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Role of Glutathione S-Transferase (*GSTM*1 and *GSTT*1) Genes Deletion in Susceptibility to HIV-1 Disease Progression

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Abstract

Background: Glutathione S-transferases (GSTs) are multifunctional enzymes which play an important role in oxidative stress pathways by conjugation with glutathione. Oxidative stress is one of several risk factors that may be associated with many types of diseases progression such as cancer and infectious diseases. In this study, we investigated the association between the polymorphism of *GSTM*1 and *GSTT*1 genes and the risk of HIV-1 disease progression. **Methods:** We conducted a case-control study including 313 participants of Burkina Faso: 153 HIV-1 infected individuals on antiretroviral treatment (ART) and 160 HIV-1 negative individuals as controls. Presence or absence of the *GSTM*1 and *GSTT*1 genes was determined using multiplex polymerase chain reaction (PCR). $CD4^+$ T counts and HIV-1 viral load were measured in patients using respectively BD FACSCount and Abbott m2000rt instruments. **Results:** Frequencies of *GSTM*1-null and *GSTT*1-null were 30.35% and 35.46% respectively and the frequency of double deletion *GSTM*1-null/*GSTT*1-null was 14.38% in the general study population. *GSTM*1-null (30.35% *versus* 69.65%; OR = 1.90; p = 0.010), *GSTT*1-null (35.46% *versus* 64.54%; OR = 3.11; p < 0.001), *GSTM*1-active/*GSTT*1-null (21.08% *versus* 48.56%; OR = 3.17; p < 0.001) and the double deletion *GSTM*1-null/*GSTT*1-null (14.38% *versus* 48.56%; OR = 4.46; p < 0.001) were more present in cases group than controls and differences

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were significant. *GSTM*1-null and *GSTM*1-null/*GSTT*1-null were associated with increased odds of low $CD4^+$ count (<350 cells/mm^3) and high HIV-1 viral load (≥1000 copies/mL). **Conclusion:** *GSTM*1-null, *GSTT*1-null genotype, the double genotypes *GSTM*1-active/*GSTT*1-null and *GSTM*1-null/*GSTT*1-null were associated with HIV-1 disease progression and *GSTM*1-null and *GSTM*1-null/*GSTT*1-null genotypes were associated with low $CD4^+$ T cells counts and high HIV-1 viral load in HIV-1infected patients on ART.

Keywords

HIV-1, *GSTM*1, *GSTT*1, Burkina Faso

1. Introduction

Human immunodeficiency virus (HIV) and AIDS remain persistent public health concerns in Sub-Saharan Africa. In 2018, the World health organization reported that more about 35 million patients had died due to HIV infection, making it one of the most serious life-threatening human diseases in both 20th and 21st century [1]. Sub-Saharan Africa is one of the most affected regions by HIV infection globally, with an estimated 25.6 million people living with the disease [1]. In 2016, in Burkina Faso 3400 new cases of HIV infection and approximately 95,000 people who are living with HIV were reported [2]. As HIV progresses, host immunity is depleted from its most effective immune cells ($CD4^+$ T cells), thus increasing body's vulnerability to opportunistic infections. Antiretroviral treatment is therefore needed to prevent viral multiplication and correct CD4 T cell levels.

Several studies have reported high rate of therapeutic failures [3] [4] [5] and investigations have been conducted to develop more effective therapies to inhibit HIV replication in infected patients. Moreover, studies on host/pathogen interactions have contributed to improve our knowledge on HIV molecular pathogenicity in human. Currently, investigations have focused on understanding host-genetic factors that could potentially modulate cellular susceptibility to HIV replication [6] [7].

Glutathione S-transferase (GSTs) are a super family of drug metabolizing enzymes with a high level of conjugation specificity for glutathione (GSH) and the enzymes are essential for metabolism of many substances, responsible for response to oxidative stress in humans. There are eight groups of enzyme namely *alpha* (*GSTA*), *mu* (*GSTM*), *theta* (*GSTT*), *pi* (*GSTP*), *sigma* (*GSTS*), *kappa* (*GSTK*), *omega* (*GSTO*) *and zeta* (*GSTZ*) which are involved in the detoxification of compounds in drugs and carcinogens, and for inhibition of oxidative damage to tissues [8]. The Glutathione S-transferases *GSTM*1 and *GSTT*1 are highly polymorphic genes belonging, respectively to the *mu* and *theta* classes [9] [10], and they are the most studied. Polymorphisms in GST are associated to higher risk of oxidative stress, which has been suggested to promote HIV replication [11] [12]. There are two types of polymorphisms in glutathione S-Transferase genes: the

homozygous deletion genotype (null genotype) which has been associated with loss of enzymatic activity and one or two undeleted genotype (called non-null or present genotype). *GSTM*1 and *GSTT*1 are located respectively on chromosome 1p13.3 and 22q11.23 and the enzymes are involved in the conjugation and detoxification of some drug containing butadiene epoxide, bromodichloromethane, dichloromethane, ethylene dibromide, methylene chloride and ethylene oxide [13] [14] [15]. The *GSTM*1-null and *GSTT*1-null genotypes are deletion variants associated with the lack of a group of enzymes associated to the susceptibility of developing certain diseases, such as infectious diseases, cancers and others, possibly due to an amplified susceptibility to the harmful effects of oxidative stress, environmental toxins and carcinogens [15]-[20]. Studies on *GSTM*1 and *GSTT*1 genotypes have been associated to the risk of HIV-1 disease progression, but rather the results are still controversial. This study was designed to investigate the association between the polymorphisms of *GSTM*1 and *GSTT*1 genes and the risk of HIV-1 disease progression in Burkina Faso.

2. Material and Methods

2.1. Ethical Consideration

This study protocol was approved by CERBA/LABIOGENE Ethics Committee. All participants have given written and informed consent according to the Helsinki's Declarations.

2.2. Type and Population of Study

This is a case-control study which was conducted from December 2018 to June 2019. A total of 313 individuals were included in this investigation, which consisted of 153 HIV-1 infected patients on antiretroviral treatment (ART) and 160 HIV-1 negative individuals as controls. All subjects were seronegative for hepatitis B (HBV) and C (HCV) infections.

2.3. Samples Collection and Research for HIV, HBV and HCV Viral Markers

After giving their informed consent, approximately 10 mL of venous blood of HIV-1 infected patients and healthy voluntary non-remunerated blood donors was collected in dry and EDTA tubes. Serological tests using four-generation ELISA Ag/Ab were performed for HIV, HBV and HCV screening and confirmation in the control group, using cobas e 411 Analyzer (Roche Diagnostics GmbH Mannheim Germany) according to the manufacturer's protocol.

2.4. Determination of Lymphocyte $CD4^+$ Count and HIV-1 Viral Load

Becton Dickson FACSCount machine (Becton, Dickson and company, San Jose, CA) was used to determine $CD4^+$T cells counts following the manufacturer's protocol.

Viral RNA was extracted from 200 µL of plasma using the "Abbott HIV-1

m-sample system preparation Kit (Promega, USA)" according to the manufacturer's protocol. HIV-1 viral load was determined using the "Abbott HIV-1 Real Time kit (Promega, USA)" on the Abbott m2000rt system (Abbott Laboratories, Illinois, USA) according to the manufacturer's protocol.

2.5. Genomic DNA Extraction and Genotyping of *GSTM*1/*GSTT*1

Whole blood was used for genomic DNA extraction using the salting-out method as previously described [21]. DNA purity and concentration were determined using a Biodrop (Isogen Life Science, NV/S.A, Temse, Belgium). *GSTM*1 and *GSTT*1 Genotyping was performed according to the method described by Chen *et al*., (1997) [22]. Briefly we performed multiplex PCR with the GeneAmp PCR system 9700 (Applied Biosystem, USA) in a reaction volume of 25 µL including 10 µL of Master Mix Ampli Taq Gold® (Appleid Biosystems, USA), 1 µL of each of the primer pairs of each gene (Table 1), 7 µL of nuclease-free water and 2 µL of DNA. The amplification program was as follows: 94˚C for 5 min for initial denaturation; 40 cycles of a series of denaturation at 94˚C for 1 min, hybridization at 57˚C for 1 min, elongation at 72˚C for 1 min; and a final extension at 72˚C for 7 min. PCR products migrated on a 3% agarose gel migration during 45 min and visualized under UV light at 312 nm using the Geneflash revelation device. PCR amplification was considered valid if the sample had a band corresponding to *β-globine* gene (Figure 1).

Table 1. Sequence of primers for multiplex PCR.

Genes	Sequences	Amplicon length (bp)
*GSTM*1	5'-GAACTCCCTGAAAAGCTAAAGC-3' 5'-GTTGGGCTCAAATATACGGTGG-3'	215
*GSTT*1	5'-TTCCTTACTGGTCCTCACATCTC-3' 5'-TCACCGGATCATGGCCAGCA-3'	480
β-globin	5'-CAACTTCATCCACGTTCACC-3' 5'-GAAGAGCCAAGGACAGGTAC-3'	268

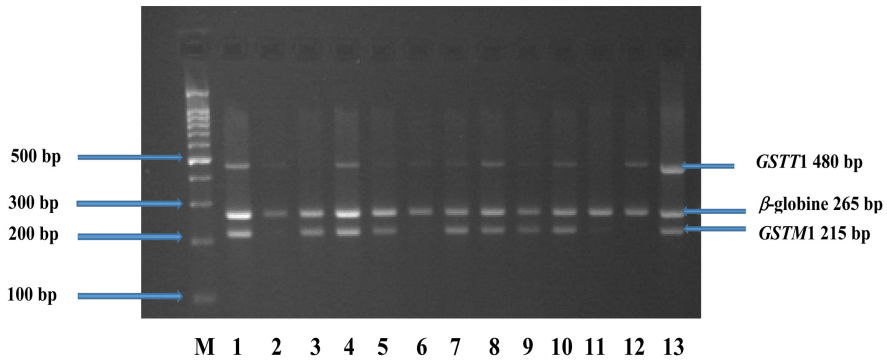

Figure 1. Electrophoresis agarose 3% gel of DNA fragment of *GSTM*1 and *GSTT*1 genes. M = Molecular weight ladder (100 bp); 1, 4, 5, 7, 8, 9, 10, 13 = Double present genotypes of *GSTM*1 and *GSTT*1; 3 = Genotypes of *GSTM*1 present and *GSTT*1 null; 11 = Double genotypes null of *GSTM*1 and *GSTT*1; 2, 6, 12 = *GSTM*1 null and GSTT1 present.

3. Statistical Analysis

The data was analyzed with the standard Statistical Package for Social Sciences (SPSS) software version 20.0 and Epi-info version 7.1 software (CDC, Atlanta, USA). Association between polymorphisms and HIV-1 infection were established by comparing frequencies between cases and controls using the chi-square test. Relative risk was estimated with Odds Ratio (OR) and 95% of confidence interval (95% CI). p-values < 0.05 or Odds Ratio with a 95% CI were considered statistically significant.

4. Results

The distributions of sociodemographic characteristics are shown in Table 2. In the general study population females were more represented than males (76.70% versus 23.30%) and were more infected by HIV-1 than males in case group (66.7% versus 33.3%). In overall, the individuals aged ≥ 40 years was the most represented with 55.90%, characterized by 9.82-fold increased risk to be infected with HIV-1 than individuals aged ≤ 39 years (OR = 9.82, 95% CI = 5.78 - 16.66, p < 0.001).

The lymphocytes $CD4^+$ cells counts were stratified according to the Centers for Diseases Control and Prevention criteria [23]. Among HIV-1 infected patients, 7.84% and 81.04% had respectively T CD4+ counts < 200 cells/mm^3 and ≥ 350 cells/mm^3. Also we found that 92.2% of HIV-1 infected patients had viral load ≤ 1000 copies/mL and patients who had $CD4^+$ ≥ 350 cells/mm^3 and viral load < 1000 copies/mL were 81.04%.

The distribution of *GSTM*1 and *GSTT*1 polymorphism in the study population are shown in Table 3. In the general study population, we found that the frequencies of *GSTM*1-active and *GSTT*1-active were 69.65% and 64.54% respectively; those of *GSTM*1-null and *GSTT*1-null were 30.35% and 35.46% respectively.

Table 2. Sociodemographic characteristic of the study population.

	Variables	HIV+ *n* (%)	Controls *n* (%)	Total *n* (%)	OR	95% CI	p-value
	Gender						
#	**Male**	51 (33.30)	22 (13.70)	73 (23.30)			
	Female	102 (66.70)	138 (86.30)	240 (76.70)	**0.31**	**0.18 - 0.55**	**<0.001***
	Age (years)						
#	**≤39**	28 (18.30)	110 (68.70)	138 (44.10)			
	≥40	125 (81.70)	50 (31.30)	175 (55.90)	**9.82**	**5.78 - 16.66**	**<0.001***
	Serological status						
	HIV+	153 (100.00)	0 (0.00)	153 (100.00)	-	-	-
	HIV−	0 (0.00)	160 (100.00)	160 (100.00)	-	-	-
	HBV−/HCV−	153 (100.00)	160 (100.00)	313 (100.00)	-	-	-

Analysis by chi-square to obtain odds ratio values (OR) and confidence interval; HIV+: patients group with HIV-1 infection, HIV−/HBV−/HVC−: controls group without HIV-1; HBV and HCV infection CI: confidence interval; OR: odds ratio; #: reference; *: significant difference between groups (p < 0.05).

Table 3. Frequencies of *GSTM*1 and *GSTT*1 in the general study population.

Variables	HIV+ *n* (%)	Controls *n* (%)	Total *n* (%)	OR	95% CI	p-value
#*GSTM*1(+)	**96 (62.75)**	**122 (76.25)**	**218 (69.65)**	**1.00**		
*GSTM*1(−)	57 (37.25)	38 (23.75)	95 (30.35)	**1.90**	**1.16 - 3.11**	**0.010***
#*GSTT*1(+)	**79 (51.63)**	**123 (76.90)**	**202 (64.54)**	**1.00**		
*GSTT*1(−)	74 (48.37)	37 (23.10)	111 (35.46)	**3.11**	**1.91 - 5.05**	**<0.001***
#*GSTM*1(+)/*GSTT*1(+)	**54 (35.29)**	**98 (61.25)**	**152 (48.56)**	**1.00**		
*GSTM*1(−)/*GSTT*1(+)	25 (16.34)	25 (15.62)	50 (15.97)	**1.81**	**0.95 - 3.46**	**0.094**
*GSTM*1(+)/*GSTT*1(−)	42 (27.45)	24 (15.00)	66 (21.08)	**3.17**	**1.74 - 5.79**	**<0.001***
*GSTM*1(−)/*GSTT*1(−)	32 (20.91)	13 (8.13)	45 (14.38)	**4.46**	**2.16 - 9.22**	**<0.001***

Analysis by chi-square to obtain odds ratio values (OR) and confidence interval; +: active; −: null; CI: confidence interval; OR: odds ratio; #: reference; *: significant difference between groups ($p < 0.05$).

When we compared frequencies between cases and controls, we found that subjects with *GSTM*1-null and *GSTT*1-null genotype were more present in the case group than controls and difference between the two group was significant respectively (37.25% versus 23.75% for *GSTM*1-null, OR = 1.90, 95% CI = 1.16 - 3.11, p = 0.010 and 48.37% versus 23.10% for *GSTT*1-null OR = 3.11, 95% CI = 1.91 - 5.05, $p < 0.001$). We found significant difference between cases and controls concerning the double genotype *GSTM*1-active/*GSTT*1-null (27.45% versus 15.00%, OR = 3.17, 95% CI = 1.74 - 5.79, $p < 0.001$) and the double deletion *GSTM*1-null/*GSTT*1-null (20.91% versus 8.13%; OR = 4.46; 95% CI = 2.16 - 9.22**,** $p < 0.001$). But we didn't find any significant difference between cases and controls concerning the double genotype *GSTM*1-null/*GSTT*1-active (16.34% versus 15.62%; OR = 1.81; 95% CI = 0.95 - 3.46, p = 0.094).

Table 4 shown the impact of the polymorphisms of *GSTM*1 and *GSTT*1 genes in HIV-1 infected patients according to the $CD4^+$ T cells counts. $CD4^+$ T cells counts was stratified according to the Centers for Diseases Control and Prevention criteria [23]. HIV-1 infected patients with the *GSTM*1-null were 57 and 41 of them had $CD4^+$ counts ≥ 350 cells/mm^3, 9 of them had $CD4^+$ count between 200 and 349 cells/mm^3 and 7 had $CD4^+$ count < 200 cells/mm^3. A total of 74 HIV-1 infected patients had *GSTT*1-null and among them 56 had $CD4^+$ counts ≥ 350 cells/mm^3, 9 had $CD4^+$ count between 200 and 349 cells/mm^3 and 9 had $CD4^+$ count below 200 cells/mm^3. HIV-1 infected patients with the double genotype *GSTM*1-null/*GSTT*1-null were 32 and among them 22 had $CD4^+$ count ≥ 350 cells/mm^3, 5 had $CD4^+$ count between 200 and 349 cells/mm^3 and 5 too equally had $CD4^+$ below 200 cells/mm^3. A statistically significant difference was found when we compared *GSTM*1 and *GSTT*1 variants frequencies in patients with $CD4^+$ counts ≥ 350 cells/mm^3 and those with 350 < cells/mm^3. *GSTM*1-null genotype and the double genotype *GSTM*1-null/*GSTT*1-null variants were less frequent in patients with $CD4^+$ counts < 350 cells/mm^3, suggesting that *GSTM*1-null genotype (OR = 2.49, 95% CI = 1.095 - 5.66, p = 0.033) and the double genotype *GSTM*1-null/*GSTT*1-null (OR = 4.45, 95% CI = 1.36 - 14.57, p = 0.016) were associated with an higher risk to have $CD4^+$ count less than 350 cells/mm^3.

Table 4. Impact of *GSTM*1/*GSTT*1 deletion on T CD4 count in HIV-1 patients.

Variables	CD4 ≥ 350 *n* (%)	CD4 = 200 - 349 *n* (%)	CD4 < 200 *n* (%)	OR	95% CI	p-value
#*GSTM*1(+)	**83 (66.94)**	8 (47.05)	5 (41.67)	1.00		
*GSTM*1(−)	41 (33.06)	9 (52.94)	7 (58.33)	**2.49**	**1.095 - 5.66**	**0.033***
#*GSTT*1(+)	**68 (54.84)**	8 (47.05)	3 (25.00)	1.00		
*GSTT*1(−)	56 (45.16)	9 (52.94)	9 (75.00)	**1.98**	**0.86 - 4.55**	**0.147**
#*GSTM*1(+)/*GSTT*1(+)	49 (39.52)	4 (23.53)	1 (8.33)	1.00		
*GSTM*1(−)/*GSTT*1(+)	19 (15.32)	4 (23.53)	2 (16.67)	**3.09**	**0.84 - 11.35**	**0.09**
*GSTM*1(+)/*GSTT*1(−)	34 (27.42)	4 (23.53)	4 (33.33)	**2.30**	**0.69 - 7.65**	**0.23**
*GSTM*1(−)/*GSTT*1(−)	22 (17.74)	5 (29.41)	5 (41.67)	**4.45**	**1.36 - 14.57**	**0.016***

Analysis by chi-square to obtain odds ratio values (OR) and confidence interval; +: active; −: null; CD4+: Lymphocyte T CD4; CI: confidence interval; OR: odds ratio; #: reference; *: significant difference between groups ($p < 0.05$). The comparison was done between patients with CD4+ counts ≥ 350 cells/mm^3 and 350 < cells/mm^3.

The impact of *GSTM*1 and *GSTT*1 genes deletion on viral load of HIV-1 infected patient was show in Table 5. The baseline viral load level for failure or therapeutic success is 1000 copies/mL in accordance with WHO Consolidated Guidelines for the Use of Antiretroviral Drugs for the Treatment and Prevention of HIV Infections in 2016 [24]. Patients with viral load test results below the threshold should be considered as having suppressed viral loads but patients with viral load greater than 1000 copies/mL after 12 months of treatment were defined as virological failures. A total of 57 HIV-1 patients had *GSTM*1-null, among them 48 had HIV-1 viral load < 1000 copies/mL and 9 had HIV-1 viral load ≥ 1000 copies/mL. Those with *GSTT*1-null were 74 and among them 66 had HIV-1 viral load < 1000 copies/mL and 8 had HIV-1 viral load ≥ 1000 copies/mL. HIV-1 infected patients with the double genotype *GSTM*1-null/*GSTT*1-null were 32 and among them 25 and 7 had respectively HIV-1 viral load < 1000 copies/mL and ≥1000 copies/mL. A statistically significant difference was found when we compared *GSTM*1 and *GSTT*1 variants frequencies in patients with HIV-1 viral load < 1000 copies/mL and those HIV-1 viral load ≥ 1000 copies/mL. *GSTM*1-null genotype and the double genotype *GSTM*1-null/*GSTT*1-null variants were less frequent in patients with HIV-1 viral load ≥ 1000 copies/mL, suggesting that *GSTM*1-null genotype (OR = 5.81, 95% CI = 1.50 - 22.74, p = 0.009) and the double genotype *GSTM*1-null/*GSTT*1-null (OR = 7.28, 95% CI = 1.40 - 37.61, p = 0.011) were associated with an higher risk to have HIV-1 viral load ≥ 1000 copies/mL.

5. Discussion

From our knowledge, this study is the first to assess the association between *GSTM*1 and *GSTT*1 genes deletion with HIV-1 infection and disease progression in Burkinabe patients.

Table 5. Impact of *GSTM*1 and *GSTT*1 deletion on HIV-1 patients' viral loads.

Variables	VL < 1000 *n* (%)	VL ≥ 1000 *n* (%)	Total *n* (%)	OR	95% CI	p-value
#*GSTM*1(+)	93 (65.96)	3 (25.00)	**96 (63.00)**	**1.00**		
*GSTM*1(−)	48 (34.04)	9 (75.00)	**57 (37.00)**	**5.81**	**1.50 - 22.74**	**0.009***
#*GSTT*1(+)	75 (53.19)	4 (33.33)	**79 (51.63)**	**1.00**		
*GSTT*1(−)	66 (46.81)	8 (66.67)	**74** (48.37)	**2.27**	**0.65 - 7.89**	**0.23**
#*GSTM*1(+)/*GSTT*1(+)	52 (36.88)	2 (16.70)	54 (35.29)	**1.00**		
*GSTM*1(−)/*GSTT*1(+)	23 (16.31)	2 (16.70)	25 (16.34)	**2.26**	**0.29 - 17.05**	**0.58**
*GSTM*1(+)/*GSTT*1(−)	41 (29.07)	1 (8.33)	42 (27.45)	**0.63**	**0.05 - 7.24**	**1.00**
*GSTM*1(−)/*GSTT*1(−)	25 (17.73)	7 (58.33)	32 (20.91)	**7.28**	**1.40 - 37.61**	**0.011***

Analysis by chi-square to obtain odds ratio values (OR) and confidence interval; +: active; −: null; VL: HIV-1 Viral Load; CI: confidence interval; OR: odds ratio; #: reference; *: significant difference between groups ($p < 0.05$).

In the general population study, women were more represented than men and among HIV-1 infected patients, they were more infected by HIV-1 than men (66.7% versus 33.3% respectively) (Table 2). Due to the high proportion of women in HIV-1 infected patients, certain studies suggested that women had an increasing risk of being infected by HIV than men. According to World health Organization, Women are more likely to be infected with HIV in any type of sexual intercourse than men because of biological factors; the mucosal areas exposed during sexual intercourse are larger in women than in men [25]. Moreover some, countries as Burkina Faso, through the prevention of mother to child program of HIV infection, HIV test for all pregnant women is recommended. This could explain the high proportion of HIV-1 infected women. The proportions of HIV-1 infected patients aged ≥ 40 years were high (81.70%). Decreasing in HIV-related mortality since the introduction of combination antiretroviral therapy has resulted in increased life expectancy and an aging HIV-positive population [26]. Individuals aged ≥ 40 years in the general study population were 9.82 times more likely to be infected by HIV-1 compared to individuals aged ≤ 39 years (Table 2). HIV, HBV and HCV tests were performed in controlled subjects; HBV and HVC tests were performed in HIV positive patients to rule out possible cases of infection with these viruses.

In accordance with WHO Consolidated Guidelines for the Use of Antiretroviral Drugs for the Treatment and Prevention of HIV Infections in 2016 [24], 81.04% of patients ($CD4^+ \geq 350$ cells/mm^3 and viral load < 1000 copies/mL) should be considered as having suppressed viral load and 7.8% of patients ($CD4^+ < 200$ cells/mm^3 and viral load ≥1000 copies/mL) were defined as virological failure. The therapeutic failure could be due to virus factors and/or host-genetic factors that could potentially modulate cellular susceptibility to HIV replication. Indeed, some studies in Burkina Faso have shown that host genetic factors could confer susceptibility or protection against HIV infection, Kagoné *et al*. (2014) in their study suggested a protective role of a variation of *DC-SIGN* promoter and

genetic resistance to HIV-1 in serodiscordant couples, Compaore *et al*., (2016) demonstrate that some *APOBEC3G* variants were associated with HIV-1 infection [6] [7].

Glutathione S-transferase (GSTs) are a super family of drug metabolizing enzymes with a high level of conjugation specificity for glutathione (GSH) and the enzymes are essential for metabolism of many substances, responsible in part for response to oxidative stress in humans. *GSTM*1-null and *GSTT*1-null genotypes are deletion variants associated with the lack of a group of enzymes associated to the susceptibility of drug metabolizing and progression of certain diseases, such as infectious diseases, cancers and others.

Our study showed in the general study population that the frequency of *GSTM*1-null and *GSTT*1-null were 30.35% and 35.46% respectively (**Table 3**). There were several studies about *GSTM*1 and *GSTT*1 gene polymorphisms implication in some diseases, Piacentini *et al*., (2011) who showed that the distribution of genotypes varies among ethnic groups [27]. Palma-Cano *et al*., (2017) estimated that in worldwide frequencies of the *GSTT*1-null ranges from 10% to 51% and those of *GSTM*1-null genotypes from 11% to 67% [28]. In our study, *GSTM*1-null frequency (30.35%) is comparable with those in African population such as Cameroon (28%) [27], Tanzania (33%) [29], higher than Zimbabwe (24%) [29], but lower than those such as Ivory Coast (36%) [30], Egypt (55%) [31], Tunisia (46%) [32], Morocco (45%) [33]. Concerning the frequency of *GSTT*1-null genotype in our population (35.46%), it is comparable with those in Gambian (37%) [34], higher than Egypt (30%) [31], Morocco (22%) [33], but lower than Cameroon (47%) [27], Somalia (44%) [35] and Tunisia (44%) [32].

In the present study we also analyzed the relationship between *GSTM*1 and *GSTT*1 variants and HIV-1 infection and disease progression in Burkina Faso. Association between *GSTM*1 and *GSTT*1 polymorphisms and HIV-1 disease progression has long been studied. Singh *et al*., (2017) showed that *GSTT*1-null and *GSTM*1-null genotypes alone and in combination may predict the acquisition of hepatotoxicity, so disease progression [36]. Ciccacci *et al*., (2017) shown that only *GSTM*1-null was associated to HIV disease progression [37]. Kuleape *et al*., (2018) found that double deletion of glutathione S-transferase M1 and T1 is statistically associated with normal CD4+ count in Ghanaians patients diagnosed with HIV/AIDS [38]. Parsons *et al*., (2013) shown that the *GSTM*1 genotype coding for the functional antioxidant enzyme is associated with lower HIV disease severity and with lower oxidative stress, compared to *GSTM*1 null-allele polymorphism, HIV infected patients with *GSTM*1 genotype coding for the functional antioxidant enzyme had higher CD4 cell count, lower HIV viral load and ART reduced oxidative stress [39].

This study showed that the frequency of *GSTM*1-null, *GSTT*1-null, *GSTM*1-active/*GSTT*1-null and the double genotype *GSTM*1-null/*GSTT*1-null were higher in HIV-1 infected patients group than controls group and differences were significant, indicating a possible association between *GSTM*1-null genotype, *GSTT*1-null and the double genotype *GSTM*1-null/*GSTT*1-null and risk of

HIV-1 infection.

When we grouped the GST polymorphism according to CDC staging of CD4+ count (Table 4) and HIV-1 viral Load according to WHO Consolidated Guidelines for the Use of Antiretroviral Drugs for the Treatment and Prevention of HIV Infections in 2016 (Table 5), we found that *GSTM*1-null genotype and the double genotype *GSTM*1-null/*GSTT*1-null were associated with low $CD4^+$ count (<350 cells/mm^3) and high HIV-1 viral load (≥1000 copies/mL). This indicate that *GSTM*1-null genotype and the double genotype *GSTM*1-null/*GSTT*1-null were deletion variants associated with the lack of enzymes activity and the susceptibility to antiretroviral drug metabolizing. Glutathione S-transferase (GSTs) play a role in the detoxification of the reactive oxygen species [40]. Several studies showed that *GSTM*1-null *and GSTT*1-null allele polymorphism is associated with reduced mitochondrial enzyme activity, decreased ability to detoxify compounds, increased level of reactive oxygen species, and increased risk of cancers [41] [42] [43]. Increased levels of oxidative stress in HIV infected patients, relative to healthy subjects, have been demonstrated [44] [45] [46]. The deletion of *GSTM*1 and both *GSTM*1/*GSTT*1 could favor accumulation of reactive oxygen species and increased the risk of HIV-1 disease progression by some difficulty to metabolize antiretroviral drug. Polymorphism in GST is associated to higher risk of oxidative stress, which has been suggested to favor HIV replication and disease progression [11] [12].

6. Conclusion

Our results suggest that *GSTM*1-null genotype, *GSTT*1-null genotype and the double genotype *GSTM*1-null/*GSTT*1-null were associated with HIV-1 disease progression in the Burkinabe population. The study showed also that *GSTM*1-null genotype and the double genotype *GSTM*1-null/*GSTT*1-null were associated with low $CD4^+$ T cells counts and high HIV-1 viral load in HIV-1 infected patients on ART. However, larger studies will be necessary to fully understand the role of *GST* variant in the HIV-1 disease progression.

Authors' Contributions

Study concept and design: PAS, FWD, ATY and JS.

Sampling and Laboratory analysis: FWD, PAS, STS, HKS, ITK, ATY and JS.

Statistical analysis and interpretation of data: FWD, PAS, STS, ATY, TRC and AKO.

Drafting of the manuscript: FWD, PAS, STS, ATY, BMN, TRC, HKS, ITK, AKO, BVJTEB and JS.

Critical revision of the manuscript for important intellectual content: FWD, ATY, BMN and JS.

Administrative, technical, and material support: BMN, ATY, FWD and JS.

Study supervision: FWD and JS.

Manuscript Approval: All authors have read and approved the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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