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Correlation Analysis of DNA UGT1A1 Gene Expression in Hyperbilirubinemia and Central Nervous System-Related Adverse Reactions Following Oral Dolutegravir Administration

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Abstract: Major pharmaceutical guidelines have identified dolutegravir (DTG) as a critical medicine in the first-line treatment of HIV/AIDS. The goal of the study was to correlate DNA UGT1A1 gene expression in hyperbilirubinemia and central nervous system-related adverse reactions following oral DTG administration, using a NanoDrop-1000 spectrophotometer and real-time polymerase chain reaction (RT-PCR). Fifty-two seropositive patients were recruited using a standardized questionnaire having different components, including gender, demographic data, and educational qualifications; when highly active antiretroviral therapy (HAART) was initiated, the nature of adverse or side effects experienced, modalities used to overcome such events, and other laboratory parameters were carefully collected. Informed consent was obtained from all potential participants after an adequate explanation of the study and possible areas they would be involved, as well as samples to be collected. Blood samples were collected via venous puncture from all participants, and the same was used to quantify the level of UGT1A1 expressed in each participant using the NanoDrop-1000 spectrophotometer and RT-PCR. The outcome was compared with the side effects or adverse events experienced by each participant using ANOVA. The NanoDrop-1000 spectrophotometric results showed adequate DNA yield from 0.65 (lowest) to 104.71 ng/µl (highest) at 260 and 280 nm, respectively. At 260 nm, the absorbance ranges from 0.01 to 2.09, while at 280 nm from −0.01 to 1.12, respectively. Some of these participants reported having some level of anxiety, consistent headache, insomnia, drowsiness, dizziness, etc., which are clear neuropsychiatric symptoms, loss of appetite, dry throat, and anemia as adverse reactions due to HAART. There was a positive but mildly significant correlation between UGT1A1 gene expression and CNS-related adverse reactions and hyperbilirubinemia, with a p-value of 0.08.

Keywords: HIV/AIDS, dolutegravir, HAART, UGT1A1, hyperbilirubinemia

1. Introduction

Dolutegravir (DTG) is a classical second-generation integrase inhibitor used in the management of human immunodeficiency virus (HIV) infection. DTG is extensively metabolized by the uridine-diphosphate glucuronosyltransferase 1A1 (UGT1A1) and CYP3A4 enzymes. Because there are no documented inhibitory or inducing effects on these enzymes, DTG is said to have a lower likelihood of drug–drug interaction than other antiretroviral medicines (Anstett et al., 2017; Singh et al., 2016).

DTG absorption from the suspension formulation is well tolerated due to its rapid (time to peak concentration, 1/5 h) and biphasic absorption (Castellino et al., 2013). Systemic radiation has just a weak relationship with the organic constituents of blood. In stools and urine, 64.0% and 31.6% of the dosage, respectively, were recovered, showing that recovery was almost complete (Furdui, 2014). DTG remained mostly unaltered and circulating in plasma, which was consistent with very little pre-systemic clearance. The primary biotransformation product of DTG, an inactive ether-glucuronide, was the main metabolite in plasma and accounted for 18.9% of the drug's urine excretion. Two minor biotransformation pathways included oxidative defluorination and glutathione substitution (1.8%) and CYP3A4 oxidation (7.9%). No excessively high quantities of human metabolites were detected in this experiment (Castellino et al., 2013; Moss et al., 2015). Human plasma proteins have a strong affinity for DTG, which accounts for 98.9% of the dosage that is administered (Anderson & Anderson, 2002; Gele et al., 2020). Through three different metabolic routes, DTG is swiftly digested without creating any persistent metabolites. The UGT1A1 enzyme is responsible for the first pipeline, which involves glucuronidation. The second channel,

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which involves carbon oxidation, is controlled by the cytochrome P450 enzyme (CYP3A4). The third stage appears to involve oxidative defluorination followed by glutathione conjugation (Castellino et al., 2013; Zhou et al., 2022). However, due to its chemical makeup, ether in glucuronide form is the most frequent metabolite in plasma (Castellino et al., 2013; Miners & Mackenzie, 1991; Yang et al., 2017). After oral administration, DTG is nearly completely recovered, with 31% excreted unchanged in the urine and 53% excreted unchanged in the feces. DTG-ether-glucuronide (18.9%) and other metabolites make up the renally removed recovered dose (Ribera & Podzamczer, 2015). DTG has a half-life of about 14 h and an apparent clearance rate of 1.0 L/h (Griesel et al., 2021). No significant drug-related malignancies, genotoxic effects, or impacts on fertility (reproductive ability) have been reported on DTG (Belfrage et al., 2023; Turkez et al., 2017).

Reports have shown that UGT1A1 gene mutations substantially impair bilirubin metabolism. Gilbert's syndrome (GS), commonly referred to as hyperbilirubinemia among African Americans and Caucasians, is connected to the UGT1A1*28 allele polymorphism as a result of the UGT1A1 enzyme's lower transcriptional activity (Gil & Sasiadek, 2012; Li et al., 2014). Genetic polymorphisms of the UGT1A1 enzyme have been connected to a variety of patient reactions in clinical settings. A significant occurrence of severe harmfulness has been related to the lack of this enzyme (Liu et al., 2022; Teh et al., 2012). Bilirubin uridine-diphosphate glucuronosyltransferase (bilirubin-UGT), which is glucuronidated bilirubin, is made by the UGT1A1 gene. This enzyme converts dangerous unconjugated bilirubin into innocuous conjugated bilirubin, enabling the body to break it down and discard it. The liver cells where bilirubin glucuronidation takes place contain a considerable amount of the bilirubin-UGT enzyme. Among other clinical issues is that UGT1A1 gene mutation leads to GS, and warfarin resistance, among others (Kamisako et al., 2000; Rossi et al., 2005). This is because, drug biotransformation or metabolism has direct impacts on its safety, as well as efficacy (Bunu et al., 2020a).

A genetic mutation is responsible for the pigmentary hepatosis known as GS. Common signs include icteritiousness of the skin, sclera, and mucous tunics. The most frequent causes of pathological symptoms, which can also be brought on by a low-calorie diet, hunger, or some medicines, are physical exhaustion or infectious diseases (Chen et al., 2002; MedlinePlus, 2012). A fundamental laboratory characteristic that results in elevated bilirubin levels in the blood is an indirect fraction (Singh et al., 2023). Basic GS symptoms are transient and are not thought to cause severe liver damage. However, GS frequently coexists with other gastrointestinal disorders (Ferrara et al., 1996), and in certain people, cholelithiasis may be a possible distant consequence of the illness (Littlefield & Lenahan, 2019). In the presence of AIDS or sickle cell anemia, GS substantially increases the risk of cholelithiasis (Nouraie et al., 2012; Owusu et al., 2015). GS raises the likelihood of difficulties and death in newborns with hemolytic disorders (Horsfall et al., 2013).

It was revealed that *1/*28 carriers, especially *28/*28, had greater bilirubin levels in the blood than homozygotes *1/*1 carriers (Peer et al., 2012; Qosa et al., 2018). There are very few data on UGT1A1 genetic variations and its bio-physiological expressions in the Russian population (Goon et al., 2016; Liu et al., 2022). The Caucasian population in the Kemerovo region showed a 47.0% (*1/*1) prevalence of GS (Mendez et al., 2013). Minor allele *28 was linked to a pathological condition in 33.3% of people. The proportion of people with GS that belonged to the *28/*28 genotype was 13.6%. It reveals that no genotype has clear de-adaptation and that there is no selection in contradiction of this genotype among the studied population. Potential patients and those suffering from GS make up a substantial fraction of the population (Chandrasekar et al., 2023; Wagner et al., 2018). Immediate measurement and early identification of individuals with GS at genetic risk, as well as preventive and treatment methods to prevent illness manifestations, are required (Wray et al., 2007). Therefore, the current study aimed analyze and correlate the DNA UGT1A1 gene expression in hyperbilirubinemia and central nervous system-related adverse reactions following oral DTG administration, using a NanoDrop-1000 spectrophotometer and real-time polymerase chain reaction (RT-PCR).

2. Methods and Materials

2.1. Study participants and data collection instrument

A total of 52 seropositive patients' data were collected using a coded questionnaire for each participant. Information such as demographic data including age, gender, body weight, height, ethnicity, use of other medications including contraceptives, and concurrent illness was collected. Clinical data from the patient's file that were collected include the viral load before drug administration, viral load at the time of sample collection, CD4 cell count, and experienced or any reported side effects. Other laboratory parameters such as liver enzymes, complete blood count, blood glucose, and creatinine were collected. A questionnaire and consent form were designed to obtain participants' consent and clinical data to ascertain exclusion and inclusion criteria. Blood samples were collected from consented participants

2.2. DNA quantification and RT-PCR analysis

The NanoDrop-1000 spectrophotometer was used to quantify DNA. A software installation system was linked to the spectrophotometer. To blank the machine, 2 µl of nuclease-free water was utilized. Two microliters of extracted DNA products was placed on the pedestal, and the quantity and purity of the extracted DNA were determined at 260 and 280 nm (A260/A280) wavelength, as displayed on the monitor by the program (Bunu et al., 2020b). The presence or absence of genetic polymorphism was confirmed using the RT-PCR. UGT1A1 genotyping was carried out using RT-PCR and restriction fragment length polymorphism (PCR-RFLP) techniques, as described by Ebeshi et al. (2011). Specific primers such as 5-AGATACTGTTGATCCCAGTG-3 were used as the forward primer, while 5-CTTCAAGGTGTAAAA TGGTC-3 was used as the reverse primer for amplification and RFLP after digestion with Ava II (Huang et al., 2004).

2.3. Study population and location

The study population consisted of Southern Nigeria HIV/AIDS-positive patients aged 18 and above who agreed to participate in the study. They were recruited at the point of sample collection for their routine CD4 count check-up at the Federal Medical Centre Yenagoa, Bayelsa State's Medical Laboratory Department. Fifty-two HIV/AIDS positive but unrelated patients, aged 18 years and above, who were receiving DTG (50 mg daily) in combination with either lamivudine (TLD) or tenofovir and met the study inclusion criteria were chosen at random from various States of Southern Nigeria, including Akwa Ibom, Bayelsa, Cross River, Delta, Edo, Ondo, Lagos, Enugu, Abia, Imo, and Anambra. Potential subjects were explained the study procedures, after which they were free to

choose whether or not to participate in the study. Subjects who met the eligibility requirements were enrolled and signed the consent form. The Federal Medical Centre, Yenagoa's Research and Ethics Committees approved the study.

2.4. Inclusion criteria and ethical approval

Inclusion criteria include participants must be HIV-positive patients who are not related by blood, who have received highly active antiretroviral therapy (HAART) that includes DTG for ≥ 3 weeks, must be 18 years and above, both male and female, and a signed informed consent, while exclusion criteria were those with severe underlying concurrent illness, pregnant women and children less than 18 years of age, patients on medication other than antiretrovirals that might interfere with DTG, and patients who are smokers and alcoholics

The study protocol was submitted to the Federal Medical Centre, Yenagoa, Bayelsa State, within the Southern Nigeria region for approval before the initiation of the study. This is a center where almost the whole of Nigeria has access to their health needs, hence served as a focal point for the study. Consent forms were designed, and study aims, procedures, benefits, and risks were explained to every potential study subject before seeking informed consent. The information on the consent form was read out, and the technical terms were explained to all the participants. In cases where volunteers neither speak nor read the English language, appropriate interpretation was provided in the individual's native language to ensure that every participant understood all the basics of the study before giving their consent. Before being enrolled in the study, all patients provided written informed consent. The study was approved by the Research and Ethics Committee of the Federal Medical Centre Yenagoa in Bayelsa State.

2.5. Data analysis

Retrieved statistical data obtained from study were analyzed using analysis of variance (ANOVA) with IBM SPSS version 23.0 computer software program, Microsoft Excel, and GraphPad Inc USA software IBM (n.d.).

3. Results and Discussion

Data were generated using a standard questionnaire, including demographics, medication history, when antiretroviral therapy was initiated, unwanted adverse reactions experienced during therapy, and social history. These are presented in frequency tables, charts, percentages, etc.

Participants were chosen at random from among some States in Southern Nigeria. The 52 seropositive patients who took part in the study ranged in age from 27 to 63 years old, with 13 (25%) being male and 39 (75%) being female (Figure 1).

Among the study participants; 8% were from Abia and Anambra state, 15% from Akwa Ibom and Rivers state, 6% from Cross River and Delta state, 4% from Edo and Enugu, while Ebonyi, Imo and Bayelsa states had 2%, 10% and 23%, respectively. All these patients had taken DTG-based combination therapy with tenofovir disoproxil fumarate and TLD for at least 3 weeks before the study. The highest body weight among the participants was 103 g, while the lowest observed was 51 g. They were allocated study codes at the point of recruitment in the health facility (Table 1).

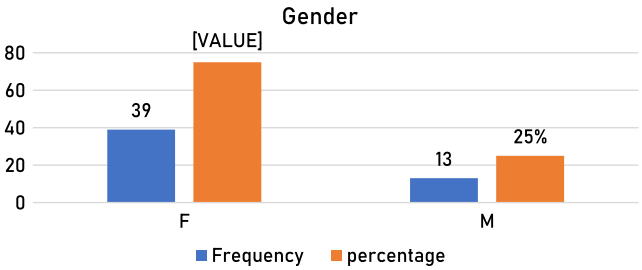

Figure 1. Gender distribution of participants. Legend: F = female participants, M = male participants. The blue and orange chart box shows the frequency (*N*) and percentage (%) of participants based on their gender distribution, respectively

Table 1. DNA concentration and participants clinical data

Lab code	ng/ul	A260	A280	260/280	260/230	Duration of HAART (Years)	ADRs	Comorbidities	Initial viral load	Current viral load
A01	4.18	0.08	0.01	9.95	0.19	3	Nil	Nil	<20	<20
A02	9.60	0.19	0.07	2.77	0.04	1.5	Nil	Nil	<20	<20
A03	3.40	0.07	0.02	3.30	0.22	7	Nil	Nil	<20	<20
A04	5.95	0.12	0.01	15.84	0.23	11	Nil	Nil	23215	<20
A05	3.39	0.07	0.02	2.79	0.27	7 ms	Nil	Nil	BL	<20
A06	16.36	0.33	0.15	2.15	0.50	8	Nil	Nil	<20	71
A07	9.27	0.19	0.08	2.31	0.17	2	Nil	Nil	<20	<20
A08	3.76	0.08	0.04	1.73	0.10	10	Nil	Nil	14517	<20
A09	2.61	0.05	0.01	5.39	0.02	3	Nil	Nil	<20	<20
A10	1.45	0.03	−0.02	−0.13	0.07	1	Nil	Nil	BL	<20
A11	6.53	0.13	0.03	4.74	0.14	14	Nil	Nil	<20	2460
A12	19.35	0.39	0.19	2.09	0.46	7.5	Nil	Nil	<20	<20
A13	18.75	0.38	0.23	1.67	0.40	5	Nil	Nil	<40	<28
A14	16.73	0.34	0.17	2.02	0.45	3	Anemia	Malaria	<20	<20
A15	15.86	0.32	0.16	2.04	0.12	2	Nil	Nil	<20	<20
A16	2.49	0.05	0.00	−12.99	0.08	2	Nil	Nil	129	<20
A17	25.93	0.52	0.25	2.10	0.29	8	Insomnia	Nil	33800	38682
A18	6.19	0.12	0.03	4.31	0.13	12	Nil	Nil	28721	205
A19	10.40	0.21	0.10	2.14	0.03	6	Nil	Nil	<20	<20

(*Continued*)

Table 1. (*Continued*)

Lab code	ng/ul	A260	A280	260/280	260/230	Duration of HAART (Years)	ADRs	Comorbidities	Initial viral load	Current viral load
A20	7.97	0.16	0.08	2.08	0.21	6 ms	Nil	Nil	<20	<20
A21	3.54	0.07	0.04	1.63	0.02	7	Nil	Nil	<20	<20
A22	22.16	0.44	0.02	2.17	0.54	8	Nil	Malaria, Htn	<20	<20
A23	19.98	0.40	0.19	2.09	0.66	4	Nil	Nil	<20	<20
A24	0.74	0.02	−0.04	−0.38	0.02	7 ms	Anxiety	Nil	<20	<20
A25	10.60	0.21	0.06	3.74	0.02	9	Headache	Nil	<20	44126
A26	16.11	0.32	0.18	1.82	0.43	8	Nil	Nil	<20	<20
A27	13.91	0.28	0.15	1.85	0.20	7	Headache, No appetite	Nil	<20	<20
A28	4.96	0.10	0.03	3.87	0.03	4	Dry throat	Nil	<20	<20
A29	10.64	0.21	0.08	2.67	0.16	4	Nil	Nil	<20	<20
A30	1.21	0.02	−0.04	−0.65	0.02	4	Nil	Nil	178	28
A31	20.58	0.41	0.18	2.30	0.57	11	Nil	Htn	<20	<20
A32	9.65	0.19	0.08	2.51	0.26	14	Dizziness, drowsiness	Htn	33	29
A33	4.62	0.09	0.01	7.43	0.03	1	Nil	Malaria	<20	<20
A34	6.49	0.13	0.03	3.92	0.10	4	Nil	Nil	<20	<20
A35	12.87	0.11	0.11	2.29	0.04	13	Nil	Nil	<20	<20
A36	34.00	0.68	0.33	2.09	0.06	4	Nil	TB	<20	<20
A37	6.81	0.14	0.06	2.25	0.12	5 ms	Nil	Malaria	<20	<20
A38	10.63	0.21	0.07	2.96	0.32	3	Headache	Malaria	<20	<20
A39	18.73	0.38	0.15	2.48	0.40	6	Nil	Nil	<40	<20
A40	18.36	0.37	0.14	2.64	0.13	2	Nil	Hiccups	<20	<20
A41	18.47	0.37	0.15	2.44	0.70	9	Nil	Nil	<20	<20
A42	11.02	0.22	0.09	2.54	0.40	10	Nil	Nil	<20	<20
A43	104.71	2.09	1.12	1.88	0.87	3	Nil	Nil	<20	<20
A44	12.85	0.26	0.12	2.22	0.18	13	Nil	Htn	<20	<20
A45	6.58	0.13	0.03	4.22	0.10	9	Nil	Nil	<20	<20
A46	7.55	0.15	0.06	2.60	0.13	7 ms	Headache	Malaria	<20	<20
A47	16.58	0.33	0.16	2.04	0.04	7	Nil	Malaria, TB	11106	<20
A48	10.59	0.21	0.08	2.74	0.05	3	Nil	Malaria, Htn	<20	30969
A49	51.02	1.02	0.49	2.08	0.72	1.5	Nil	Nil	<20	<20
A50	15.71	0.31	0.13	2.49	0.02	3	Nil	Nil	<20	<20
A51	60.45	1.21	0.85	1.42	1.26	2	Nil	Malaria, Htn	<20	<20
A52	0.65	0.01	−0.01	−1.62	0.01	3	Nil	Nil	<20	<20

Legend: BL – baseline, Htn – hypertension, WT – distilled water, Yrs – years, Ms – months, TB – tuberculosis

The majority (61.3%) of the participants had just secondary education, 23.1% (tertiary), 11.5% (primary), and 3.8% had no formal educational qualification. More so, 82.7% were self-employed, 9.6% unemployed, 5.8% were civil servants, and 1.9% were retirees (Figure 2).

The NanoDrop-1000 spectrophotometer with relative absorbance at 260/280 was used to quantify and purify DNA samples from each participant. DNA samples should absorb more at 260 nm than at 280 nm, whereas protein samples should do the opposite (Brescia et al., 2012).

One of the participants whose DNA was 0.74 ng/µl had reported anxiety as an adverse reaction due to HARRT, with no comorbidities and acceptable viral load. Four patients had DNA concentrations of 4.0–5.95 ng/µl. One of which reported dry throat as an ADR observed during therapy for a period of 4 years. Another group of patients (7) had DNA levels of 6.19–7.97 ng/µl, and one of them had experienced consistent headaches as ADR, which could be due to neuropsychiatric side effects caused by the combination therapy. Eight of the participants had DNA levels of 9.27–10.64 ng/µl, and three of these patients had experienced drowsiness, dizziness, and headache during therapy, which are clear neuropsychiatric symptoms (Table 2).

Furthermore, six of the participants had DNA levels of 11.02–15.71 ng/µl. One of these groups reported having headaches and loss of appetite during treatment. One of the patients (16.73 ng/µl), out of ten that had DNA levels of 16.11–19.98 ng/µl

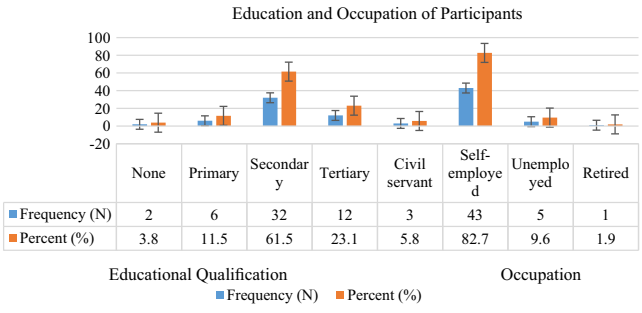

Figure 2. Educational qualification and occupation of study participants ($N = 52$). Legend: the blue and orange chart box shows the frequency (N) and percentage (%) of participants based on the participants' occupational distribution, respectively

Table 2. Summary of reported adverse reaction among participants

Reported adverse drug reactions (ADRS)	N	%
Nil	41	78.8
Anxiety	1	1.9
Dry throat	1	1.9
Headache	4	7.7
Dizziness	1	1.9
Drowsiness	1	1.9
Insomnia	1	1.9
Loss of apatite	1	1.9
Anemia	1	1.9
ΣN	52	100
MEAN ± SEM	5.8 ± 4.4	11.1 ± 8.5
p-value	0.08	

Key: SD – standard deviation, ΣN = sum of participants, the *P value is 0.08, considered not significant*

developed anemia (reduced level of red blood cells), attributed to the HAART regimen. This supports Al Mamun Bhuyan et al.'s (2016) research on the increased eryptosis after DTG exposure. They discovered that adding DTG to human erythrocytes for 48 h increased the percentage of annexin-V-binding cells, caused hemolysis, and that removing extracellular calcium ions reduced the effect of DTG on annexin-V-binding but not the protein kinase C inhibitor staurosporine. As a result, they concluded that DTG promotes erythrocyte cell shrinkage and phospholipid scrambling, which they attribute to Ca^{2+} access, ceramide formation, as well as oxidative stress. In addition, three individuals had DNA levels ranging from 20.58 to 25.93 ng/l, with one reporting sleeplessness. Finally, one had 34.00, 51.02, 60.45, and 104.71 ng/µl of DNA concentration in their serum, respectively (Table 2 and Figure 3). This justifies the claims that integrase inhibitors especially DTG have a series of neuropsychiatric adverse events such as insomnia, drowsiness, dizziness, and anxiety (Chan et al., 2020; Hoffmann & Llibre, 2019; Povar-Echeverria et al., 2021).

Finally, Yagura and colleagues identified sleeplessness, dizziness, headache, anxiety, and restlessness as neuropsychiatric adverse effects in 107 Japanese HIV-1 infected patients taking DTG in a 2017 research. The normal allele was identified in 7% of *6 homozygotes, 3% of *28 homozygotes, 4% of *6/*28 heterozygotes, 21% of *6 heterozygotes, 17% of *28 heterozygotes, and 48% of patients. Plasma DTG levels were substantially greater in homozygous patients than in people with the normal genotype. Patients with the heterozygous alleles *6 and *28 performed much better than those with the normal allele. Patients who suffered from neuropsychiatric side effects had significantly higher median DTG plasma concentrations than those who did not (Yagura et al., 2017). Furthermore, the RT-PCR and RFLP gave almost the same results (Figure 4), indicating there is little or no quantifiable level of DTG polymorphism among the study group (Bunu et al., 2022).

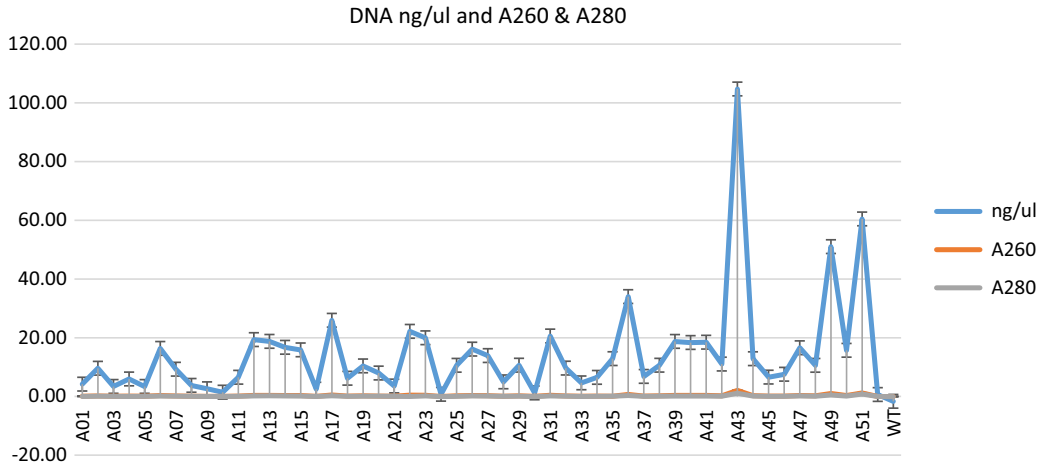

Figure 3. DNA quantification and NanoDrop-1000 absorbance at 260 and 280 nm. Legend: A1–A51 = study code assigned to each participant, WT – water used as standard control, A260, A280 = wavelengths of NanoDrop-1000 spectrophotometer

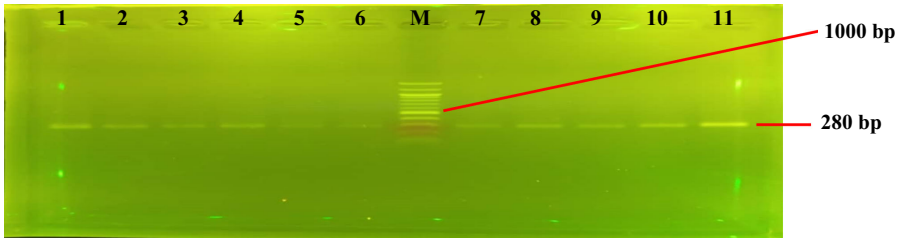

Figure 4. RT-PCR-gel electrophoretic analysis of participants' DNA. Legend: 1–11 = number of samples introduced to gel electrophoretic medium. M = DNA molecular ladder used for the analysis

4. Conclusion

The study included 52 HIV-positive patients, both male and female, from all states in Nigeria's South-South and South-East who had been receiving DTG-based combination therapy with tenofovir and TLD. A NanoDrop-1000 spectrophotometer set to 260/280 relative absorbance was used to measure each participant's DNA samples. Acceptable yields at 260 and 280 nm ranged from 0.65 (lowest) to 104.71 ng/µl (highest). As a result, except for ten people, the vast majority of the DNA products obtained were of high purity. The absorbance ranges from 0.01 to 2.09 at 260 nm and from −0.01 to 1.12 at 280 nm. Anxiety was noted as an adverse effect of HARRT by one of the participants whose DNA was 0.74 ng/µl. Other individuals experienced headaches, insomnia, sleepiness, dizziness, and other evident neuropsychiatric symptoms, as well as lack of appetite, dry throat, and anemia. When the DNA samples from the HIV-positive patients recruited for the study were visualized on 1% agarose gel electrophoretic media, they all appeared at 280 bp after amplification, demonstrating that all participants had the correct gene (UGT1A1) required to code for the UGT1A1 enzyme, which is liable for the metabolism of DTG. The correlation of DTG administration with neuropsychiatric adverse events and hyperbilirubinemia was sparingly significant at a *p*-value of 0.08.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

The data that support this work are available upon reasonable request to the corresponding author.

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