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IMPLICATION OF FIVE AIDS RELATED GENES IN MOTHER-TO-CHILD TRANSMISSION AND ACQUISITION OF HUMAN IMMUNODEFICIENCY VIRUS 1 IN CAMEROON

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Abstract

Background: Genetic variants in the mother and/or infant have been described with evidence to be associated with mother-to-child transmission of HIV, but somehow with contradictory results depending on ethnic or geographic populations. We aimed at looking at the association between the allelic frequency of some genes with vertical transmission or acquisition of HIV in Cameroon.
Methodology: A total of 262 mothers (212 HIV-infected and 50 HIV non-infected) with their babies (270 in total, 42 HIV exposed-infected, 178 HIV exposed non-infected and 50 HIV non-exposed) were recruited in Yaounde-Cameroon. Their genotypes for *CCR5-Delta32*, *CCR5 promoter59029A/G*, *CCR2-64I*, *SDF1-3'A* and*TRIM5α-136Q* were analyzed using polymerase chain reaction and restriction fragment length polymorphisms.
Results: Allelic frequencies were 14.7%, 41.9%, 9.5% and 14.7% for *CCR2-64I*, *CCR5-59029-A/G*, *TRIM5α-136Q*, *SDF1-3'A* respectively in the mothers and 18.8%, 35.9%, 11.3% and 20.5% in the babies. No delta 32 mutation in the *CCR5* gene was found. The mutant genotype was most significantly frequent in the non-transmitter than in the transmitter (p= 0.005) for the *SDF-1 3'A*. *SDF1-3'A* [Odd ratio = 1.69; 95% confidence interval: 0.1158 to 0.7277); was associated to MTCT, *P* = 0.008.The homozygote mutants for the *CCR5-59029-G* were significantly higher in the infected than in the exposed uninfected babies (p=0.04). The mutations in the other genes were neither implicated in the acquisition nor in the transmission.
Conclusion: *SDF1-3'A* was associated to the reduction of MTCT. The *CCR5-59029-A/G* favored acquisition of HIV by babies. Our study showed that polymorphisms in chemokine ligand may be involved in MTCT.

Key words: HIV; Host genetic factors; Mother-to-child-transmission, Cameroon

Introduction

After the discovery of the African HIV-protected sex workers (Fowke *et al*., 1996), followed by the "Berlin patient" who was functionally cured of HIV-1-infection by receiving a hematopoietic stem cell transplant from a donor with a defective HIV CCR5 co-receptor (Hütter et al., 2009) the possibility of 'natural' protective immunity to HIV was raised. Indeed, despite 9 months in an intra-uterine environment with HIV, prolonged exposure to virus-containing blood and secretions during labor and delivery and ingestion of breast milk over many months which contain virus-free cells, babies born to HIV-infected mothers may remain non-infected. Many factors have been studied and proposed to explain these observations. These factors include maternal viral load and immune status, timing and route of delivery, viral subtype, and host genetics. Genetic variants in the mother and/or infant have been described with evidence to be associated with susceptibility or protection to HIV MTCT by many authors.

The HIV-1 virus entry and infectivity of a cell need the CD4 receptor and at least one co-receptor from multi-CC and CXC chemokine receptors (Cicala et al., 2011). Polymorphisms in these CC and CXC chemokine receptors and ligand have been found to modulate the infection by HIV. Among these receptors we can list the 32 bp deletion in the coding region of the CCR5 receptor (*CCR5-Δ32*, rs333). Homozygous for this mutation resists against R5 strains infection and the heterozygous genotype gives limited resistance and/or delays the progression to AIDS (Ometto et al., 2000 ; de Silva and Stumpf, 2004) . The *CCR5-59029-A/G (*rs1799987) in the promoter region of the *CCR5* gene, lead to higher expression of this gene. Children with the CCR5-59029-A allele, are less likely to be infected (Singh et al., 2008). The *CCR2-64I* polymorphism (rs1799864) has been well-documented in the HIV infection. Individual homozygote or heterozygote for 64I mutant have a delay in the progression to AIDS after infection (Berger et al.1999). Then the *SDF-1-3′A* polymorphism (Rs1801157) at the 3′untranslated region of the *SDF-1* gene, which codes for the CXCR4 receptor' ligand, was associated with delayed progression to AIDS in homozygous mutant individuals and perinatal transmission of HIV-1 in heterozygous pregnant women (John et al., 2000 ; Ma et al., 2005 ; Alagarasu et al., 2009) . Lastly a single amino acid substitution (R136Q) in the human Trim5α can confer the ability to restrict HIV-1 (Javanbakht et al., 2006).

CCR5 Δ32 heterozygosity exerts a protective effect against perinatal transmission in a Jordanian population (Ometto et al., 2000). In a cohort of Kenyan HIV-1-infected, anti-retroviral therapy (ART)-naïve pregnant women and their infants, the maternal *CCR5* promoter polymorphisms at positions 59029, 59353, 59356, and 59402 were not associated with MTCT (John et al., 2001). Katz et al. (2010) found no association between maternal genetic polymorphisms in *CCR5* and mother-to-child HIV-1 transmission in a Kenyan population (Katz et al., 2010). The same findings were reported by singh et al. (2008) from three African cohorts. There was an increased risk of MTCT among Kenyan children born to women heterozygous for the *SDF-1* 3′A polymorphism (John et al., 2000). The *CCR2-64I* allele was associated with protection against early HIV-1 transmission in Argentinian population (Mangano et al., 2000). This same allele increases the transmission in Kenyan, South African, Ugandan and Malawian population or has no impact in the MTCT (Teglas et al., 1999; Brouwer et al., 2005). It was found that polymorphism in human *TRIM5* may influence susceptibility to HIV-1 infection (Javanbakht et al., 2006) and many more studies later on have demonstrated the impact of *TRIM5* SNP in HIV infection from an Amsterdam cohort (van Manen et al., 2008; Price et al., 2009). A recent review published by Mouafo et al, 2017 brought out the contradictory results obtained in Sub Saharan Africa regarding the implications of host genes in HIV/AIDS transmission.

These polymorphisms have not yet been studied in the context of MTCT in a Cameroonian population. A study done by Nkenfou et al in 2013 described just the allelic frequencies of some of these genes. It is possible that the genetic risk factors shown to be involved in MTCT in other populations do not have the same impact in our study population, as the results obtained by different groups of investigators are contradictory. We hypothesized that, the presence of genetic variants modulating the expression and/or function of HIV-1 co-receptors or their chemokine ligands could affect MTCT in Cameroon.

Materials and Methods

Study Subjects

HIV infected mothers with babies less than 1 year were enrolled in the study. As a control group, a set of HIV non-infected mothers with babies less than one year old were also recruited, all from Yaounde city in Cameroon. Yaounde being the Capital of Cameroon, receives patients from almost all the geographic and ethnic groups of the country for their care and management. Every mother with her baby who accepted to participate and signed the consent form was included in the study**.** The mother-baby pair who has incomplete clinical data or has insufficient biological samples was excluded from the study.

Blood was collected from these mothers and babies for laboratory analyses.

Maternal HIV status was established by Determine HIV 1/2 (Alere, 357 Matsuhidai, Matsuda-shi, Chiba, 270–2214 Japan) and confirmed using the ONE STEP Anti-HIV1/2 TEST (STANDARD DIAGNOSTIC, INC 156-68 Hadal-dong, Korea). Babies' HIV status was determined by real time PCR using the Roche Amplicor HIV-1 DNA assay, version 1.5 (Roche Molecular Systems Inc, Branchburg, NJ).

Mothers and babies were grouped mainly according to the status of the mothers/ babies. We therefore had 3 group of subjects in our study population:

- Group 1: Mothers who did not transmit HIV to their babies (NT), hence their babies were exposed non-infected (EN).
- Group 2: Mothers who have transmitted HIV to their babies (T), hence their babies were exposed infected (EI).
- Control group: mothers who were not infected by HIV, thus non-exposed, non-infected babies.
- In the HIV infected mothers there were some that were on treatment or prophylaxis and the babies also.

CD4+T Cell Counts and Plasma Viral Loads

CD4+ T cell counts of peripheral blood were determined using a FACS Calibur flow cytometer (Becton Dickinson Immuno-cytometry System (BDIS), San Jose, CA, USA). Plasma HIV-1 RNA loads were determined using the 200 µl protocol of Abbott real-time HIV-1 assay (Abbott Molecular Diagnostics, Wiesbaden, Germany) with a detection limit of 150 copies/ml (2.18 log) according to the manufacturer's instructions.
The HIV status of the babies was determined using the Amplicor HIV-1 Monitor kit version 1.5 (Roche Diagnostics, Alameda, CA) according to the manufacturer's instructions.

Genomic DNA Extraction and Genotyping

Genomic DNA was extracted from buffy coat using the QIAamp DNA Mini Kit (QiagenGmbH, D-40724 Hilden). The genotyping of *CCR5-Δ32, CCR5 promoter 59029 A/G, CCR2-64I, SDF1-3'A* was performed by PCR followed by RFLP using the protocol described previously by Magierowska et al. (1999), Kristiansen et al. (2001), Nkenfou et al., (2013). The genotyping of *TRIM5α 136Q* was done following the protocol described by van Manen et al. (2008).

Ethical Considerations

The study was reviewed and approved by the national ethic committee under the Number N°2013/11/375/L/CNERH/SP and the division of operational research of the Ministry of Public Health of Cameroon under the number D30-63/L/MINSANTE/SG/DROS/CRC/CEA2/DTLC. The national and international regulations guiding the use of human subjects in biomedical research were followed during the study. Written informed consent was obtained from the mothers as well as proxi consent for their babies.

Statistical Methods

The allelic frequencies were calculated as (h + 2H)/2N, where H is the number of samples with a homozygous mutation genotype, h is the number with a heterozygous mutation genotype and N the total number of samples. The difference in the allele frequencies in between the different groups was further assessed using exact *p*-values from chi-square test. Logistic regression was used to evaluate the association of genotypes with risk of HIV transmission and acquisition by the baby, with wild type as the references. Heterozygous and homozygous mutant genotypes compared to the homozygous wild type referent genotypes were examined. All analyses were adjusted for *Randomized intervention study*, Mother's CD4 count and log HIV-1 RNA when assessing the implication of these polymorphisms in the MTCT, using the Epi info version 7.1.3.3 software.

Results

Study Population

A total of 262 mothers (212 HIV infected and 50 HIV non-infected) with their 270 babies (42 HIV exposed infected, 178 HIV exposed non-infected and 50 HIV non-exposed, non-infected) were recruited. Of the 212 HIV infected mothers, 72.6 % (154/212) were under treatment, among which 12.3% (19/154) transmit HIV and 87.6% (135/154) did not transmit. The rest of 58 mothers who were not on treatment, 39.6% (23/58) transmit and 60.4% (35/58) did not. Eight mothers gave birth to twins. From the 270 children, 50.7% (137/270) were girls and 49.3% (133/270) were boys. From the 42 HIV exposed infected infants, 45.2% (19/42) have received prophylaxis and 54.8% (23/42) did not. From the 178 exposed non-infected, 78.7% (140/178) have received prophylaxis and 21.3% (38/178) did not. 92.9% (158/170) of the non-transmitting mothers and 90.5% (38/42) of the transmitting mothers delivered by normal route. The three main ways of feeding were found in the study population. From the non-transmitting mothers 37.7% (64/170) practice breast feeding, 53.5% (91/170) artificial and 8.8% (15/170) mixed feeding. In the transmitting mothers 40.5% (17/42) breast fed their babies, 33.3% (14/42) gave them bottle feeding (artificial) and 26.2% (11/42) practice mixed feeding. This population description is presented in Table 1.

Table 1: Demographic and clinical characteristics of the mothers and babies in the study population

		group	Age (Years for mother and weeks for babies)	CD4 (cells/mml)	Viral laod (Log_{10} RNA copies/ml)	Feeding mode	Delivery mode
Mothers	T (*n*=42)	TWP (*n*=19)	26.8±6.3	398(62-880)	2.94 (1.65-5.08)	Maternal (40.5%) Artificial(33.3%) Mixed(26.2%)	Caesarean (9.5) Normal (90.5%)
		TWDP (*n*=23)	28.4±5.5	338(44-999)	4.95 (2.52-5.79)		
	NT (*n*=170)	NTWP (*n*=135)	29.6±5.5	475(135-1159)	3.71 (ND-5.56)	Maternal (37.7%) Artificial(53.5% Mixed (8.8%)	Caesarean (7.1%) Normal (92.9%)
		NTWDP (*n*=35)	26.9±4.4	447.5 (250-791)	4.59 (ND-6.43)		
		HIV neg (*n*=50)	25.7±5.4	843(513-1390)	NA	Maternal (70%) Artificial (10% Mixed (20%)	Caesarean(4% Normal (96%)
Babies	EI (n=42)	EIWP (n=19)	20.1± 11.5	2198 (621-3050)	5.4 (3-7)	NA	NA
		EIWDP (n=23)	24.8±13.1	1040 (810-2257)	5.1 (2.74-8.1)	NA	NA
	EN (n=178)	ENWP (n=140)	12.7±10.4	2083 (442-3759)	NA	NA	NA
		ENWDP (n= 38)	12.1±8.7	2234 (1732-2897)	NA	NA	NA
		HIV neg (*n*=50)	5.7±3.8	2043 (1005-3374)	NA		

Continuous variables are presented as (Mean ±SD) and [median (range)]. NA stand for not applicalble. TWP: transmitter with prevention protocole, TWDP: transmitter without prevention protocol, NTWP: non-transmitter with prevention protocol, NTWDP: non-transmitter without prevention protocol. EIWP : exposedinfectedwith prevention protocole, EIWDP : exposedinfectedwithout prevention protocol, ENWP : exposed non-infectedwith prevention protocole, ENWDP : exposed non-infectedwithout prevention protocol. HIV neg: Humanimmunodeficiency virus negative.

The *CCR5- Δ32* mutation was completely absent from our study population.
The allelic frequencies were 14.7%, 41.9%, 9.5% and 14.7% for *CCR*2-64I, *CCR5-59029-A/G, TRIM5α-136Q, SDF1-3'A* respectively in the mothers and 18.8%, 35.9%, 11.3% and 20.5% in the babies (Table 2).

Table 2: Allelic frequencies of the five ARG variants in the mother and baby study population

Gene	Allele	Mothers Quantity (n)	Mothers Number of subject (N)	Mothers Allelic frequency (%)	babies Quantity (n)	babies Number of subject (N)	babies Allelic frequency (%)
CCR5-Δ32	WT	524	262	100	540	270	100
	- Δ32	0	0	0	0	0	0
CCR2-64I	G	447	258	85.3	439	266	81.2
	A	77	73	14.7	101	97	18.8
CCR5-59029-A/G	A	304	223	58.1	345	238	64.1
	G	220	181	41.9	195	163	35.9
TRIM5α-136Q	G	474	262	90.5	479	269	88.7
	A	50	50	9.5	61	60	11.3
SDF1-3'A	G	447	262	85.3	429	269	79.5
	A	77	77	14.7	111	110	20.5

Association of chemokine receptors/ligands polymorphisms with the risk of HIV-1 transmission from mother-to-child

There was no significant difference in the frequencies of the AIDS related genes studied between the HIV infected and non-infected mothers, except for *SDF1-3'A* (p=0.025) as shown in Table 3.

Table 3: Frequencies of polymorphisms among HIV-infected and non-infected mothers

Gene	Genotype	HIV-infected mothers N (%)	HIV non-infected mothers N (%)	*P* value*
CCR5-Δ32	WT	212 (100)	50 (100)	NA
	Δ32	0 (0)	0 (0)	
CCR2-64I	GG	154 (72.6)	34 (68)	/
	GA	53 (25)	16 (32)	0.37
	AA	5 (2.4)	0 (0)	0.5
CCR*5-59029-A/G*	AA	63 (29.7)	18 (36)	/
	AG	115 (54.2)	27 (54)	0.47
	GG	34 (16.1)	5 (10)	0.37
TRIM5α- 136Q	GG	169 (79.7)	43 (86)	/
	GA	43 (20.3)	7 (14)	0.42
	AA	0 (0)	0 (0)	1
SDF1-3'A	GG	144 (67.9)	41 (82)	/
	GA	68 (32.1)	9 (8)	**0.04**
	AA	0 (0)	0 (0)	1

There was a significant difference in the frequency of *SDF1-3'A* (p=0.005) between the sub-populations of transmitter and non-transmitter mothers. Mothers, heterozygote for *SDF1-3'A*, were more frequent in the population of the non-transmitter than in the transmitters (36.5% and 14.3%). These data are presented in Table 4. The association of these different polymorphisms with the risk of HIV-1 transmission by logistic regression was analyzed: none of the polymorphisms were associated with the risk of transmission except for the *SDF1-3'A* (Table 5). We found that *SDF1-3'A* [Odd ratio (OR) = 1.69; 95% confidence interval (CI): 0.1158 to 0.7277); P = 0.008) was associated with the protection against the transmission.

Table 4: polymorphism in the different sub-group of mothers (Transmitter versus non-transmitter)

Gene	Genotype	Transmitters N (%)	Non-transmitters N (%)	P value*
CCR5-Δ32	WT	42 (100)	170 (100)	NA
	Δ32	0 (0)	0 (0)	
CCR2-64I	GG	29 (69.1)	126 (74.1)	/
	GA	13 (30.9)	40 (23.5)	0.5
	AA	0 (0)	4 (2.4)	0.5
CCR*5-59029-A/G*	AA	14 (33.3)	49 (28.8)	/
	AG	24 (57.1)	91 (53.5)	0.7
	GG	4 (9.6)	30 (17.6)	0.2
TRIM5α- 136Q	GG	34 (80.1)	135 (79.4)	/
	GA	8 (19.1)	35 (20.6)	1
	AA	0 (0)	0 (0)	1
SDF1-3'A	GG	36 (85.7)	108 (63.5)	/
	GA	6 (14.3)	62 (36.5)	**0.005**
	AA	0 (0)	0 (0)	1

* P-value from chi-square test. Statistically significant results are marked in bold.

Table 5: Association of chemokine receptor and chemokine ligand polymorphism in the mother- baby pairs with MTCT of HIV-1

Gene	Genotype in mothers	Percent transmission	OR (95% CI)[a]	P*	Genotype in babies	Percent of acquisition	OR (95% CI)	P*
CCR2-64I	GG	16.8 (29/155)	1.4318 (0.6917-2.9639)	0.3336	GG	20.4 (29/142)	0.9313 (0.4637 - 1.8704)	0.8415
	GA or AA	22.8 (13/57)			GA or AA	17.7 (14/79)		
CCR5-59029-A/G	AA	22.2 (14/63)	0.8099 (0.3933 to 1.6678	0.5673	AA	14.9 (10/67)	1.5545 (0.7167 - 3.3720	0.2641
	AG or GG	18.8 (28/149)			AG or GG	21.4 (33/154)		
TRIM5-136Q	GG	20.1 (34/169)	0.9076 (0.3859 to 2.13)	0.8241	GG	19.2 (33/171)	1.0455 (0.4744 - 2.3039)	0.9122
	GA or AA	18.6 (8/43)			GA or AA	20 (10/50)		
SDF1-3'A	GG	24.2 (36/149)	0.2903 (0.11 to 0.72)	**0.0083**	GG	17.9 (24/134)	1.6947 (0.86 - 3.31)	0.1228
	GA or AA	9.5 (6/63)			GA or AA	21.8 (19/87)		

[a]Adjusted for mother' CD4 count and RNA viral load. * P-value from the Logistic regression analysis. Statistically significant results are marked in bold.

Association of chemokine receptors/ligands polymorphisms with the risk of HIV-1 acquisition by the baby from mother

Looking at the two groups of exposed children, there was no significant difference in the distribution of the different polymorphisms except for the *CCR5-59029-A/G*. The Homozygote mutants for the *CCR5-59029-A/G* were significantly higher in the exposed infected than in the non-infected children (23.8% Vs.11.3%, p=0.04), see Table 6.

For *TRIM5α-136Q*, infected babies had the higher frequencies of the heterozygote mutant genotype compared to the non-infected babies, with p=0.08, as shown in Table 6. For the two other genes, *CCR*2-64I and *CCR5-59029-A/G* mutation, there was no difference in the distribution between exposed-infected and exposed-non infected children. The frequency of Homozygote mutant genotypes did not show any difference between the two groups of children, data presented in Table 6. The regression analysis shows that no polymorphism was associated with the risk of HIV acquisition (Table 5).

Table 6: Polymorphism of the study genes in the children population

Gene	Genotype	HIV exposed infected N (%)	HIV exposed non –infected N (%)	p-value*
CCR5-Δ32	WT	42 (100)	178 (100)	NA
	Δ32	0 (0)	0 (0)	
CCR2-64I	GG	29 (69.1)	113 (63.5)	/
	GA	11 (26.2)	63 (35.4)	0.3
	AA	2 (4.7)	2 (1.1)	0.1
CCR*5-59029-A/G*	AA	10 (23.8)	57 (32)	/
	AG	22 (52.4)	101 (56.7)	0.7
	GG	10 (23.8)	20 (11.3)	**0.04**
TRIM5α- 136Q	GG	32 (76.2)	138 (77.5)	/
	GA	10 (23.8)	39 (21.9)	0.8
	AA	0 (0)	1(0.6)	1
SDF1-3'A	GG	20 (47.6)	110 (6.8)	/
	GA	22 (52.4)	67(37.6)	0.08
	AA	0 (0)	1 (0.6)	1

* P-value from chi-square test. NA: Not applicable. Statistically significant results are marked in bold

Association of chemokine receptors, intake of antiretroviral and chemokine polymorphisms with the risk of HIV-1 transmission from mother to child

In the multivariate regression analysis model the implication of both the ARV intake and the genotype mutation did not show any significant result concerning MTCT or the acquisition of HIV by the babies. Even though we found as already known that the intake of ARV reduced both the transmission and the level of acquisition (OR = 0.2065; 95% CI: 0.1011 to 0.4219; *P*< 0.001 and OR = 0.2149; 95% CI: 0.1066 to 0.4330; P<0.001 respectively). This intake of ARV do not have an effect on the protective role of the *SDF1-3'A* mutation in reducing the MTCT which remains the same.

Discussion

The aim of this study was to determine the distribution of *CCR5-Δ32*, *CCR5-59029A/G*, *CCR2-64I*, *SDF1-3'A* and *TRIM5α-136Q* polymorphisms in a Cameroonian cohort of mother-baby and also to look at their association with the MTCT and acquisition of HIV-1. To the best of our knowledge, no report has been published on the potential effects of these polymorphisms in a mother-baby Cameroonian population where some mothers have not transmitted HIV to their babies without any prevention.

We have found that, *CCR*5-59029 G and *SDF-1 3'801* were more frequent in the non-transmitter mothers than the transmitter mothers. *SDF1-3'A* was associated with the protection of the transmission. The *CCR*5-59029 G homozygote mutant was found to favor the acquisition of HIV by the babies from mothers.

Compared to other studies, the allelic frequencies of the different mutant alleles were consistent with previous studies from African populations. In fact the homozygote *CCR5 Δ32* mutation conferring resistance to R5-HIV-1 infection is rare or completely absent in African populations (Su et al., 2000; Sabeti et al., 2005, Torimiro et al., 2007; Nkenfou et al., 2013). The enrichment of the *CCR5-Δ32* allele in European populations suggests that, this polymorphism most likely originated in Europe and then spread globally under natural positive selection, this can explain its absence in African population.

For *CCR2 64I*, the allelic frequency in mothers and babies of 14.7 and 18.8% is similar to those obtained in other African populations (Su et al., 2000; Nkenfou et al., 2013), but higher than that of European and Asian populations (Su *et al*, 2000; Khabour et al., 2013). Although the frequency of *CCR2 64I* GA genotype was higher (35.4% versus 26.2%) in HIV exposed non-infected babies than in exposed infected, the difference was not significant. This may suggest its non-implication in the protection against acquisition of HIV by the babies from mothers. This result is not in agreement with previous reports (Mangano et al., 2000; Mabuka et al., 2009), where this genotype was involved in the protection against MTCT, as well as to those of Brouwer et al. (2005) and Singh et al. (2008) in Kenyan, South African, Ugandan and Malawian population (Singh et al., 2008), where this mutation has no impact in the MTCT.

The CCR5-*59029A/G* mutation in the promoter region of the *CCR5* gene has been widely studied in the pattern of HIV infection. The allelic frequency found in the studied population of 41.9%, and 35.9% (for the mother and baby respectively) were in the same ranges as those reported in the other studies of MTCT cohorts (Singh et al., 2008; Rathore et al., 2009), but less than what Katz et al. (2010) found in Kenyan population. The *CCR*5-59029 G homozygote mutant was more frequent in the non-transmitters than in the transmitters (17.6% Vs 9.6%), but with non significant p value (p=0.2). This may suggest a neutral role in the MTCT and this with adjusted mothers' CD4 count and RNA viral load. The viral load and CD4 count are known to impact the transmission and the Carriage of CCR5 -2459G mutation has been associated with reduced density of CCR5 on CD14+ monocytes and lower levels of R5 HIV propagation when compared to CCR5 -2459A (Kawamura et al., 2003; Salkowitz et al., 2003). A contradicting observation was found by Singh *et al* in 2008 and another study from Katz et al. (2010) did not find any association between *CCR*5-59029 G and the MTCT. In the babies population, the homozygote mutant of this mutation was significantly most frequent in the exposed infected babies than the exposed non-infected, thus favoring the acquisition of HIV (23.8% Vs 11.3%, p=0.04).

The frequency of the allele*TRIM5α-136Q* has not to the best of our knowledge, been reported in a study population regarding its implication in the MTCT. The observed 9.5% and 11.3% allelic frequencies (for the mother and baby respectively) are lower than the frequencies reported in American and Caucasian populations (Speelmon et al., 2006; van Manen et al., 2008). No association was found neither with the risk of transmission nor the acquisition of HIV. This has to be further investigated in a follow up cohort, as the reported implication of this mutation was mainly in disease progression and infectivity (Javanbakht et al., 2006; Speelmon et al., 2006).

The *SDF-1 3'A1* allelic frequency was higher among HIV non-infected than those reported among HIV-1 infected women in Sub-Saharan Africa (John et al., 2000; Singh et al., 2008). Nkenfou et al. (2013) from a population of the same country found that all participants recruited were heterozygous for the *SDF1-3'A* allele. The genotypes of this allele were not in hardy Weinberg equilibrium. We think that it may be due to our sample size, as small population size can cause a random change in allele frequencies due to genetic drift. The effect of this allele has been suggested to protect from HIV-1 infection in women. There was a protective effect of this mutation in the MTCT based on its

frequency in the mothers who did not transmit, and this was further confirmed after the adjustment of mothers' CD4 count and RNA viral load. But none of this effect was found in babies' population. Our results showed that the polymorphism in chemokine ligand may be involved in protecting against MTCT. Such protective effect has not been found by previous studies done on 19 cohorts from the United States, Europe, and Australia (Ioannidis et al., 2001).

Although we did not have data on the duration of the infection in mothers, we may assume that most of the mothers were at the chronic stage of the infection. The effect of *SDF-1 3'A1* variant occurs during the advanced stages of infection when the virus shifts from R5 to X4 strains.

The discrepancy of our results with other studies may be explained by the difference in ethnicity and geography location and or the population size.

Our study brought a contribution towards understanding host genetic variations with regard to MTCT among Africans, more specifically Cameroonians. However, there is a need to carry the study on a larger size population to understand the deviation from the hardy Weinberg equilibrium in respect to *SDF-1 3'A1*.

Conclusions. From our study what came out was that *SDF1-3'A* was associated with the reduction of MTCT. The *CCR5-59029-A/G* favored the acquisition of HIV by babies.

Conflict of Interest: There is no conflict of interest.

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Authors contributions: LMM contributed to the study design, enrolled the patients, recorded clinical data performed laboratory and statistical analysis and drafted the manuscript; CNN designed the study, contributed to the enrolled the patients, revised the manuscript and approved the version to be published; BD contribute to the study design and the laboratory analysis; IF Contributed to data analysis and approved the manuscript, FN, NF, and EEL contributed to patients enrollment and revised the manuscript; JK and AN contributed to study design and revised the manuscript. All authors revised and approved the final manuscript version.

References

1. Alagarasu, K., Selvaraj, P., Swaminathan, S., Raghavan, S., Narendran, G and Narayanan, P.R. (2009). CCR2, MCP-1, SDF-1a & DC-SIGN gene polymorphisms in HIV-1 infected patients with & without tuberculosis. Indian Journal of Medical Research, 130(4):444–450.
2. Berger, E.A., Murphy, P.M and Farber, J.M. (1999). Chemokine receptors as HIV-1 coreceptors: Roles in viral entry, tropism, and disease. Annual Review of Immunology, 17:657–700.
3. Brouwer, K.C., Yang, C., Parekh, S., Mirel, L.B., Shi, Y.P., Otieno, J., Lal, A.A and Lal, R.B. (2005). Effect of CCR2 chemokine receptor polymorphism on HIV type 1 mother-to-child transmission and child survival in Western Kenya. AIDS Research and Human Retroviruses, 21(5):358–362.
4. Cicala, C., Arthos, J and Fauci, A.S. (2011). HIV-1 envelope, integrins and co-receptor use in mucosal transmission of HIV. Journal of Translational Medicine, 9(Suppl 1):S2.
5. de Silva, E. and Stumpf, M.P. (2004). HIV and the CCR5-Delta32 resistance allele. FEMS Microbiology Letters, 241:1–12.
6. Fowke, K.R., Nagelkerke, N.J., Kimani, J., Simonsen, J.N., Anzala, A.O., Bwayo, J.J., MacDonald, K.S., Ngugi, E.N and Plummer, F.A. (1996). Resistance to HIV-1 infection among persistently seronegative prostitutes in Nairobi, Kenya. Lancet (London England), 348(9038):1347–1351.
7. Hütter, G., Nowak, D., Mossner, M., Ganepola, S., Müssig, A., Allers, K., Schneider, T., Hofmann, J., Kücherer, C., Blau, O., Blau, I.W., Hofmann, W.K and Thiel, E. (2009). Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. New England Journal of Medicine, 360(7):692–698.
8. Ioannidis JP, Rosenberg PS, Goedert JJ Ashton, L.J., Benfield, T.L., Buchbinder, S.P., Coutinho, R.A., Eugen-Olsen, J., Gallart, T., Katzenstein, T.L., Kostrikis, L.G., Kuipers, H., Louie, L.G., Mallal, S.A., Margolick, J.B., Martinez, O.P., Meyer, L., Michael, N.L., Operskalski, E., Pantaleo, G., Rizzardi, G.P., Schuitemaker, H., Sheppard, H.W., Stewart, G.J., Theodorou, I.D., Ullum, H., Vicenzi, E., Vlahov, D., Wilkinson, D., Workman, C., Zagury, J.F and O'Brien, T.R. (2001). International Meta-Analysis of HIV Host Genetics Effects of *CCR5-Delta32*, *CCR2-64I*, and *SDF1-3'A* alleles on HIV-1 disease progression: an international meta-analysis of individual-patient data. Annals of Internal Medicine, 135 (9):782–795.

9. Javanbakht, H., Yuan, W., Yeung, D.F., Song, B., Diaz-Griffero, F., Li, Y., Li, X., Stremlau, M and Sodroski J. (2006). Characterization of TRIM5alpha trimerization and its contribution to human immunodeficiency virus capsid binding. Virology, 353 (1):234–246.
10. John, G.C., Rousseau, C., Dong, T., Rowland-Jones, S., Nduati, R., Mbori-Ngacha, D., Rostron, T., Kreiss, J.K., Richardson, B.A and Overbaugh J. (2000). Maternal SDF1 3′A polymorphism is associated with increased perinatal Human Immunodeficiency Virus Type 1 Transmission. Journal of Virology, 74(12):5736–5739.
11. John, G.C., Bird, T., Overbaugh, J., Nduati, R., Mbori-Ngacha, D., Rostron, T. Dong, T., Kostrikis, L., Richardson, B and Rowland-Jones, S. (2001) CCR5 Promoter Polymorphisms in a Kenyan Perinatal Human Immunodeficiency Virus Type 1 Cohort: Association with Increased 2-Year Maternal Mortality. Journal of Infectious Disease, 184(1):89–92.
12. Katz, D.A., John-Stewart, G.C., Richardson, B.A., Majiwa, M., Mabuka, J.M., Lohman-Payne, B and Farquhar C. (2010). CCR5, RANTES, and SDF-1 polymorphisms and mother-to-child HIV-1 transmission. International Journal Immunogentics, 37(4):301–305.
13. Kawamura, T., Gulden, F. O., Sugaya, M., McNamara, D. T., Borris, D. L., Lederman, M. M., Orenstein, J.M., Zimmerman PA and Blauvelt, A. (2003). R5 HIV productively infects Langerhans cells, and infection levels are regulated by compound CCR5 polymorphisms. Proceedings of the National Academy of Sciences of the United States of America, 100(14):8401–8406.
14. Khabour, O.F., Abu-Haweleh, L.J and Alzoubi, K.H. (2013). Distribution of CCR 5Δ32, CCR2-64I, and SDF-1-3′A Alleles Among Jordanians. AIDS Research and Human Retroviruses, 29(1):151–155.
15. Kristiansen, T.B., Knudsen, T.B., Ohlendorff, S and Eugen-Olsen, J. (2001). A new multiplex PCR strategy for the simultaneous determination of four genetic polymorphisms affecting HIV-1 disease progression. Journal of Immunological Methods, 252(1-2):147–151.
16. Ma, L., Marmor, M., Zhong, P., Ewane, L., Su and Nyambi, P. (2005). Distribution of CCR2-64I and SDF1-3'A alleles and HIV status in 7 ethnic populations of Cameroon. Journal of Acquired Immune Deficiency Syndromes, 40(1):89–95.
17. Mabuka, J.M., Mackelprang, R.D., Lohman-Payne, B., Majiwa, M., Bosire, R., John-Stewart, G., Rowland-Jones, S. Overbaugh, J and Farquhar, C. (2009). CCR2-64I Polymorphism Is Associated With Lower Maternal HIV-1 Viral Load and Reduced Vertical HIV-1 Transmission. Journal of Acquired Immune Deficiency Syndromes, 51(2):235–237.
18. Magierowska, M., Theodorou, I., Debré, P., Sanson, F., Autran, B., Rivière, Y., Charron, D and Costagliola, D. (1999). Combined Genotypes of CCR5, CCR2, SDF1, and HLA Genes Can Predict the Long-Term Nonprogressor Status in Human Immunodeficiency Virus-1–Infected Individuals. Blood, 93(3):936–941.
19. Mangano, A., Kopka, J., Batalla, M., Bologna, R and Sen, L. (2000). Protective effect of CCR2-64I and not of CCR5-delta32 and SDF1-3'A in pediatric HIV-1 infection. Journal of Acquired Immune Deficiency Syndromes, 23(1):52–57.
20. Mouafo, L.C.M., Dambaya, B., Ngoufack, N.N and Nkenfou, C.N. (2017). Host Molecular Factors and Viral Genotypes in the Mother-to-Child HIV-1 Transmission in Sub-Saharan Africa. Journal of Public Health in Africa 8:(1). Pp. 16-22.
21. Nkenfou, C.N., Mekue, L.C.M., Nana, C.T and Kuiate, J.R. (2013). Distribution of CCR5-Delta32, CCR5 promoter 59029 A/G, CCR2-64I and SDF1-3'A genetic polymorphisms in HIV-1 infected and uninfected patients in the west region of Cameroon. BMC Research Notes, 6:288.
22. Ometto, L., Zanchetta, M., Mainardi, M., De Salvo, G.L., Garcia-Rodriguez, M.C., Gray, L., Newell, M.L., Chieco-Bianchi L and De Rossi, A. (2000). Co-receptor usage of HIV-1 primary isolates, viral burden, and CCR5 genotype in mother-to-child HIV-1 transmission. AIDS, 14(12):1721–1729.
23. Price, A.J., Marzetta, F., Lammers, M., Ylinen, L.M., Schaller, T., Wilson, S.J., Towers, G.J and James, L.C. (2009). Active site remodeling switches HIV specificity of antiretroviral TRIMCyp. Nature structural and molecular biology, 16 (10):1036–1042.
24. Rathore, A., Chatterjee, A., Sivarama, P., Yamamoto, N., Singhal, P.K and Dhole, T.N. (2009). Association of CCR5-59029 A/G and CCL3L1 copy number polymorphism with HIV type 1 transmission/progression among HIV type 1-seropositive and repeatedly sexually exposed HIV type 1-seronegative North Indians. AIDS Research and Human Retroviruses, 25(11):1149–1156.
25. Sabeti, P.C., Walsh, E and Schaffner, S.F. (2005). The case for selection at CCR5 Delta32. PLoS Biology, 3:e378.
26. Salkowitz, J. R., Bruse, S. E., Meyerson, H., Valdez, H., Mosier, D. E., Harding, C. V., Zimmerman, P.A and Lederman, M. M. (2003). CCR5 promoter polymorphism determines macrophage CCR5 density and magnitude of HIV-1 propagation in vitro. Clinical Immunology, 108(3):234–240.
27. Singh, K.K., Hughes, M.D., Chen, J., Phiri, K., Rousseau, C., Kuhn, L., Coutsoudis, A., Jackson, J.B., Guay, L.A., Musoke, P., Mmiro, F., Semba, R.D and Spector SA (2008). Associations of Chemokine Receptor Polymorphisms With HIV-1 Mother-to-Child Transmission in Sub-Saharan Africa: Possible Modulation of Genetic Effects by Antiretrovirals. Journal of Acquired Immune Deficiency Syndromes, 49:259–265.

28. Speelmon, E.C., Livingston-Rosanoff, D., Li, S.S. Vu, Q., Bui, J., Geraghty, D. E., Zhao L.P. and McElrath, M. J (2006). Genetic Association of the Antiviral Restriction Factor TRIM5α with Human Immunodeficiency Virus Type 1 Infection. Journal of Virology, 80(5):2463–2471.
29. Su, B., Sun, G., Lu, D., Xiao, J., Hu, F., Chakraborty, R., Deka, R and Jin, L (2000). Distribution of three HIV-1 resistance-conferring polymorphisms (SDF1-3 [variant prime] A, CCR2-64I, and CCR5-[Delta] 32) in global populations. European Journal of Human Genetics**,** 8 (12):975.
30. Teglas, J.P., N'Go, N., Burgard, M., Mayaux, M.J., Rouzioux, C., Blanche, S., Delfraissy, J.F., Misrahi, M. (1999). CCR2B-64I chemokine receptor allele and mother-to-child HIV-1 transmission or disease progression in children. French pediatric HIV infection study group. Journal of Acquired Immune Deficiency Syndromes, 22(3):267–271.
31. Torimiro, J.N., Wolfe, N.D., Thomas, A., Martin, M.P., Mpoudi-Ngole, E., Tamoufe, U., Birx, D.L., Carrington, M., Burke, D.S and Carr, J.K (2007). Frequency of CCR5 variants among rural populations with low HIV-1 prevalence in Cameroon. AIDS, 21(4):527–528.
32. van Manen, D., Rits M.A.N., Beugeling, C., van Dort, K., Schuitemaker, H., Kootstra, N.A. (2008). The Effect of Trim5 Polymorphisms on the Clinical Course of HIV-1 Infection. PLoS Pathogens, 4(2).