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GENETIC VARIABILITY OF CYP2B6 G516T AND THEIR IMPACT IN EFAVIRENZ BASED HAART: A META-ANALYSIS

Anwar Mulugeta*[1] Abiy H. Eyakim [2] and Yewbdar Belew [1]

Department of Pharmacology, School of Pharmacy, Mekelle University [1], P.O. Box 1871, Ethiopia
Department of Pharmacology, Faculty of Medicine, Addis Ababa University [2], P.O. Box 1176, Addis Ababa, Ethiopia

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Correspondence to Author:

Anwar Mulugeta

Department of Pharmacology, School of Pharmacy, Mekelle University, P.O. Box 1871, Ethiopia

ABSTRACT

Background: The non-nucleoside reverse transcriptase inhibitor efavirenz is recommended as part of first-line therapy in HIV-infected patients and prescribed at a standard dose of 600 mg once daily. EFV is extensively metabolized primarily by hepatic CYP2B6 with partial involvement of CYP3A4 and CYP2A6. The aim of the study was to assess CYP 2B6 G516T polymorphism and their impact in efavirenz based therapy

Methods: A computerized literature search was conducted using the Medline, PubMed, and High wire. Statistical analysis was conducted using comprehensive Meta analysis version 2 software.

Result: From fifty four articles only twenty two articles were included in the study based on the inclusion criteria. The average frequency of CYP 2B6 G516T polymorphism, from forest plot of 7 studies, was around 30% which strengthened the idea of substantial number of this polymorphism. Most of the studies had high proportion of mutant allele and the average of the all is around 49%. The mean plasma efavirenz concentration among 516GG, 516 GT and 516 TT holders was 2.869 ± 0.294 µg/ml, 3.464 ± 0.276 µg/ml and 9.659 ± 1.262 µg/ml, respectively and it has significant association with genetic polymorphism of CYP 2B6 G516T.

Conclusion: The most common type of CYP 2B6 polymorphism is CYP 2B6 G516T that have significant association with plasma efavirenz concentration. Having genetic test before drug starting is promising in HIV therapy to decrease side effects and to have better treatment outcome.

INTRODUCTION: HIV/AIDS is a pandemic disease that has high morbidity and mortality rate. According to 2008 HIV/AIDS report by WHO/UNAIDS, the number of people living with HIV/AIDS was 33 million [31.1 million–35.8 million] from which 31.3 million [29.2 million–33.7 million] were adults. There were 2.7 million people with new infection of HIV and 2.0 million [1.7 million–2.4 million] deaths due to HIV/ADIS in 2008. Sub-Saharan Africa remains the most heavily affected region, accounting for 71% of all new HIV infections in 2008 [1].

But after the introduction of antiretroviral drugs the morbidity and mortality rate of HIV/AIDS decrease from time to time. There have been remarkable advances in the treatment of HIV/AIDS during the last 20 years. Today there are over 20 antiretroviral agents representing five therapeutic drug classes, each with a unique mechanism of action [2]. Non nucleotide reverse transcriptases are the major component of combination therapy in which efavirenz and nevirapine are the widely and mainly used drugs of this group.

Even though there is a decrease in mortality and morbidity rate, there are still a challenge in treatment of HIV/AIDS patients with antiretroviral therapy which include resistance, adverse effect and variation of a given regimen to different individual [3].

The non-nucleoside reverse transcriptase inhibitor, efavirenz, is recommended as part of first-line therapy in HIV-infected patients and prescribed at a standard dose of 600 mg once daily [4]. Efavirenz undergo phase I, functionalizing reaction, and phase II, conjugation reaction. EFV is extensively metabolized primarily by hepatic CYP2B6 with partial involvement of CYP3A4 and CYP2A6 to inactive hydroxylated metabolites that include 8-hydoxy and 7-hydroxyefavirenz [5, 6, 7]. The 8-hydroxyefavirenz is the major metabolite of EFV in vitro and in vivo, and the contribution of 7-hydroxylation to the overall clearance of EFV is considered to be small [6].

Recent studies suggest that CYP2A6 is primarily responsible for 7-hydroxylation [8]. CYP2B6 further catalyzes second step of hydroxylation of the 8-hydroxymetabolite to 8, 14-dihydroxyefavirenz and it is estimated that ~ 17% of 8-hydroxyefavirenz is further oxidized to 8, 14-dihydroxyefavirenz in vitro [5, 6]. Hydroxylated EFV metabolites undergo subsequent urinary and biliary excretion after conjugation (mainly glucuronidation) [8].

A number of factors may contribute to variable drug response in patients with HIV infection: Virologic, immunologic, pharmacologic, and pharmacokinetic differences between HIV-infected patients have all been noted to contribute to interpatient variability in drug response [9, 10]. Recent data suggest that pharmacogenetic differences among HIV-infected individuals may also be an important variable that contributes to antiretroviral drug response [10].

Several studies have shown that *CYP2B6* is highly polymorphic and that genetic variations play an important part in EFV plasma concentration variability and associated with central nervous system toxicity [11, 12]. However, so far there was no Meta analysis study that shows the impact of CYB 2B6 polymorphism in plasma concentration, CNS toxicity and relation this polymorphism with ethnicity.

Therefore, this study was important in comparing polymorphism of CYP2B6G516T, its impact in plasma concentration and clearance of efavirenz, and its relation with different ethnicity across different articles.

Methods:

Literature Search: A computerized literature search was conducted using the Medline, PubMed, and Highwire. Keywords used to identify articles included "CYP 2B6", "efavirenz", "polymorphism", and "HIV*/AIDS"* were used. Different styles of the search terms were also used in order to obtain every relevant article.

Inclusion Criteria: Studies which involves individuals who were either HIV/AIDS patient that were under HAART or healthy individual who took efavirenz for short term to study polymorphism of CYP 2B6 and undergone genotyping study at least for CYP 2B6 enzyme were included in the study. And in this review the articles were not filtered by age of the study participant. All articles included in this study were those that published in between 2000 to 2010. So, fifty four articles were obtained but based on the inclusion criteria, only twenty two of which were included in analysis of some of the common variables.

Data Extraction: Data from each paper fulfilling inclusion criteria were reviewed and separately extracted. Coding of articles and common variables in analysis, such as CYP 2B6 G516T polymorphism, ethnicity, EFV plasma concentration, clearance, and CNS side effect, were done.

Statistical Analysis: The analysis was conducted using comprehensive Meta analysis version 2 software. For the summary value of different articles, different statistical measuring unit were used; including percentage, mean, median, inter quantile range, standard deviation, and p values. Table and forest plot, which summarize the different reviews were used and P- Value less than 0.05 is considered as significant. P value was calculated by online chi-square analysis using-http://www.quantitativeskills.com/sisa/statistics/twoby2.htm.

RESULTS:

1. **Population characteristic of Reviews:** From a total of 54 full articles only twenty two were included in the analysis. As shown in the **table 1**, most of the participants of the studies were above 18 years old, except one study conducted in children (mean age=6) and most of these studies were conducted in already HIV positive patients however there were three studies which conducted in healthy volunteers. Those studies conducted in HIV positive individuals were taking HAART regimen mainly whereas study conducted in healthy volunteers mainly took single dose efavirenz for short term. All of the study included male and female individuals. All of the studies had at least CYP 2B6 genotype polymorphism in addition to other CYP polymorphism which shown in six of the study.

2. **Frequency of CYP 2B6 G516T polymorphism relative to other CYP 2B6 polymorphism:** As shown in **figure 1**, forest plot, the average frequency of CYP 2B6 G516T polymorphism of the seven studies is around 30%.

3. **Frequency of mutant and wild type allele of CYP 2B6 G516T:** An individual may have homozygote wild type, heterozygote mutant allele, or homozygote mutant allele of CYP 2B6 G516T which is represented as CYP 2B6 516GG, CYP 2B6 516GT and CYP 2B6 516TT, respectively. Since the standard deviation was not given for the following table, so as to get the forest plot, the proportion of mutant allele of CYP 2B6 and sample size is used. As shown in **figure 2** most of the studies have high proportion of mutant allele and the average of the all is around 49%, which show that how much the mutant allele of G516T is significantly common.

4. **CYP 2B6 G516T Polymorphism and Ethnicity:** As shown in **figure 3**, the frequency of combination of heterozygote and homozygote mutant allele of CYP 2B6G516T (516 GT and 516 TT) in white and black is 35.9 % and 45.2 %, respectively with p value= 0.0001.

5. **CYP 2B6 G516T Polymorphism and plasma efavirenz concentration:** All of the study in **table 4** showed that there is significant association, that all have p value less than 0.05, between plasma concentration and CYP 2B6 G516T polymorphism. Efavirenz plasma concentration varies in different study populations who have different polymorphism which is showed in **figure 4**, mean plasma efavirenz concentration among 516GG, 516 GT and 516 TT holders is 2.869±0.294 µg/ml, 3.464±0.276 µg/ml and 9.659±1.262 µg/ml, respectively.

TABLE 1: POPULATION CHARACTERISTIC OF TWENTY TWO REVIEWS

Review (reference number)	Age (median or mean)	Female (%)	EFV taking population (N)	Study Population	Genotype
Rotger et al. [13]	44	24	167	HIV patients	CYP2B6
Klein et al [14]	-	-	238	HIV patients	CYP2B6
Wang et al [15]	-	-	51	HIV patients	CYP2B6
Haas et al [16]	39	18	157	HIV patients	CYP2B6, CYP 3A4, CYP 3A5, MDR1
Wyen et al [17]	43	-	186	HIV patients	CYP2B6
Leger et al [18]	36	60	45	HIV patients	CYP2B6
Kwara et al [19]	39	47	94	HIV patients	CYP2B6,CYP2A6, UGT2B7
Mukonzo et al [20]	26	57	121	Healthy	ABCB1, CYP2B6
Kwara et al [21]	38	55	74	HIV patients	CYP2B6, CYP2A6
Novoa et al [22]	40	20	104	HIV patients	CYP2B6
Haas et al [23]	24	76	34	Healthy	CYP2B6
Gatanaga et al [24]	-	-	456	HIV patients	CYP 2B6
Uttayamakul et al [25]	36	35	65	HIV patients	CYP 2B6
Wang et al [26]	40	35	79	HIV patients	CYP 2B6
Chen et al [27]	40	19	70	HIV patients	CYP 2B6
Saitoh et al [28]	6	61	71	HIV patients	CYP 2B6
Powers et al [29]	39	36	73	HIV patients	CYP 2B6
Tsuchiya et al [30]	42	3	35	HIV patients	CYP 2B6
Xu et al [31]	29	-	507	Healthy	CYP 2B6
Carr et al [32]	-	-	219	HIV patients	CYP 2B6
Haas et al [33]	37.7	-	504	HIV patients	CYP2B6, CYP2C19, MDR1
Ribaudo et al [34]	-	19	831	HIV patients	CYP 2B6, ABCB1,CYP3A5

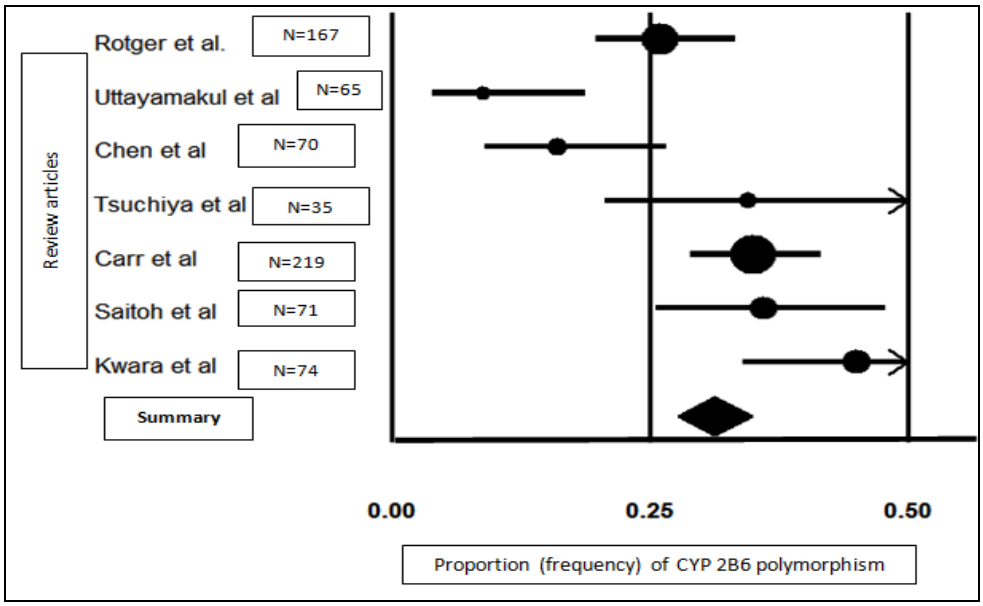


FIGURE 1: FOREST PLOT SHOWING THE FREQUENCY OF CYP2B6 G516T POLYMORPHISM IN DIFFERENT REVIEW AND ITS SUMMARY

TABLE 2: FREQUENCY OF HOMOZYGOTE WILD TYPE, HETEROZYGOTE MUTANT AND HOMOZYGOTE MUTANT ALLELE OF CYP 2B6 G516T POLYMORPHISM FROM DIFFERENT STUDY.

Articles	Sample size of CYP2B6 G516T Polymorphism	Frequency of CYP 2B6 G516T polymorphism, n (%)		
		GG	GT	TT
Wang et al	46	24 (52.2)	18 (39.1)	4 (8.7)
Haas et al	157	83 (52.9)	60 (38.2)	14 (8.9)
Wyen et al	170	85 (48.9)	67 (38.5)	18 (10.3)
Kwara et al	74	22 (30)	38 (51)	14 (19)
Novoa et al	100	52 (52)	43 (43)	5 (5)
Uttayamakul et al	101	67 (66.3)	28 (27.7)	6 (6.0)
Gatanaga et al	65	25 (38.46)	31 (47.69)	9 (13.85)
Wang et al	79	42 (53.2)	34 (43.0)	3 (3.7)
Chen et al	159	111 (69.8)	46 (28.9)	2 (1.3)
Haas et al	71	31 (44)	28 (39)	12 (17)
Powers et al	206	105 (51.0)	82 (39.8)	19 (9.2)
Saitoh et al	367	187 (51.0)	148 (40.3)	32 (8.7)
Total *		1119 (49.9)	859 (38.3)	264 (11.8)

* Pooled percentage of different allele of CYP 2B6 G516T

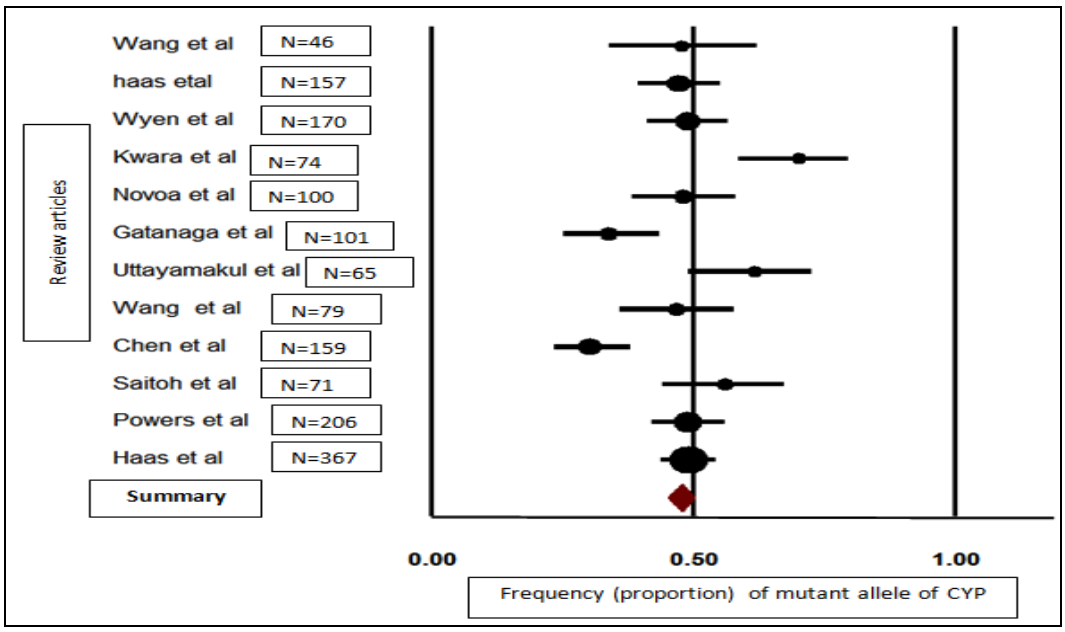


FIGURE 2: FOREST PLOT OF FREQUENCY OF MUTANT ALLELE OF CYP 2B6 G516T ENZYME

TABLE 3: FREQUENCY OF CYP 2B6 G516T POLYMORPHISM AMONG WHITE, BLACK AND HISPANIC ETHNICITY

Articles	Ethnicity n(%)									P-Value
	White			Black			Hispanic			
	GG	GT	TT	GG	GT	TT	GG	GT	TT	
Haas et al	53 (59.6)	33 (37.1)	3 (3.4)	22 (44.0)	18 (36.0)	10 (20.0)	8 (53.3)	6(40.0)	1 (6.7)	0.005
Wyen et al	58 (51.3)	44 (38.9)	11 (9.7)	27 (47.4)	23 (40.4)	7 (12.3)	-	-	-	0.693
Saitoh et al	2 (25)	5 (63)	1 (12)	20 (44)	19 (41)	7 (15)	9 (56)	3 (19)	4 (25)	0.93
Powers et a	80 (55.9)	54 (37.8)	9 (6.3)	25 (39.7)	28 (44.4)	10 (15.9)	-	-	-	<0.05
Haas et al	185 (75.6)	60 (24.4)		107 (68.7)	48 (31.3)		68 (65.1)	36 (34.9)		0.09
Ribaudo et al	301 (75.5)	98 (24.5)		186 (65.8)	97 (34.2)		101 (67.8)	48 (32.2)		0.008

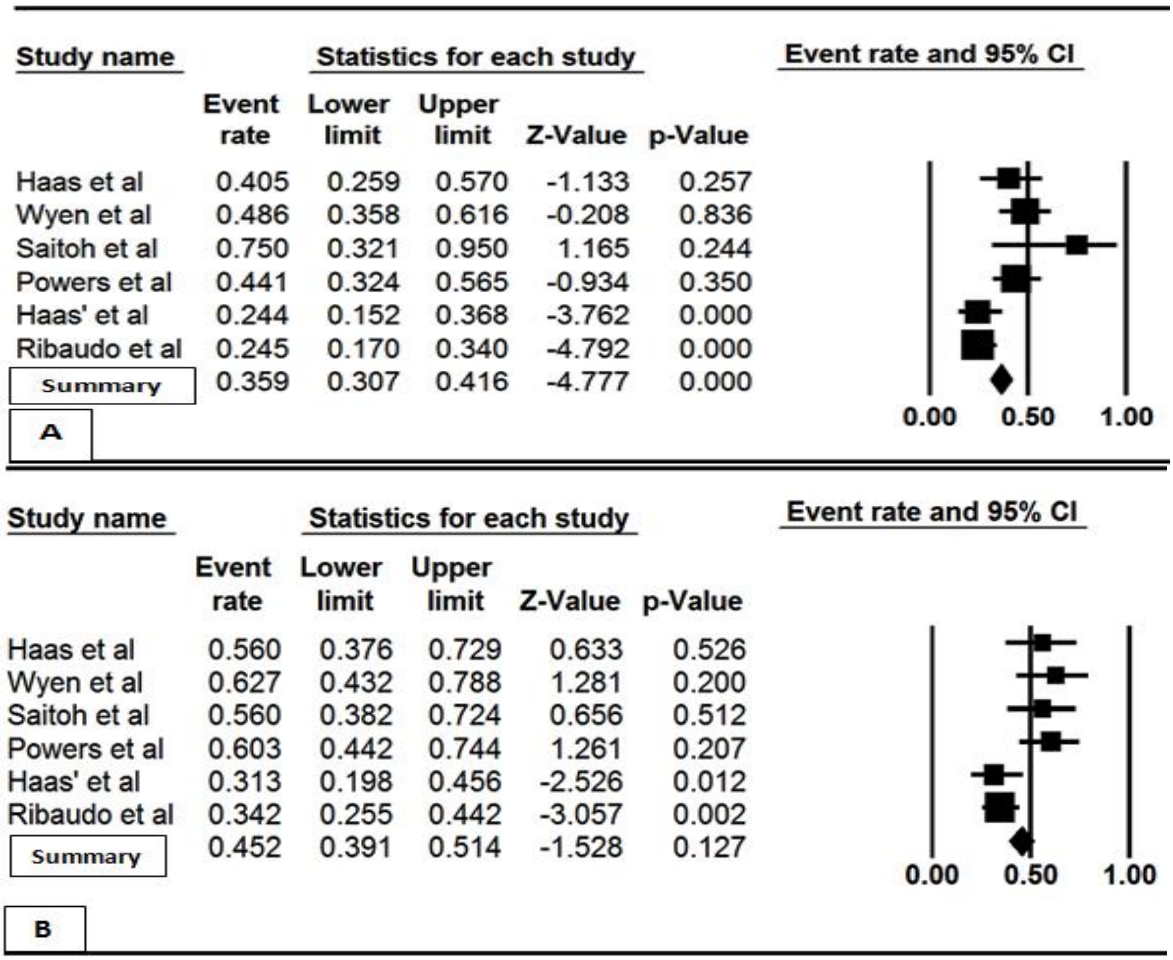


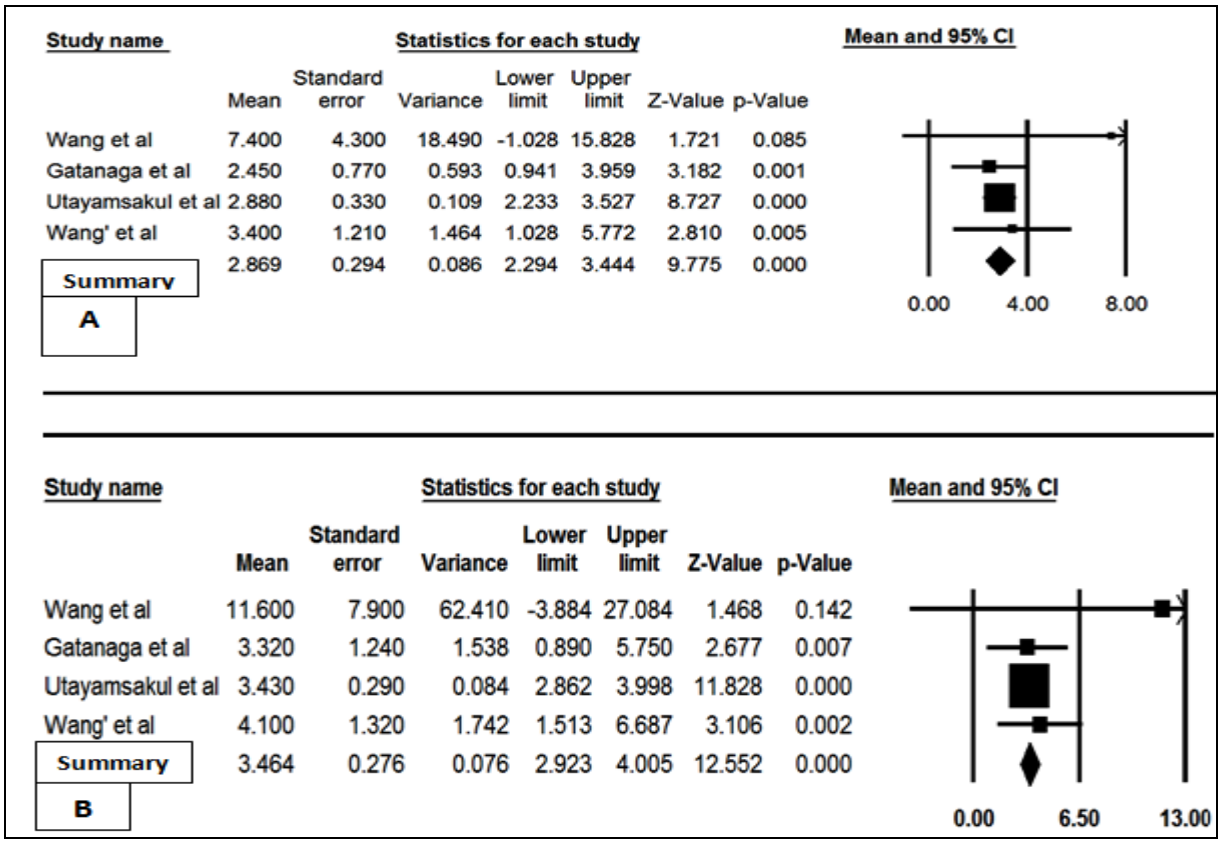
FIGURE 3: GENETIC POLYMORPHISM OF CYP2B6 G516T VERSUS ETHNICITY: (A) FREQUENCY OF MUTANT ALLELE OF G516T IN WHITE POPULATION, (B) FREQUENCY OF MUTANT ALLELE OF G516T IN BLACK POPULATION

TABLE 4: ASSOCIATION BETWEEN PLASMA EFAVIRENZ CONCENTRATION AND CYP 2B6 G516T POLYMORPHISM AMONG DIFFERENT STUDY

Reviews	G516T polymorphism	EFV plasma concentration	P-value
Wang et al[a]	516 GG	7.4 ± 4.3 µM	<0.05
	516 GT	11.6 ± 7.9 µM	
	516 TT	13.1 ± 4.6 µM	
Haas et al [b]	516 GG	44.0 (38.0 - 52.4 µg h/ml)	<0.0001
	516 GT	60.3 (46.0 - 70.9 µg h/ml)	
	516 TT	130.0 (80.3 - 158 µg h/ml)	
Wyen et al [c]	516 GG	1.779 (0.53 - 26.018 µg/ml)	<0.0001
	516 GT	2.299(0.487 – 11.198 µg/ml)	
	516 TT	6.248 (1.345 – 23.59 µg/ml)	
Kwara et a[d]	516 GG 516 GT	1.528 (1.138 – 2.161 µg/ml)	<0.001
	516 TT	7.568(5.092- 10.726 µg /ml)	

Kwara et al [d]	516 GG	1.282 (1.089-1.901 µg /ml)	<0.001
	516 GT	1.56(1.379-2.205 µg /ml)	
	516 TT	8.32(6.085-10.673 µg /ml)	
Novoa et al [d]	516 GG	1.71(1.09-2.53 µg /ml)	<0.01
	516 GT	2.6 (1.73 – 3.5 µg /ml)	
	516 TT	3.57 (2.55 – 6.07 µg /ml)	
Haas et al [e]*	516 GG	68 (47 - 102 µg h/ml)	0.007
	516 GT**	77 (63 – 99 µg h/ml)	
	516 TT***	123 (102 - 128 µg h/ml)	
Gatanaga et al [a]	516 GG	2.45 ± 0.77µg/ml	<0.0001
	516 GT	3.32 ±1.24 µg/ml	
	516 TT	9.5 ± 2.58µg/ml	
Uttayamsakul et al [a]	516 GG	2.88 ± 0.33 µg/ml	<0.0001
	516 GT	3.43 ± 0.29 µg/ml	
	516 TT	10.97 ± 2.32 µg/ml	
Wang et al [a]	516 GG	3.4 µg/ml	0.02
	516 GT	4.1 µg/ml	
	516 TT	8.1 µg/ml	
Chen et al [a]	516 GG	2.5 (0.584 – 6.34 µg/ml)	<0.01
	516 GT	4.023 (1.75 – 23.6 µg/ml)	
	516 TT		
Carr et al [c]	516 GG	2.24 (0.13 – 4.44 µg/ml)	5.6×10^{-20}
	516 GT	2.92 (0.78 – 9.58 µg/ml)	
	516 TT	4.95 (1.37 – 10.2 µg/ml)	
Haas et al [b]	516 GG	49.4 (43.2–57.2 µg h/ml)	<0001
	516 GT	57.9 (49.1–75.8 µg h/ml)	
	516 TT	101.4 (75.8–163.4 µg h/ml)	

Note: (a-e) indicate plasma efavirenz concentration with different measuring unit. a -mean plasma concentration with or without standard deviation or range, b –median (interquantile range, IQR) AUC $_{0\text{-}24}$hplasma efavirenz concentration, c -median (range) plasma efavirenz concentration, d -median (IQR) mid dose plasma efavirenz concentration, e -median (IQR) AUC$0_{\text{-}312h}$ plasma efavirenz concentration. * - polymorphism is combination of G516T and T984C, **- polymorphism include 28 516GT carriers and 25 CYP 2B6*6 heterozygote, ***- polymorphism include fourteen 516TT/785GC and two516TT /499GG.



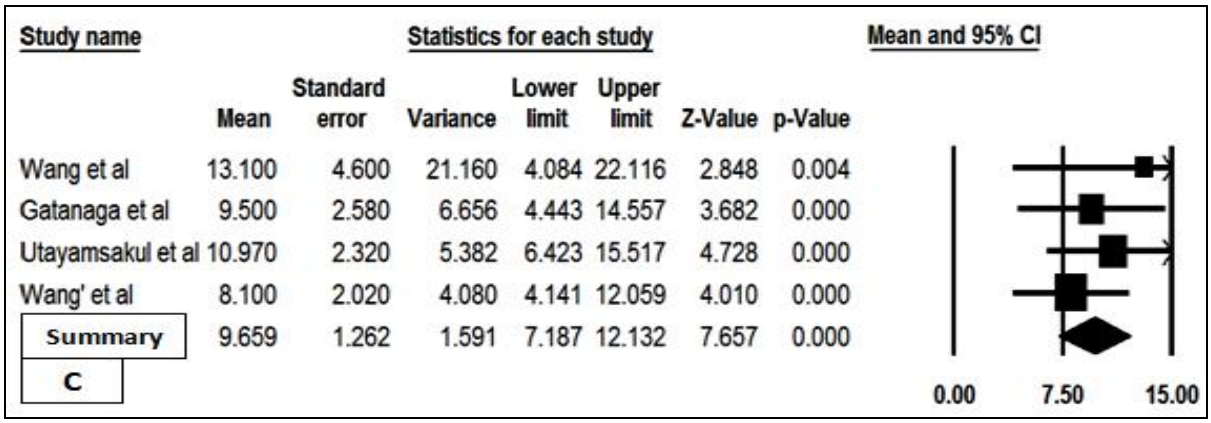


FIGURE 4: PLASMA EFAVIRENZ CONCENTRATION VERSUS CYP 2B6 G516T POLYMORPHISM: (A) EFAVIRENZ PLASMA CONCENTRATION (MEAN±SD) IN 516GG HOLDERS, (B) EFAVIRENZ PLASMA CONCENTRATION (MEAN±SD) IN 516GT HOLDERS, (C) EFAVIRENZ PLASMA CONCENTRATION (MEAN±SD) IN 516TT HOLDERS

DISCUSSION: In present study, the impact of CYP 2B6G516T polymorphism in efavirenz therapy was assessed since the frequency of these polymorphism is commonly higher in most study [21, 28, 30, 32] including this study (30%) and when compared it to other polymorphism of CYP 2B6 like A785G with frequency of 24% [27], T983C with frequency of 4 % [21] and C64T with frequency of 11.6 [31], polymorphism of CYP2B6 G516T is significantly higher. The proportion of mutant allele of CYP 2B6 G516T was significantly high in this study with frequency of 49%. Different study showed that heterozygote mutant and homozygote mutant allele of CYP 2B6 G516T polymorphism is associated with decrease metabolism of EFV which intern affect further pharmacokinetic profile of the drug [9, 30].

Plasma efavirenz concentration is primary one which is affected by CYP 2B6 polymorphism. The current study showed that individual with homozygote mutant allele of G516T had three folds increase in plasma efavirenz concentration than wild type allele holders individuals which was consistence with Rotger study that showed individuals homozygous for the variant allele of CYP 2B6 G516T (516TT), the geometric mean of plasma AUC of EFV was three-fold higher than individuals homozygous for the common (wild type) allele (516GG) [13]. This study showed that there is significant association between plasma efavirenz concentration and CYP 2B6 G516Tpolymorphism, so it is possible to conclude that individuals who have mutant allele of CYP 2B6 G516T polymorphism could have significantly high plasma level of efavirenz than those peoples who have wild type allele.

The polymorphism of CYP 2B6 enzyme not only has an effect on the plasma concentration of the drug but it also has an effect in other pharmacokinetics parameters including clearance of the drug (not included in analysis part) and even the untoward effect of the drug. Since metabolism is one way or pre requisite of clearance of a drug, decreasing in metabolic activity of CYP 2B6 (mainly in G516T polymorphism) could result in decreasing the clearance of efavirenz and this was supported by Haas et al study of decreased efavirenz clearance by 23% in 516 GT holder and 54% in 516TT holder compared to those who have 516 GG allele with P value less than 0.0001 [16]. Homozygous CYP 2B6*6 (G516T, A785G) poor metabolizer (mutant allele) had 21% lower mean apparent clearance than extensive efavirenz metabolizers (wild type) [20].

Even if this study failed to do analysis on relationship between CNS side effect and G516T polymorphism, this study believe that, decrease in clearance and hence increase in plasma concentration of efavirenz in variant allele holder individuals were related with adverse effect of efavirenz mainly CNS side effect which is supported by Haas et al that identified the presence of the variant allele was two to three times more frequent among individuals describing sleep or mood disorders or fatigue [13].

However, the CNS side effect resolve after 2 – 4 weeks which is evidenced by Haas study of CYP2B6 G516T genotype was associated with efavirenz adverse central nervous system symptoms at 1 week but not significantly at week 24.

The possible reason for these could be development of tolerance by different mechanism. Interestingly, neurons and astrocytes in human brain express CYP2B6 [35], suggesting potential intracranial influences on efavirenz metabolism that may not be apparent by assaying peripheral plasma [16]. Even if in the majority of the individuals these side effect was not severe and are found to resolve with time, in some individuals there was discontinuation of therapy because of severe side effect of efavirenz [16]. However the power et al study showed there is significant association between CYP 2B6 polymorphism and EFV based regimen discontinuation and the reason for drug discontinuation are likely to be multifactorial [29].

In treatment of HIV/AIDS using antiretroviral based regimen the other big challenge is the development of resistance and hence treatment failure. This treatment failure could be virolgical failure, immunological failure or clinical failure. Most of the time treatment failures associated with decreases plasma concentration of antiretroviral drug that mainly associated with CYP 2B6 enzyme activity. Ribaudo et al suggested that slow metabolizer genotypes (516TT) may confer some virological benefit [34].

Even if variation in treatment outcome is due to variation by age, sex, disease status, and quality of life, ethnicity was found important variable in this study that have relation with polymorphism of CYP 2B6 [36]. Different studies indicate that there are variations in expression of CYP 2B6 enzyme among different ethnicities [3, 37, 14, 29]. The study conducted by Klein *et al*, eight new nucleotide changes in the coding region were indentified, from these 76A>T (T26S), 83A>G (D28G), 85C>A and 86G>C (together resulting in R29T) were observed only in African- Americans, whereas g.15618C>T (T168I), g.18038G>A (D257N), g.21034C>T (R336C) and g.21498C>A (P428T) SNPs were found exclusively in Ghanaians. No novel amino acid changes were observed in Asian individuals [14].

In this study the frequency of mutant allele of G516T in white individuals was 35.9 % compared to blacks with 45.2% which also showed the presence of significant association between ethnicity and G516T polymorphism. The current study and different previous studies showed that mutant allele of G516T is most common in blacks than any other ethnicity.

Powers et al study showed that the 516TT homozygote frequency in the study population was found to be 16% in Blacks compared with 6% in Caucasians [29]. Global data analysis revealed a generally lower extent of polymorphism of CYP2B6 in Asians, as already observed in other studies [24, 27]. This is reflected in an overall higher frequency of the wild type CYP 2B6 (*1 allele) of 68.4% in all Asians; compared to 50.7% in Caucasians [29].

Plasma efavirenz concentration may vary among different ethnicity; the reason behind these might be difference in frequency of mutant allele among these ethnicities. The present study showed that since the frequency of CYP G516T mutant allele was more common in black (higher in frequency) than other ethnicity of white, Asian or Hispanic, blacks had higher plasma efavirenz concentration which is evidenced by Haas et al study, the CYP2B6 T/T genotype at position 516 (Gln172His) was more common in African-Americans (20%) than in European-Americans (3%), and was associated with greater efavirenz plasma exposure [16].

The main limitations while doing this study were: some of the variables like CNS side effect, virological and immunological response, which were important in this study didn't include in most reviews, as a result this study failed to do the analysis in those variables. Having most study in a given race or lacking enough study across different race limited the outcome analysis of association of ethnicity with CYP 2B6 polymorphism and generalization of effect of ethnicity on plasma efavirenz concentration. Articles which were difficult to access or not free limit the extent of articles on analysis and its outcome.

CONCLUSION AND RECOMMENDATIONS: CYP 2B6 G516T is most frequent polymorphism that significantly affect with efavirenz pharmacokinetics activities or profiles. Generally there is variation in expression of CYP 2B6 G516T polymorphism in various ethnicities while not forgetting that in black population mutant allele of G516T is most common. Plasma efavirenz concentration is significantly higher in 516TT holder than in 516GG holders. HIV/AIDS prevalence and infection rate is so high in African countries in addition to highly pronounced CYP 2B6 polymorphism in blacks which may show that there could be high CNS

side effects. The common trend or measurement when the patient faced severe side effect, including CNS side effect is treatment switch which limit the treatment option. But it could be easy if a drug is given based on the individual enzymatic expression or if not, just undergo dose adjustment by taking plasma drug concentration of a drug. Lowering EFV dose reduce side effect without affecting efficacy of drug.

In general, genetic testing is promising in individual based therapy of antiretroviral regimens that improve antiretroviral therapy out come by increasing the efficacy of the drug, decreasing the side effect, and decreasing treatment failure.

Since pharmacogenetic study, especially in HIV therapy, is new and only few studies were undergone, further studies which include large population size and broad variables mainly immunological, virological response, adherence, CNS side effect addressed variable should be conducted.

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