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CASE REPORT

# Pre-existing singleton E138A mutations in the reverse transcriptase gene do not affect the efficacy of first-line antiretroviral therapy regimens using rilpivirine in human immunodeficiency virus-infected patients

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**Abstract**

General consensus suggests that even singleton E138A mutations in HIV reverse transcriptase at baseline are associated with resistance to rilpivirine (RPV). We detected 11 pre-existing E138A carriers treated with RPV in the pan European EuResist database. However, all 11 patients presented with full virological efficacy for first-line RPV-based ART regimens.

**KEYWORDS**

*E138A*, *HIV*, reverse transcriptase, RPV

## 1 | INTRODUCTION

Rilpivirine (RPV), a second-generation non-nucleoside inhibitor (NNRTI) with confirmed efficacy, safety, and tolerability[1] is currently approved for the treatment of HIV infection in the first-line three-drug antiretroviral therapy (ART) and in two-drug (dolutegravir, DTG/RPV) maintenance regimens as described by the European guidelines.[2] Recently, RPV has been reported to be safe and effective as a tool for HIV pre-exposure prophylaxis.[3] RPV is also under evaluation as a component in long-acting intramuscular ART in combination with cabotegravir treatment,[4] which may expand the use of RPV in the future.

The HIV Drug Resistance Stanford database defines E138A as a polymorphic mutation weakly associated with reduced susceptibility to etravirine (ETR) and RPV,[5] whereas the French HIV Resistance database (ANRS) defines E138A viruses as fully resistant to RPV.[6] Phenotype studies have shown that E138A mutation decreases viral susceptibility to RPV by approximately 2-fold.[7] This data means that it is generally accepted that the presence of E138A at baseline may be an indicator for subsequent ART failure. Thus, in countries where HIV genotypic resistance testing (GRT) is performed before ART initiation, the presence of E138A is a counter-indicator for the use of RPV as a first-line regimen.

E138A was not previously included in the surveillance drug resistance mutation (SDRMs) list recommended by the World Health Organization (WHO) for the surveillance of transmitted HIV drug resistance.[8] However, some researchers have added this mutation to their list when monitoring for non-nucleoside reverse transcriptase inhibitor (NNRTIs) drug resistance in treatment naive HIV-1 patients.[9–12]

The global prevalence of E138 mutations in ART-naive patients varies significantly by HIV-1 subtype and is highest for subtypes C (6.1%), F (5.1%), and A (3.3%).[9] HIV-1 subsubtype A6, which caused the HIV-1 epidemic in Russia, is responsible for more than 70% of HIV-infections in this region[13,14] and presents with E138A polymorphic mutations in around 4%–8% of viruses, depending on the geographical region.[14] Current ART guidelines in Russia do not mandate HIV genotyping at baseline[15]; however, there are growing concerns around the effectiveness of RPV in a significant proportion of Russian patients on first-line ART regimens. Our investigation of the available information on the effect of singleton polymorphic E138A mutations on RPV activity as part of first-line ART regimens provided conflicting information; so, we undertook a small study of our own to determine more localized recommendations.

The aim of this study was to evaluate the virological efficacy of first-line ART regimens using RPV in HIV-1 patients with pre-existing E138A mutations in their reverse transcriptase gene. Current recommendations mean that it is very rare that an HIV patient with this mutation is treated with RPV and as a result, we were only able to identify 11 patients with such a history of ART in the EuResist database, one of the most complete databases of its kind with more than 100,000 registered participants.[16] Nevertheless, the analysis of the efficacy of such an unconventional therapeutic approach may be of interest to both clinicians and virologists studying HIV drug resistance.

## 2 | CASE HISTORY/EXAMINATION

### 2.1 | Study design and participants

The pan European EuResist Integrated Database (EIDB)[16] was queried for cases satisfying the following criteria: a) patient is 18 years or older, (b) RPV was a part of their first-line ART regimen, (c) patient followed ART for more than 40 weeks, (d) the E138A mutation was present at baseline and there were no other RPV resistance mutations, and (e) there was an absence of any major NRTI mutations. We then extracted the data on the viral genome (HIV-1 reverse transcriptase and protease sequences), HIV subtype and mutations (PR major, PR accessory, PR other, NRTI, NNRTI, and RT), and basic epidemiological (country of origin and risk factor for HIV acquisition), demographic (gender, age, and ethnic group), and ART data (data of regimen start and viral load) from each of the included samples.

Patients were followed up at the Italian and Swedish national clinical centers participating in the EuResist Network and provided written informed consent for data analysis. Ethical approval was not required in this case.

The analysis of the ART virological outcomes was based on the definition of effective therapy and virological failure as described in the European guidelines and in the Russian national and Department of Health and Human Services (DHHS) clinical guidelines[2,15,17] (Table 1).

The combination of these three clinical guidelines produced a clinical rebound cut-off for ART of a viral load (VL) of below 50 copies/ml. This means that viral rebound during the follow-up period was defined as any VL of >50 copies/ml in PLWH (people living with HIV) with previously undetectable HIV VL.[2]

**TABLE 1** Criteria of virological ART effectiveness and failure in European,[2] DHHS,[17] and Russian guidelines[15]

| | VL at 4 weeks | VL at 12 weeks | VL at 24 weeks | VL follow-up |
|---|---|---|---|---|
| | Effect | Effect | Failure (copies/ml) | Rebound (copies/ml) |
| European guidelines | n/a | n/a | >200 | >50 |
| DHHS | n/a | n/a | >200 | ≥200 |
| Russian guidelines | decrease by ≥1 lg | decrease below 400 copies/mL | >50 | >50 |

## 3 | OUTCOMES

Our evaluation strategy identified only 11 patients out of the more than 100,000 cases in the database that met our selection criteria. These cases were then selected for further evaluation and their epidemiological, demographic, and first-line ART data were extracted. The data are summarized in Table 2. The follow-up period and the frequency of VL testing varied from 78 to 209 weeks and from 5 to 14 times, respectively, over this period (Table 3).

The results of the VL measurements at 4 ± 2, 12 ± 4, and 24 ± 4 weeks after ART initiation were analyzed, with these values available for 9, 7, and 8 of our 11 patients, respectively.

Table 3 summarizes the compliance of these patients with the criteria for ART effectiveness in the Russian ART guidelines at 4, 12, and 24 weeks, as well as the absence of virological failure using the European and DHHS ART guidelines at 24 weeks.

In one patient (number 7), the VL at 10 weeks decreased down to 147 RNA copies/ml, the next measurement point was at 40 weeks and VL was below 50 copies/ml.

Moreover, all 11 patients were shown to experience sustained viral suppression maintaining VL levels well below the cut-off value (<50 copies/ml) throughout the observation period (Figure 1). These VL values all corresponded to an absence of virological failure when evaluated using the European, Russian, and DHHS guidelines.[2,15,17]

**TABLE 2** Epidemiological and demographic characteristics of the patients participated in the study

| | |
|---|---|
| Number of patients | 11 |
| Median age, years | 35.5 |
| Sex | |
| Male | 8 |
| Female | 3 |
| Ethnicity | |
| Caucasian | 3 |
| African | 3 |
| Unknown | 5 |
| Country of origin | |
| Italy | 4 |
| Eritrea | 1 |
| Greece | 1 |
| South Africa | 1 |
| Gambia | 1 |
| Unknown | 3 |
| Mode of transmission | |
| MSM/bisexual | 5 |
| Heterosexual | 2 |
| IVDU | 1 |
| Unknown | 3 |
| HIV-1 subtype | |
| A1 | 1 |
| B | 6 |
| C | 3 |
| CRF02_AG | 1 |
| ART first-line regimen[a] | FTC/TDF/RPV |
| Baseline mutations | |
| PR major mutations | 0 |
| NRTI | 0 |
| NNRTI | 12 |
| E138A | 10 |
| E138A/V179E | 1 |

[a] Emtricitabine, tenofovir, rilpivirine.

## 4 | DISCUSSION

Despite the obvious benefits of ART, the emergence of drug resistance mutations in the HIV genome can severely compromise its long-term efficacy. The possibility of transmission of resistant viral strains and infection with resistant HIV poses additional challenges for treatment and can compromise public ART programs in settings that use standardized first-line regimens. However, mutations in positions associated with resistance are not always a consequence of treatment or transmission of resistant viruses but may reflect the natural evolution of the HIV genome and demonstrate some subtype-specific behaviors resulting from the founder effect during subtype emergence. Knowledge of the impact of such pre-existing mutations on phenotypic HIV drug resistance remains limited.

It is well established that polymorphic mutations are not fully indifferent to ART effectiveness and may promote resistance to treatment. In this role, they can compensate for the deleterious effects of major mutations, accelerate their selection, influence the time to resistance development, and the choice of mutational pathway.[18]

It is also well established that polymorphisms at sites associated with HIV drug resistance occur frequently[19] and that the response to these polymorphisms is different for experts in different countries. Some authors suggest not using drugs in cases of detection of mutations before starting therapy, regardless of their origin. For example, several studies in Germany highlighted a relatively high prevalence of NNRTI mutations at polymorphic position E138 and experts in this country proposed that the alternative first-line regimens, combining two nucleoside reverse transcriptase inhibitors (NRTIs) and dolutegravir (DTG), should be preferentially applied.[11] In another paper,[20]

**TABLE 3** Viral load measurement points and results obtained

| Patient № | VL at baseline, RNA copies/ml | Follow-up period, weeks | Number of VL measurements during the observation period[a] | VL at 4 weeks, RNA copies/ml | VL decrease at 4 weeks (Δ Lg)[a] | VL at 12 weeks, RNA copies/ml[b] | VL at 24 weeks, RNA copies/ml[c] |
|---|---|---|---|---|---|---|---|
| 1 | 2625 | 149 | 7 | 40 | 1.8 | — | 40 |
| 2 | 4445 | 106 | 8 | 26 | 2.2 | 13 | — |
| 3 | 5900 | 78 | 6 | 0 | [d] | — | 0 |
| 4 | 6282 | 111 | 7 | — | — | 40 | 40 |
| 5 | 16010 | 165 | 11 | 263 | 1.8 | 37 | 1 |
| 6 | 19260 | 188 | 12 | 144 | 2.1 | 32 | 20 |
| 7 | 22583 | 90 | 5 | — | — | 147 | — |
| 8 | 30270 | 209 | 14 | 217 | 2.1 | 6 | 1 |
| 9 | 39500 | 209 | 12 | 35 | 3.1 | — | 0 |
| 10 | 53100 | 136 | 9 | 525 | 2.0 | 266 | — |
| 11 | 57500 | 179 | 10 | 821 | 1.8 | — | 0 |

[a] Including baseline point.

[b] The criterion for effective therapy in Russian national guidelines: at 4 weeks since ART start VL should decrease by >1 lg.

[c] The criterion for effective therapy in Russian national guidelines at 12 weeks since ART start VL should decrease below 400 RNβA copies/ml.

[d] In the European clinical guidelines and in the DHHS guidelines VL >200 copies/ml at 24 weeks after starting therapy is the criteria for virological failure. The criterion for effective therapy in Russian national guidelines: VL <50 copies/ml at 24 weeks after starting therapy.

* not applicable.

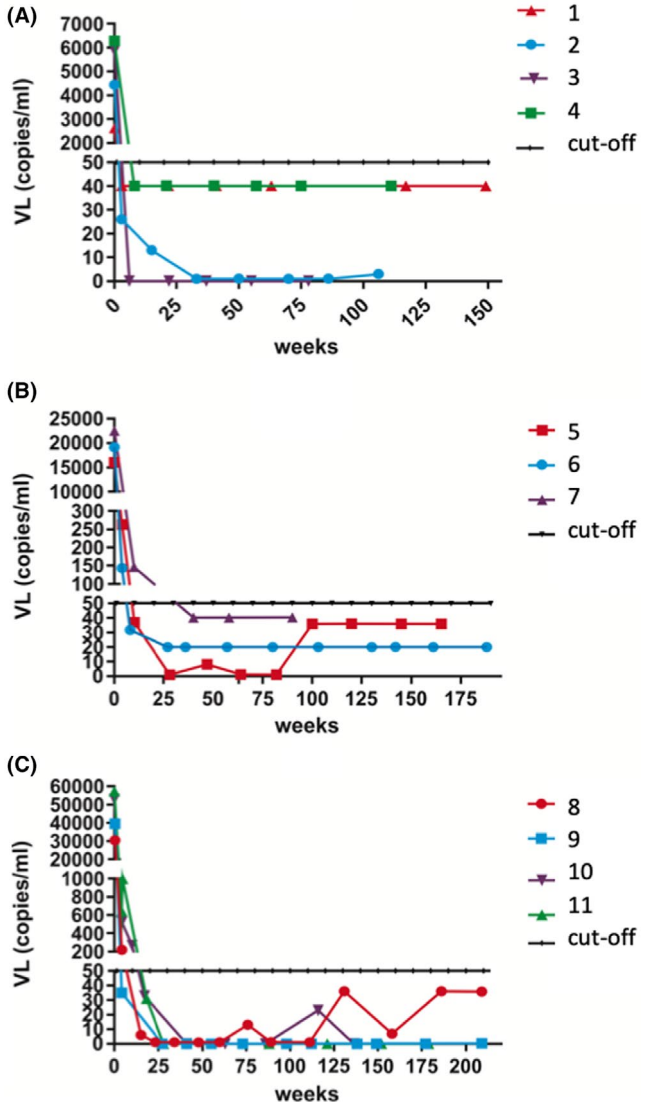


**FIGURE 1** The viral load (RNA copies/ml) in HIV-infected patients with pre-existing E138A mutation on RPVbased therapy. (A) patients 1, 2, 3, 4; (B) patients 5, 6, 7; (C) patients 8, 9, 10, 11. Patient data are presented in three graphs, depending on the viral load interval. VL level below 50 copies/mL was defined as a cut-off

the authors suggested that in geographical regions with high E138A prevalence, RPV-based first-line ART could be compromised when initiated in the absence of routine GRT in treatment-naive patients. It was also suggested that the presence of these E138A mutations could impact treatment efficacy or prevention strategies that include RPV in geographical areas with an elevated prevalence of subtype C infection.[21]

Nevertheless, a literature review revealed that there is no consensus on the significance of pre-existing HIV drug resistance mutations, and the separate analysis of genotype and phenotype in ART-naive subjects may provide conflicting results. For example, the analysis of 18 subjects with minor resistance mutations in HIV-1 protease at baseline showed no signs of clinical resistance during ART.[22] There was no association between the pre-existing resistance to single NNRTIs and the rates of virological suppression in patients receiving an efavirenz/emtricitabine/tenofovir regimen.[23] It was also shown that the antiviral activity of integrase strand transfer inhibitors (INSTIs) was retained in HIV-1 mutants with minor resistance-associated mutations.[24]

There are only a limited number of publications describing the association between pre-existing E138A mutations and ART. One such study, the SPIRIT study, showed that none of the virologically suppressed patients with a single E138A mutation experienced any virological failure through Week 48 after switching to rilpivirine/emtricitabine/tenofovir from disoproxil fumarate.[25] In a study of patients entering the SENSE trial for first-line ART in Europe, Russia, and Israel, 13.9% of patients presented with at least one polymorphic mutation in their baseline plasma (V90I, V106I, or E138A), without any impact on the virological outcomes of an etravirine-based ART program.[26] In a South African cohort, the detection of drug-resistant mutations alone, including E138A, did not predict an increased risk of virological failure.[27] Additionally, there was one patient in the Eviplera clinical trial, who presented with an E138A mutation at baseline and was shown to maintain virological suppression throughout Week 48.[28]

However, in countries where HIV genotyping is routinely performed prior to ART initiation, the early detection of any mutations in positions associated with drug resistance ultimately prevents the use of inappropriate drugs. For example, as stated in the RPV package insert,[29] the presence of E138A mutations prior to therapy may reduce the antiviral activity of RPV, and RPV-based ART is not recommended for patients with this mutation in Europe.

In countries where HIV GRT is not performed before starting treatment, the widespread occurrence of such mutations could potentially lead to ART failure in a significant number of first-line patients. We observed a similar issue in Russia, where the frequency of the E138A polymorphic mutation in patients infected with the dominant HIV A6 virus ranges from 4% to 8%.[14] There is every reason to believe that this mutation is not associated with the transmission of resistant viruses, since its prevalence did not change significantly following the introduction of RPV and ETR in 2011.[30]

Knowing the high levels of E138A mutation prevalence in Russia, we were faced with a specific question, namely whether patients with pre-existing E138A mutations are more prone to rapid failure of first-line RPV-based ART. We explored this issue by searching for RPV-treated HIV patients with baseline E138A mutations. As GRT is not

performed at ART baseline in Russia, we were forced to look for such cases outside the country, namely in the largest European database of HIV genotypes, EuResist. The viral load data for each of these patients during their exposure to first-line RPV-based ART were analyzed in detail in accordance with both the Russian and international criteria.

Our study demonstrated that the effectiveness of first-line ART using RPV-based regimens produced acceptable outcomes for all of the HIV-infected patients with pre-existing E138A mutations when evaluated using Russian ART guidelines.[15] At the same time, none of this data met the criteria for virological failure according to the European and DHHS clinical guidelines.[2,17] The sustained virological response in all of these patients suggests that a single pre-existing polymorphic E138A mutation is unlikely to reduce the effectiveness of RPV-containing first-line regimens.

Given the current absence of routine HIV GRT prior to ART initiation in Russia, our results may provide support for prescribing first-line RPV in the absence of this information. Our findings provide additional information on the effect of singleton pre-existing mutations in positions associated with resistance to ART and advocate for expanding studies of this kind.

Our study has several limitations. Only a very small number of patients were observed over several time points and as this was a retrospective study both VL measurement and patient examination were not scheduled consistently. Additionally, HIV patients were infected with different non-A6 HIV-1 subtype viruses. Further investigation of the E138A mutations in the HIV A6 sub-subtype is pending and will be evaluated in larger cohorts using protocols that are more consistent.

In conclusion, our investigation of ART-naive patients with pre-existing singleton E138A mutations revealed that these mutations did not result in an increased failure of RPV-based first-line ART. The exact role of this mutation and other singleton mutations in the efficacy of first-line ART regimens merits further investigation.

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## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

## AUTHOR CONTRIBUTIONS

Kuznetsova A. involved in methodology, formal analysis, visualization, and writing—original draft. Lebedev A. involved in visualization and writing—original draft. Gromov K. involved in formal analysis and visualization. Kazennova E. involved in validation and writing—review and editing. Zazzi M., Incardona F., and Sönnerborg A. involved in investigation, resources, and writing—review and editing. Bobkova M. involved in conceptualization, methodology, and writing—review and editing.

## ETHICAL APPROVAL

None.

## CONSENT

Published with the written consent of the patient.

## DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## REFERENCES

1. Bagella P, De Socio GV, Ricci E, et al. Durability, safety, and efficacy of rilpivirine in clinical practice: results from the SCOLTA Project. *Infect Drug Resist*. 2018;11:615-623. doi:10.2147/IDR.S152090
2. EACS European AIDS Clinical Society Guidelines Version 10.0 November 2019. Accessed April 05, 2021. https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf
3. Cranston RD, Dezzutti CS, Siegel A, et al. A multiple dose phase 1 assessment of rilpivirine long acting in a model of pre-exposure prophylaxis against HIV. *AIDS Res Hum Retroviruses*. 2019;35(9):794-804. doi:10.1089/AID.2018.0265
4. Margolis DA, Gonzalez-Garcia J, Stellbrink H-J, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase2b, non-inferiority trial. *Lancet*. 2017;390(10101):1499-1510. doi:10.1016/S0140-6736(17)31917-7
5. Standford University HIV drug resistance database. NNRTI resistance notes. Accessed April 05, 2021. https://hivdb.stanford.edu/dr-summary/resistance-notes/NNRTI/#63Haddad2011
6. ANRS. HIV French Resistance. HIV genotypic drug resistance interpretation's algorithms. Tables of rules. Accessed April 05, 2021. http://www.hivfrenchresistance.org/2019/tab3.html
7. Xu H-T, Colby-Germinario SP, Asahchop EL, et al. Effect of mutations at position E138 in HIV-1 reverse transcriptase and their interactions with the M184I mutation on defining patterns of resistance to nonnucleoside reverse transcriptase inhibitors rilpivirine and etravirine. *Antimicrob Agents Chemother*. 2013;57(7):3100-3109. doi:10.1128/AAC.00348-13
8. Bennett DE, Camacho RJ, Otelea D, et al. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. *PLoS One*. 2009;4(3):e472.
9. Calvez V, Marcelin A-G, Vingerhoets J, et al. Systematic review to determine the prevalence of transmitted drug resistance mutations to rilpivirine in HIV-infected treatment-naive persons. *Antivir Ther*. 2016;21(5):405-412. doi:10.3851/IMP3024

10. Alvarez M, Monge S, Chueca N, et al. Transmitted drug resistance to rilpivirine in newly diagnosed antiretroviral naive adults. *Clin Microbiol Infect*. 2015;21(1):104.e1-104.e5. doi:10.1016/j.cmi.2014.08.005
11. Machnowska P, Meixenberger K, Schmidt D, et al. Prevalence and persistence of transmitted drug resistance mutations in the German HIV-1 Seroconverter Study Cohort. *PLoS One*. 2019;14(1):e0209605. doi:10.1371/journal.pone.0209605
12. Rhee S-Y, Clutter D, Fessel WJ, et al. Trends in the molecular epidemiology and genetic mechanisms of transmitted human immunodeficiency virus type 1 drug resistance in a large US clinic population. *Clin Infect Dis*. 2019;68(2):213-221. doi:10.1093/cid/ciy453
13. Lapovok IA, Lopatukhin AE, Kireev DE, et al. Molecular epidemiological analysis of HIV-1 genetic variants circulating in Russia in 1987–2015. *Terapevtichskij Arkhiv*. 2017;89(11):43-48 (in Russian). doi:10.17116/terarkh2017891144-49
14. Kazennova EV, Lapovok IA, Laga VY, Vasilyev AV, Bobkova MR. Natural polymorphisms of HIV-1 IDUA variant pol gene. *HIV-infection and Immune Disorders*. 2012;4:44-51 (in Russian).
15. Clinical guidelines of the Ministry of Health of the Russian Federation. HIV infection in adults. 2020. (In Russian).
16. The Euresist Integrated Database (EIDB). 2021. Accessed September 06. https://www.euresist.org/
17. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Accessed April 06, 2021. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf
18. Theys K, Abecasis AB, Vandamme AM. HIV-1 drug resistance: where do polymorphisms fit in? *Future Microbiol*. 2013;8(3):303-306. doi:10.2217/fmb.13.10
19. Vingerhoets J, et al. Pre-existing mutations in the rilpivirine Phase III trials ECHO and THRIVE: prevalence and impact on virological response. *Antivir Ther*. 2013;18(2):253-256. doi:10.3851/IMP2358
20. Theys K, Van Laethem K, Gomes P, et al. Sub-epidemics explain localized high prevalence of reduced susceptibility to rilpivirine in Treatment-Naive HIV-1-Infected Patients: subtype and geographic compartmentalization of baseline resistance mutations. *AIDS Res Hum Retroviruses*. 2016;32(5):427-433. doi:10.1089/aid.2015.0095
21. Sluis-Cremer N, Jordan MR, Huber K, et al. E138A in HIV-1 reverse transcriptase is more common in subtype C than B: implications for rilpivirine use in resource-limited settings. *Antiviral Res*. 2014;107:31-34. doi:10.1016/j.antiviral.2014.04.001
22. Gehringer H, Bogner JR, Goebel FD, Nitschko H, von der Helm K. Sequence analysis of the HIV-1 protease coding region of 18 HIV-1-infected patients prior to HAART and possible implications on HAART. *J Clin Virol*. 2000;17(2):137-141. doi:10.1016/s1386-6532(00)00086-x
23. Derache A, Iwuji CC, Baisley K, et al. Impact of Next-generation Sequencing Defined Human Immunodeficiency Virus Pretreatment Drug Resistance on Virological Outcomes in the ANRS 12249 Treatment-as-Prevention Trial. *Clin Infect Dis*. 2019;69(2):207-214. doi:10.1093/cid/ciy881
24. Margot NA, Ram RR, White KL, Abram ME, Callebaut CH. Antiviral activity of HIV - 1 integrase strand - transfer inhibitors against mutants with integrase resistance - associated mutations and their frequency in treatment - naïve individuals. *J Med Virol*. 2019;91(12):2188-2194. doi:10.1002/jmv.25564
25. Porter DP, Toma J, Tan Y, et al. Clinical Outcomes of Virologically-Suppressed Patients with Pre-existing HIV-1 Drug Resistance Mutations Switching to Rilpivirine/Emtricitabine/Tenofovir Disoproxil Fumarate in the SPIRIT Study. *HIV Clin Trials*. 2016;17(1):29-37. doi:10.1080/15284336.2015.1115585
26. Geretti AM, Conibear T, Hill A, et al. Sensitive testing of plasma HIV-1 RNA and sanger sequencing of cellular HIV-1 DNA for the detection of drug resistance prior to starting first-line antiretroviral therapy with etravirine or efavirenz. *J Antimicrob Chemother*. 2014;69(4):1090-1097. doi:10.1093/jac/dkt474
27. Li JZ, Stella N, Choudhary MC, et al. Impact of pre-existing drug resistance on risk of virological failure in South Africa. *J Antimicrob Chemother*. 2021;76(6):1558-1563. doi:10.1093/jac/dkab062
28. Assessment report of Eviplera, Committee for Medicinal Products for Human Use (CHMP), 24 October 2013. Accessed April 06, 2021. https://www.ema.europa.eu/en/documents/variation-report/eviplera-h-c-2312-ii-0021-epar-assessment-report-variation_en.pdf
29. Edurant. Highlights of prescribing information. Accessed April 06, 2021. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/Edurant-pi.pdf
30. Kirichenko AA, Kireev DE, Lopatukhin AE, et al. Prevalence and structure of hiv-1 drug resistance among treatment naïve patients since the introduction of antiretroviral therapy in the russian federation. *HIV Infection and Immunosuppressive Disorders*. 2019;11(2):75-83. doi:10.22328/2077-9828-2019-11-2-75-83

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