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BRIEF REPORT

Dolutegravir and Risk of Neuropsychiatric Adverse Events: a Pharmacogenetic Study

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Dolutegravir treatment can lead to neuropsychiatric adverse events (NPAE). This study assessed the association between NPAE and polymorphisms in dolutegravir-related pharmacogenes, determined by next-generation sequencing panel testing. Using a case-control design, 36 patients having previously discontinued dolutegravir due to NPAE were compared to 98 patients tolerating dolutegravir. In the latter group, psychometric scores were compared according to genotype,

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targeting polymorphisms associated with drug intolerance. *NR1I2* c.-22-7659C>T was independently associated with a reduced risk of NPAE-related dolutegravir discontinuation (odds ratio of 0.36 [95% confidence interval, .15–.88] for T-variant allele carriage) and was linked to decreased anxiety scores in control-group participants.

Key words: HIV, Pregnane X receptor, UGT1A1, CYP3A4, CYP3A5, POR, SLC22A2, ABCB1, ABCG2, integrase inhibitor.

Key points: Using a case-control design, we found a protective effect of the c.-22-7659C>T variant in *NR1I2* (the PXR-encoding gene) against dolutegravir discontinuation due to neuropsychiatric adverse events. Moreover, this variant was linked to decreased anxiety scores in control-group patients on dolutegravir.

BACKGROUND

Dolutegravir (DTG) is a second-generation integrase strand transfer inhibitor (INSTI) that has become a cornerstone of HIV treatment. Several reports highlighted its propensity to cause neuropsychiatric adverse effects (NPAE), which can significantly impact quality of life of people living with HIV (PLWH) and may lead to drug discontinuation. Underlying mechanisms remain poorly understood. An association with plasma concentrations remains debated [1-4], and studies investigating the impact of pharmacogenetic polymorphisms have also reported inconclusive results, especially regarding uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*), the most important DTG biotransformation enzyme [2, 3]. Besides plasma concentrations, other pharmacokinetic parameters, such as central nervous system (CNS) accumulation of DTG or its metabolites, could potentially underpin NPAE. Surprisingly, the association between NPAE and polymorphisms in the genes encoding ATP-binding cassette subfamily B member 1 (ABCB1) and subfamily G member 2 (ABCG2) has never been studied, despite both being DTG efflux transporters expressed at the blood-brain barrier (BBB) [5]. A study also suggested a possible implication of the inhibiting effect of DTG on SLC22A2, involved in neurotransmitters transport, and found an association between neuropsychiatric symptoms and the *SLC22A2* c.808C>A polymorphism, but this has not been confirmed [6, 7].

Considering those knowledge gaps, this study aims to determine the association between NPAE-related DTG discontinuation and selected pharmacogenetic polymorphisms.

MATERIAL AND METHODS

Study Design and Setting

This study is part of a phase IV study aiming to understand the interindividual variability in clinical and biological responses to INSTIs. Briefly, the parent study sought to recruit 200 participants

from different subgroups: 50 bictegravir (BIC)-treated (group A), 100 DTG-treated (group B) and 50 patients having previously discontinued DTG due to NPAE (group C). Details regarding sample size calculation and the study protocol are provided in the **Supplementary Appendix**. Participants were recruited during their regular follow-up at Saint-Luc University Hospital HIV/AIDS clinic (Brussels, Belgium), which serves a diverse patient population, predominantly of Caucasian and African descent. After providing informed consent, all participants were genotyped and measures were performed during follow-up, including psychometric evaluations for groups A and B. This manuscript reports the results of a pharmacogenetic case-control study comparing participants from groups B and C, and psychometric scores distribution across genotypes for group B. The study (ClinicalTrials.gov NCT04805944) received approval by the local Ethical committee (2020/30NOV/593).

Inclusion criteria

Cases were participants who previously discontinued DTG due to any NPAE, while controls were participants receiving DTG without discontinuation for NPAE during follow-up. Cases were identified from our pre-existing institutional database recording HIV and antiretroviral therapy-related data, including dates and reasons for treatment changes. Registered cases of DTG discontinuation due to NPAE were thoroughly reviewed to assess the plausibility of drug-induced toxicity (further details in the **Supplementary Appendix**), considering time relationship to drug intake, existence of plausible alternative explanations, response to drug withdrawal, and effect of rechallenge (when performed). DTG-treated participants initially categorized as controls for which DTG was discontinued due to NPAE during the study follow-up were reclassified as cases, following the same procedure. Importantly, causality assessment was performed blinded to the pharmacogenetic results.

Pharmacogenomic Sample Collection, DNA Extraction and Genotyping

Whole blood was collected from participants in an EDTA tube and stored at +4°C until DNA extraction using the QIAamp® DNA blood kit. Next-generation sequencing pharmacogenomic testing was performed using a 41-gene panel test (SOPHiA DDM®), on an Illumina MiSeq® platform. Additionally, *SLC22A2* c.808C>A (rs316019) genotyping was performed with Taqman assay on a StepOnePlus® RT-PCR system (Applied Biosystems). The selection process of studied candidate genes and polymorphisms is described in the **Supplementary Appendix**. The most frequent *UGT1A1* polymorphisms are characterised by the number of TA repetitions in the promoter region, with the reference allele *UGT1A1*1* containing 6 repeats (TA_6). All samples containing *36 (TA_5) and *37 (TA_8) alleles in addition to *1 or *28 (TA_7) alleles were confirmed by high-resolution melting analysis and Sanger sequencing. Additionally, *28 and *37 alleles were confirmed using the *UGT1A1*80* (rs887829) proxy.

Psychometric evaluation

Four standardized questionnaires (Pittsburgh Sleep Quality Index; Pichot fatigue Questionnaire; Hospital Anxiety and Depression Scale (HADS); Symptom Checklist-90-R; details in **Supplementary Appendix**) were used for controls to assess if a polymorphism that would be associated with NPAE-discontinuation of DTG could also be associated with adverse events not leading to drug discontinuation.

Statistical analysis

Continuous variables were compared between cases and controls using Student t-test or Wilcoxon test, and proportions were compared using Chi-squared or Fischer's Exact test, as appropriate. Risk factors for NPAE-related DTG discontinuation were identified by stepwise multivariable logistic regression. Variables with P value < .10 in univariate analysis were considered for possible inclusion in the model. Odds ratios were derived using stepwise variable forward selection with backward elimination retaining only variables with P < .05 in the final model. For the psychometric evaluation, proportions of participants with pathological scores were compared across groups and the rank of scores were compared across genotypes using the Kruskal-Wallis test, with Dunn test for multiple comparisons. Statistical analyses were performed using JMP® Pro 17.1.0.

RESULTS

A total of 137 participants were recruited in the study with 36 cases and 98 controls included in the case-control analysis (see flowchart in **Supplementary Appendix**). Main participants' characteristics are described in **Table 1**. All participants were successfully genotyped. Genotype distribution is reported in **Table 2**. All polymorphisms were in Hardy–Weinberg equilibrium, including for *CYP3A5* and *UGT1A1* after ethnic origin stratification.

Sleep-related disorders were the most prevalent NPAEs leading to DTG discontinuation (**Supplementary Table S1**). Cases had discontinued DTG due to NPAE at a median of 16.5 months (IQR 7-43) after its initiation. Median DTG treatment duration for controls, censored at the end of study follow-up, was 70 months (IQR 27.5-84). The most frequent DTG-containing regimen at the time of discontinuation was DTG/abacavir/lamivudine, received by 21 cases (58%) (regimens are detailed in **Supplementary Table S2)**.

In univariate analysis, we found a balanced distribution of all studied polymorphisms, with the exception of the *NR1I2* c.-22-7659C>T single nucleotide polymorphism (SNP) (P = .046) (**Table 2**). The multivariable analysis, considering genetic polymorphisms, sex, ethnicity, and sleep, antidepressants, and antipsychotic medication use at DTG initiation, identified *NR1I2* c.-22-7659C>T as the sole variable independently associated to a lower risk of NPAE-related DTG discontinuation, with an odds ratio for T allele carriers of 0.36 (95% CI .15-.88; P = .02).

A total of 63 (64%) controls provided valid answers to at least one questionnaire, and 56 (57%) to all questionnaires. A gradient was found in proportions of controls with an HADS-anxiety score of 8 or more based on *NR1I2* genotype, with 4/9 (44%) for CC, 8/31 (26%) for CT and 2/22 (9%) for TT carriers (P = .07) (**Supplementary Table S3**). Furthermore, a significant difference was found in HADS-anxiety scores distribution based on *NR1I2* c.-22-7659C>T (P = .037), with TT carriers displaying lower scores compared to CT (P = .079) and CC (P = .118) (**Supplementary Figure S2**). No significant difference was found for the distribution of other scores based on *NR1I2* c.-22-7659C>T genotype (**Supplementary Figures S3-15**).

DISCUSSION

This pharmacogenetic case-control study investigated risk factors for NPAE-related DTG discontinuation. The *NR1I2* c.-22-7659C>T variant was independently associated with a protective effect against DTG discontinuation due to NPAE. Notably, none of the other studied polymorphisms were associated with this outcome, despite several of them being associated with DTG plasma pharmacokinetics. Among control participants tolerating DTG, the same *NR1I2* variant was associated with reduced anxiety, as measured by the HADS-anxiety scale, further supporting the plausibility of this association.

NR1I2 is a key pharmacogene encoding the Pregnane X Receptor (PXR). Briefly, this nuclear receptor is activated by various endogenous and exogenous ligands and regulates the expression of several genes involved in drug pharmacokinetics. Among others, PXR upregulates CYP3A4 and UGT1A1, responsible for DTG biotransformation, as well as ABCB1 and ABCG2 [5], two transporters that can limit DTG absorption through intestinal epithelium apical expression.

The precise effect of the *NR1I2* c.-22-7659C>T SNP on drug metabolism remains uncertain. The TT genotype has been associated with increased basal CYP3A4 expression, but the CC genotype has been associated with enhanced rifampin induction [8]. Regarding antiretrovirals, studies have demonstrated that TT carriers display a reduced systemic exposure to unboosted atazanavir [9], a drug primarily metabolized by CYP3A4 and transported by ABCB1. TT carriers also displayed a reduced risk of efavirenz discontinuation [10], a drug mainly metabolized by CYP2B6 and transported by ABCB1. The specific effect of this SNP on DTG pharmacokinetics remains unknown. DTG is a moderate PXR activator, and clinical studies have provided inconclusive results: one adult trial reported a modest increase in DTG exposure associated with the SNP [11] but a large study carried in Southern African adults found no effect of the SNP [12].

Our results align with several reports that challenged the idea that NPAEs are directly linked to DTG plasma concentrations. This simplified vision has been mainly supported by a study reporting higher DTG trough concentrations in patients with NPAE compared to those without. That study also found an increased cumulative incidence of NPAE in carriers of *UGT1A1*6*, *UGT1A1*28*, or both alleles [3], however these results were not confirmed by other pharmacokinetic or

pharmacogenetic studies [1, 2, 4, 7]. Our results further contradict this view as we found no association between DTG discontinuation due to NPAE and genotypes linked with a decreased UGT1A1 function, despite substantial evidence of their impact on plasma exposure [7]. Moreover, we observed no effect of the *ABCG2* c.421C>A SNP which has been previously associated with increased DTG peak concentration [7].

Other mechanisms could potentially explain the protective role of *NR1I2* c.-22-7659C>T against NPAE. First, the SNP might reduce DTG accumulation in the CNS. Indeed, both ABCB1 and ABCG2 are expressed at the BBB, where their expression can be upregulated by PXR [5]. Thus, *NR1I2* c.-22-7659C>T could exert protective effects through PXR activation and, consequently, transporter overexpression [11]. Second, CNS toxicity might not be mediated by the parent drug, but rather by DTG metabolites. Zhu and colleagues have demonstrated that CYP1A1 and CYP1B1 play key roles in the formation of important DTG aldehyde metabolites [13]. As both CYPs are expressed in the brain and given the toxicity of aldehydes, the authors proposed that these pathways could be involved in neurotoxicity. If this hypothesis holds, *NR1I2* polymorphism could thus impact on toxicity either by an upstream influence on DTG CNS concentration, or if exerting regulatory effects on those biotransformation pathways. Finally, one hypothesis could be that *NR1I2 c.-22-7659C>T* protects against neuropsychiatric manifestations independently of DTG. Indeed, PXR is expressed at the BBB as well as in specific brain regions, and its role in brain function has recently gained interest [14]. A recent study found that PXR-deficient mice exhibited increased anxiety-like behaviors and impaired recognition memory [15], an interesting finding in the light of our results, which showed lower HADS-anxiety scores in individuals homozygous for the *NR1I2* c.-22-7659C>T SNP.

Our study has several limitations. First, due to its design, we were unable to assess drug exposure in patients having discontinued DTG due to NPAE. Secondly, our analysis focused on selected polymorphisms, leaving the possibility that unexplored pharmacogenetic factors may contribute to the pathogenesis of NPAE. Thirdly, the level of evidence from our questionnaire analysis should not be overestimated. Although the decision was made *a priori* to limit this analysis to SNP(s) associated with NPAE-related DTG discontinuation in the case-control analysis, the possibility of a type I error cannot be excluded. Finally, our study did not reach the initially expected sample size. Nevertheless, we believe that the homogenous distribution across cases and controls of all studied SNPs (with the notable exception of *NR1I2* c.-22-7659C>T) provides a strong indication that those are not clinically relevant risk factors for NPAE.

In conclusion, among a selection of relevant polymorphisms in pharmacogenes influencing DTG transport and metabolism, only *NR1I2* c.-22-7659T carriage was associated with protection against NPAE-related DTG discontinuation. Our findings confirm that DTG systemic exposure is not a key determinant of NPAE. Further research is needed to clarify the interactions between *NR1I2*, DTG and brain function.

FOOTNOTE PAGE

Author contribution: J.D.G., V.H. and L.Be. conceived and designed the research. P.d.T. provided assistance for designing the psychometric evaluation. J.D.G., J.C.Y., A.V., B.V. and L.Be. recruited and took care of the participants. J.D.G., L.Bo., M.P., N.P. and V.H. performed the biological sample processing and the genotyping. J.D.G. and L.E. performed the statistical analysis. J.D.G. wrote the initial draft of the manuscript. V.H. and L.B. supervised the manuscript writing. All authors critically reviewed the manuscript.

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Table 1: General characteristics of cases and controls.

	Cases (n=36)	Controls (n=98)	*P* value
Age, mean (SD), y	50.7 (11.1)	50.5 (11.7)	0.90
Female gender, n (%)	13 (36)	38 (39)	0.78
BMI, median (IQR), kg/m²	26.5 (24.4-31.1)	26.9 (24.2-30.4)	0.86
CD4 (cell/mm³), median (IQR)	763 (604-970)	693 (533-867)	0.32
Nadir CD4[a] (cell/mm³), median (IQR)	221 (143-393)	239 (124-348)	0.92
Past AIDS diagnosis[b], n (%)	14 (41)	46 (47)	0.53
HIV viral load <40 copies/mL, n (%)	36 (100)	97 (99)	1
Ethnicity			1
White, n (%)	22 (61)	56 (57)	
Sub-saharan African, n (%)	13 (36)	36 (37)	
Tobacco use[c], n (%)	8 (22)	19 (20)	0.74
Use of sleep medications at DTG initiation[d,e], n (%)	3 (9)	14 (14)	0.56
Use of antidepressants at DTG initiation[e] , n (%)	2 (6)	7 (7)	1
Use of neuroleptics at DTG initiation[e] , n (%)	0 (0)	2 (2)	1

Data are presented at study inclusion, unless otherwise indicated. *Abbreviations*: BMI = body mass index; IQR = interquartile range; SD = standard deviation; y = years.

[a] Unavailable for 1 control.

[b] Unavailable for 2 cases and 1 control.

[c] Unavailable for 3 cases and 3 controls.

[d] Benzodiazepines, Z-drugs, melatonin, *Valeriana officinalis*.

[e] Unavailable for 1 case.

Table 2: Genotype distribution of cases and controls for selected pharmacogenes.

	All (N=134)	Controls (n=98)	Cases (n=36)	*P* Value
UGT1A1[a]				.98
Extensive metabolizer	66 (49)	48 (49)	18 (50)	
Intermediate metabolizer	52 (39)	38 (39)	14 (39)	
Poor metabolizer	16 (12)	12 (12)	4 (11)	
*CYP3A4*22* (rs35599367)				1
-/-	121 (90)	88 (90)	33 (92)	
-/*22	12 (9)	9 (9)	3 (8)	
*22/*22	1 (1)	1 (1)	0 (0)	
CYP3A5[b]				.88
Expressor	47 (35)	34 (35)	13 (36)	
Non-expressor	87 (65)	64 (65)	23 (64)	
ABCB1 c.3435C>T (rs1045642)				.96
CC	68 (51)	49 (50)	19 (53)	
CT	50 (37)	37 (38)	13 (36)	
TT	16 (12)	12 (12)	4 (11)	
ABCB1 1199G>A (rs2229109)				1
GG	127 (95)	93 (95)	34 (94)	
GA	7 (5)	5 (5)	2 (6)	
ABCG2 c.421C>A (rs2231142)				.96
CC	112 (84)	82 (84)	30 (83)	
CA	22 (16)	16 (16)	6 (17)	
NR1I2 c.-22-7659C>T (rs2472677)				.046
CC	27 (20)	15 (15)	12 (33.5)	
CT	62 (46)	46 (47)	16 (44.5)	
TT	45 (34)	37 (38)	8 (22)	
*POR*28* (rs1057868)				.90
-/-	83 (62)	60 (61)	23 (64)	
-/*28	40 (30)	29 (30)	11 (30.5)	
*28/*28	11 (8)	9 (9)	2 (5.5)	
SLC22A2 c.808C>A SNP (rs316019)				.78
CC	102 (76)	74 (76)	28 (78)	
CA	32 (24)	24 (24)	8 (22)	

Data are presented as number of subjects (%).

[a] Classified according to Clinical Pharmacogenetics Implementation Consortium (CPIC) classification for UGT1A1 genotype-predicted phenotypic function: extensive metabolizer (*1 or *36)/(*1 or *36), intermediate metabolizer (*1 or *36)/(*28 or *37), poor metabolizer (*28 or *37)/(*28 or *37). No participant displayed the *6 allele.

[b] Expressor participants display at least one copy of a normal function allele: *1/(*1 or *3 or *6 or *7); non-expressor participants have two copies of a no function allele: (*3 or *6 or *7)/(*3 or *6 or *7).