may stand to explain how some HIV strains in individuals adapt in environments where medication is not present.

Genetic exchange, re-assortment, and recombination of HIV could contribute to its adaptation at the population genetics level (Wilson et al., 2015). While the HIV virus on its own can mutate to adapt, the question of human adaptation to HIV drug resistance is largely unstudied, including the possible influences of linkage disequilibrium and epistatic interactions. Hence, there is an emphasis to assess standing genetic variation in new treatment initiation for PLWH to determine whether drug-resistant mutations are present.

First-Generation INSTIs

First-generation INSTIs are shown to have a low genetic barrier to resistance with the medications raltegravir and elvitegravir (Anstett et al., 2017). The field of virology and resistance in HIV have distinctly categorized the type of mutation from conventional evolutionary terminology. Non-polymorphic mutations are defined by a percentage of mutations occurring less than 1% of any subtype of HIV virus (Rhee, Tzou, & Shafer, 2021). Polymorphic mutations are sites with variable frequency by which the sequence of a gene is found in more than 1% of the population. The occurrence of drug resistance mutations among first-generation INSTIs appears to occur through the transmission of drug mutations rather than

naturally arising resistance mutations in PLWH. Áy et al. (2021) characterize these drug-resistant mutations as non-polymorphic. In addition, Saladini et al. (2012) provide further evidence that first-generation INSTI naive patients did not have mutant strains that contained drug resistance mutations as natural polymorphisms. Two mutations (T124A & L101I) were detected among naive and treated patients, yet their prevalence was the same for either group. However, other research in Chinese populations has found polymorphic accessory mutations, which could cause low-level resistance to first-generation INSTIs (Yu et al., 2022).

Second-Generation INSTIs

The resistance profile of dolutegravir is extensively characterized by Rhee et al. (2019). The development of resistance mutations to dolutegravir has been observed in vivo and in samples from the populations (Fourati et al., 2015). Different mutations are categorized as directly impacting the effectiveness of dolutegravir and creating possible pathways that could lead to second-generation INSTI drug-resistant mutations.

Anstett et al. (2017) suggest that the increased resistance profile of dolutegravir is associated with a longer binding half-life, which maintains activity against more resistant first-generation strains. This further supports a theory of different binding properties to explain dolutegravir's resistance profile (Garrido et al., 2011). However, the authors do not present an evolutionary mechanism for why this

Source	Mutation	Mutation Type
Anstett et al., 2017	N155; Q148	Resistant; Pathways to Resistance
Pham et al., 2021	S153F or S153Y with R263K	Resistant
Garrido et al., 2011	T124A and L101I+T124A	Resistant
Brenner et al., 2016	G118R	Resistant
Saladini et al., 2012	L101I and T124A	Resistant
Rhee et al., 2019	R263K, G118R, N155H, Q148H/R; Q148 + G140 and/or E138	Resistant
George et al., 2018	T97A	Resistant
Ndashimye et al., 2018	E157Q	Pathways to Resistance

Table 2: Description of Mutation and Mutation Types from the Current Literature

type of advantage is displayed by dolutegravir. Pham et al. (2021) offer that experiments conducted in their study show that deleterious effects of individual substitutions in the integrase codon region could lead to possible dolutegravir drug resistance. The studies listed in Table 2 largely characterize singular substitutions as a leading cause to genetic resistance, but some studies indicate that the epistasis can occur alongside these drug-resistant mutations. Epistasis occurs when the effect of a gene mutation is dependent on the presence or absence of mutations in or more other genes (Churchill, 2013; Garrido et al., 2011). Both Garrido et al. (2011) and Brenner et al. (2016) suggest that natural polymorphism in different HIV strain subtypes is partially responsible for drug resistance to dolutegravir for PLWH.

Conclusion

There is some prevalence in therapy-naive and previously treated patients of drug-resistant strains and mutations to the medication dolutegravir for PLWH. Most concerning is the high percentage of dolutegravir resistance among individuals currently taking or previously failing first-generation INSTIs, suggesting that alternative HIV medication routes may be necessary for these PLWH. Although resistance is prevalent, there is little research on the evolutionary mechanisms that may cause these drug-resistant mutations or strains. Broadly, first-generation INSTIs confer largely non-polymorphic mutations in creating dolutegravir drug resistance, while natural polymorphism is used as a primary explanation for the presence of drug-resistant mutations in second-generation INSTIs. Second-generation INSTI drug-resistant mutations appear to arise from individual substitutions with possible epistatic associations among some mutation locations.

These drug-resistant mutations against dolutegravir are critical in ending the HIV epidemic. INSTIs are quickly leading the charge on long-acting medications, while biomedical advancements in other HIV drug classes are lagging behind. Cabotegravir is a second-generation INSTI that is derived from dolutegravir and acts as a long-acting injectable medication versus a daily oral pill (Landovitz et al., 2021). If individuals do not have access to long-acting medications due to drug-resistant mutations limiting their drug class options, the treatment for PLWH may become challenging. Without further characterization and screening of drug-resistant mutations for second-generation INSTIs, potential biomedical advancements may face drug-resistant mutations in existing strains of HIV circulating in PLWH. Therefore, more research is needed to determine the evolutionary origins of drug-resistant mutations to INSTIs.

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