Published in final edited form as:
Int J Immunogenet. 2010 August ; 37(4): 301–305. doi:10.1111/j.1744-313X.2010.00924.x.

CCR5, RANTES, and SDF-1 polymorphisms and mother-to-child HIV-1 transmission

David A. Katz[a], **Grace C. John-Stewart**[a,b,c], **Barbra A. Richardson**[d,e], **Maxwell Majiwa**[c,f], **Jennifer M. Mabuka**[c,f], **Barbara Lohman-Payne**[b,c,f], and **Carey Farquhar**[a,b]

[a]Department of Epidemiology, University of Washington, Seattle, USA

[b]Department of Medicine, University of Washington, Seattle, USA

[c]Department of Global Health, University of Washington, Seattle, USA

[d]Department of Biostatistics, University of Washington, Seattle, USA

[e]Division of Public Health Sciences, Fred Hutchinson Cancer Research Cancer, Seattle, WA, USA

[f]Department of Paediatrics, University of Nairobi, Nairobi, Kenya

SUMMARY

Among 288 HIV-1-infected, breastfeeding women who received zidovudine prophylaxis and were followed with their infants in Nairobi, we found no associations between maternal genetic polymorphisms in CCR5 (59029G/A, 59353T/C, 59356T/C, 59402G/A), RANTES (−403G/A), and SDF-1 (3′801G/A) and mother-to-child HIV-1 transmission; plasma, cervical, and breastmilk viral loads; or breastmilk chemokine concentrations.

Keywords

chemokines; CCR5; RANTES; SDF-1; HIV-1 transmission

INTRODUCTION

The chemokine receptors CCR5 and CXCR4 are the primary co-receptors for human immunodeficiency virus type 1 (HIV-1) entry into host cells and are involved in viral tropism. Natural ligands for CCR5 and CXCR4 are macrophage inflammatory protein 1α (MIP-1α), macrophage inflammatory protein 1β (MIP-1β), regulated on activation normal T-cell expressed and secreted chemokine (RANTES) and stromal cell-derived factor-1 (SDF-1). Several studies suggest that these chemokines may play a role in the control of HIV-1 infection (Ferbas *et al.*, 2000; Garzino-Demo *et al.*, 1999; Scala *et al.*, 1997). Elevated levels of chemokines have been found in individuals who remained HIV-1-seronegative despite repeated exposures (Iqbal *et al.*, 2005; Shieh *et al.*, 2001; Sriwanthana *et al.*, 2001), and concentrations of these chemokines in breastmilk have been associated

Requests for reprints should be addressed to corresponding author. David A. Katz, MPH, International AIDS Research and Training Program, University of Washington, 325 Ninth Avenue, Box 359909, Seattle, WA 98104, Telephone: 206-543-4278, Fax: 206-543-4818, dkatz7@u.washington.edu.

Ethical approval:
Written informed consent was obtained from all study participants. This study received ethical approval from the Institutional Review Boards of the University of Washington and the University of Nairobi.

with differences in the risk of mother-to-child HIV-1 transmission (MTCT) (Bosire *et al.*, 2007; Farquhar *et al.*, 2005), suggesting a potential role in transmission.

A number of genetic polymorphisms in the chemokine receptor system have been associated with HIV-1 acquisition and disease progression, including single nucleotide polymorphisms in the untranslated regions of CCR5, RANTES, and SDF-1 (Kaur & Mehra, 2009; Piacentini *et al.*, 2009). Few studies, however, have investigated the role of these polymorphisms in the transmitting individual on HIV-1 transmission, and little is known regarding the mechanism by which they might affect transmission. In a previous cohort of Kenyan HIV-1-infected, antiretroviral 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, Bird, *et al.*, 2001), although there was an increased risk of MTCT among children born to women heterozygous for the SDF-1 3′A polymorphism (John *et al.*, 2000). To our knowledge, no reports have been published assessing the potential effects of these polymorphisms on MTCT in the context of ART or of maternal RANTES polymorphisms on MTCT. In this study, we followed a cohort of HIV-1-infected, breastfeeding women who received zidovudine prophylaxis and their infants in Nairobi, Kenya, to determine the effects of six maternal genetic polymorphisms in CCR5, RANTES, and SDF-1 on MTCT and on maternal factors affecting transmission.

MATERIALS AND METHODS

Study recruitment and follow-up

From July 1999 through October 2002, HIV-1-seropositive pregnant women attending greater Nairobi antenatal clinics were recruited to examine infant HIV-1-specific immune responses and vertical transmission risk (John-Stewart *et al.*, 2009). After providing written informed consent for study participation, women were followed from approximately 32 weeks gestation through delivery and postpartum with their infants for 12 months. Women were counseled regarding risks of HIV-1 transmission and infant feeding alternatives using UNAIDS guidelines and received zidovudine from 32 weeks gestation through delivery. Infants were fed according to maternal preference and mother-infant pairs were evaluated by study physicians within 48 hours of delivery, at 2 weeks postpartum, and monthly during follow-up.

Laboratory assays

For women in this cohort who intended to breastfeed, maternal CCR5 genotype at positions 59029 (A/G), 59353 (C/T), 59356 (C/T), and 59402 (G/A) in the promoter region, RANTES genotype at position −403 (G/A) in the promoter region, and SDF-1 genotype at position 801 (G/A) in the 3′ UTR were characterized by allele-specific priming amplification refractory mutation system PCR using sequence-specific primers designed to discriminate between single nucleotide mismatches on their 3′ end which coincide with the target mutation (Clegg *et al.*, 2000). The four CCR5 polymorphisms are also numbered −2459 (59029), −2132 (59353), −2135 (59356), and −2086 (59402). HIV-1 RNA viral load was determined in maternal plasma, cervical, and breastmilk specimens and RANTES, SDF-1, MIP-1α, and MIP-1β were assayed in breastmilk as described elsewhere (DeVange Panteleeff *et al.*, 2002; Emery *et al.*, 2000; Farquhar *et al.*, 2005). Infant HIV-1 infection status was determined as described elsewhere (John-Stewart *et al.*, 2009).

Statistical analyses

The effects of maternal polymorphisms on timing of infant HIV-1 infection from birth until 12 months were determined using Cox proportional hazards regression using exact marginal likelihoods, while the effects on transmission prior to 1 month were examined using logistic

regression. Infants were considered infected at the time of their first HIV-1 positive test result. Likelihood ratio test statistics were used to calculate p-values. Associations between polymorphisms and breastmilk, cervical, and plasma HIV-1 viral loads and breastmilk chemokine levels were assessed using median regression. Viral load values were $\log_{10}$-transformed for all analyses and we utilized an allele-dose model that assumed an additive change in risk as the number of alleles of the least prevalent allele increased. Data were analyzed using Stata statistical software version 9.2 (College Station, USA).

RESULTS

A total of 288 HIV-1-seropositive women who attended greater Nairobi antenatal clinics chose to breastfeed their infants and were genotyped for at least one of the target CCR5, RANTES, or SDF-1 polymorphisms. These women were 18 to 39 years of age and had a median CD4 T cell count of 451 cells/μl (range: 6-1628). Their median HIV-1 RNA viral loads were 4.76, 2.11, and 2.52 $\log_{10}$ copies/ml in plasma collected at 32 weeks gestation, cervical specimens collected at 32 weeks gestation, and breastmilk collected 1 month postpartum, respectively. Median chemokine concentrations measured in breastmilk supernatant collected at 1 month postpartum were 181, 287, 21, and 47 pg/ml for RANTES, SDF-1, MIP-1α, and MIP-1β, respectively.

Of the 286 infants for whom HIV-1 infection status was known, 66 (23%) were HIV-1 infected. Of these infections, 55 (83%) occurred prior to 1 month postpartum, and 11 (17%) occurred between months 1 and 12. Among 270 infants for whom follow-up information was available, 30 (11%) infants died during the follow-up period, 19 (63%) of whom were HIV-1-infected, and 26 (10%) were lost to follow-up.

Genotype frequencies for the six polymorphisms in this cohort of Kenyan women are shown in Figure 1. The allele frequencies for these polymorphisms were: 0.449 for CCR5 59029G; 0.448 for CCR5 59353T; 0.097 for CCR5 59356T; 0.103 for CCR5 59402G; 0.401 for RANTES −403A; and 0.056 for SDF-1 3′801A. None of the polymorphisms were associated with HIV-1 viral load measured in plasma at 32 weeks gestation, cervical fluid at 32 weeks gestation, or breastmilk at 1 month postpartum ($p>0.05$ for all); RANTES, SDF-1, MIP-1α, or MIP-1β concentrations in breastmilk at 1 month postpartum ($p>0.05$ for all); or the risk of MTCT in the first 12 months postpartum (Table 1) or prior to 1 month postpartum ($p>0.05$ for all).

Maternal viral load in plasma at 32 weeks gestation and delivery, cervical fluids at 32 weeks gestation, and breast milk at 1 month were associated with MTCT ($p < 0.001$ for all), as previously reported (Farquhar *et al.*, 2005; John, Nduati, *et al.*, 2001). The relationship between breastmilk chemokine concentrations and both breastmilk viral load and MTCT in this cohort were explored in Farquhar *et al.*, 2005.

DISCUSSION

We had hypothesized that differences in maternal genotype in CCR5, RANTES, and SDF-1 would result in differential expression of these proteins and, in doing so, influence HIV-1 co-receptor expression on cell surfaces or compete with HIV-1 for access to these receptors. These changes in CCR5 and CXCR4 availability would affect viral replication and, consequently, viral load in the mother and transmission to the infant (Blanpain *et al.*, 2002; Farquhar & John-Stewart, 2003). In addition, maternal genotype could affect the risk of breastmilk infection by altering the concentration of chemokines ingested by infants through breastmilk, which could result in similar changes to HIV-1 co-receptor availability and thus viral entry in the infant. However, we found that these polymorphisms had no effect on

maternal viral load in plasma, cervical fluids, or breastmilk or any measured breastmilk chemokine concentrations. While a previous study in Kenyan pregnant women also found no differences in plasma viral load by CCR5 promoter genotypes (John, Bird, *et al.*, 2001), the relationship between these genotypes and breastmilk chemokine levels in HIV-1 infected women has not previously been defined. Evaluating chemokine concentrations in specific compartments relevant to HIV-1 transmission or acquisition is novel and important for determining how these polymorphisms may be acting to influence transmission; previous studies have focused primarily on plasma concentrations or *in vitro* expression assays.

Few studies have investigated these chemokine receptor system polymorphisms in African populations. The allele frequencies we observed for the four CCR5 promoter polymorphisms confirm those reported from a previous cohort of HIV-1 infected pregnant women in Kenya (John, Bird, *et al.*, 2001) and are generally similar to those found in other African populations (Pedersen *et al.*, 2007; Singh *et al.*, 2008; Torimiro *et al.*, 2007). We also confirm a frequency of approximately 5-6% for the SDF-1 3′A allele among HIV-1 infected Kenyan women (John *et al.*, 2000), which is similar to the very low (<1%) allele frequencies identified in other populations of HIV-1 infected women in Sub-Saharan Africa (Singh *et al.*, 2008) and much lower than those reported in Asian, European, and U.S. populations, regardless of HIV-1 infection or disease status (Brambilla *et al.*, 2000; Koizumi *et al.*, 2007; Soriano *et al.*, 2002; Suresh *et al.*, 2006; Tresoldi *et al.*, 2002; Vidal *et al.*, 2005). The frequency of the RANTES −403A allele has not, to our knowledge, been reported in an East African population. The observed 40% frequency is similar to those reported in African American populations but lower than the 53% reported in West African blood donors (Duggal *et al.*, 2005; McDermott *et al.*, 2000), all of which are greater than the reported frequencies in individuals of European and Asian descent (Duggal *et al.*, 2005; Fernandez *et al.*, 2003; Koizumi *et al.*, 2007; McDermott *et al.*, 2000; Suresh *et al.*, 2006; Vidal *et al.*, 2006; Wichukchinda *et al.*, 2006; Zhao *et al.*, 2004).

Our study had some limitations, including limited power to detect associations between the CCR 59356, CCR5 59402, and SDF-1 polymorphisms and MTCT. Also, we did not determine the sequence for all known polymorphisms in these genes, some of which have been found to be in linkage disequilibrium or to interact with those in our study. In addition, without information regarding infant polymorphisms, effects of maternal and infant polymorphisms on MTCT could be conflated, and effects of these polymorphisms on breastmilk chemokine levels may have been masked by the effects of HIV-1 infection on the chemokine receptor system.

Because the results of studies assessing the effects of chemokine receptor system polymorphisms on HIV-1 acquisition, transmission, and progression have been inconsistent, it is important to consider negative studies such as this one and to address not only the effects of these polymorphisms on outcomes of interest but also the potential mechanisms of their effects. A better understanding of the chemokine receptor system and its interactions with HIV-1 in both infected and uninfected individuals may assist in the development of novel therapeutic or prophylactic treatments.

Acknowledgments

Research was funded by US National Institutes of Health (NIH) grants HD023412 and DE014826. DK, JM, and MM received support from the University of Washington AIDS International Training & Research Program (AITRP) supported by the Fogarty International Center, National Institutes of Health (D43 TW000007). GJS is an EGPAF Scientist. CF was supported by the National Institutes of Health (K23 HD041879).

REFERENCES

Blanpain C, Libert F, Vassart G, Parmentier M. CCR5 and HIV infection. Receptors and Channels. 2002; 8:19. [PubMed: 12402506]

Bosire R, Guthrie BL, Lohman-Payne B, Mabuka J, Majiwa M, Wariua G, et al. Longitudinal comparison of chemokines in breastmilk early postpartum among HIV-1-infected and uninfected Kenyan women. Breastfeeding Medicine. 2007; 2:129. [PubMed: 17903098]

Brambilla A, Villa C, Rizzardi G, Veglia F, Ghezzi S, Lazzarin A, et al. Shorter survival of SDF1-3′A/3′A homozygotes linked to CD4+ T cell decrease in advanced human immunodeficiency virus type 1 infection. Journal of Infectious Diseases. 2000; 182:311. [PubMed: 10882614]

Clegg AO, Ashoton LJ, Biti RA, Badhwar P, Williamson P, Kaldor JM, et al. The Australian Long-Term Non-Progressor Study Group. CCR5 promoter polymorphisms, CCR59029A and CCR5 59353C, are under represented in HIV-1-infected long-term non-progressors. AIDS. 2000; 14:103. [PubMed: 10708279]

DeVange Panteleeff D, Emery S, Richardson BA, Rousseau C, Benki S, Bodrug S, et al. Validation of performance of the Gen-Probe human immunodeficiency virus type 1 viral load assay with genital swabs and breast milk samples. Journal of Clinical Microbiology. 2002; 40:3929. [PubMed: 12409354]

Duggal P, Winkler CA, An P, Yu XF, Farzadegan H, O'Brien SJ, et al. The effect of RANTES chemokine genetic variants on early HIV-1 plasma RNA among African American injection drug users. Journal of Acquired Immune Deficiency Syndromes. 2005; 38:584. [PubMed: 15793370]

Emery S, Bodrug S, Richardson BA, Giachetti C, Bott MA, Panteleeff D, et al. Evaluation of performance of the Gen-Probe human immunodeficiency virus type 1 viral load assay using primary subtype A, C, and D isolates from Kenya. Journal of Clinical Microbiology. 2000; 38:2688. [PubMed: 10878065]

Farquhar C, John-Stewart G. The role of infant immune responses and genetic factors in preventing HIV-1 acquisition and disease progression. Clinical and Experimental Immunology. 2003; 134:367. [PubMed: 14632739]

Farquhar C, Mbori-Ngacha DA, Redman MW, Bosire RK, Lohman BL, Piantadosi AL, et al. CC and CXC chemokines in breastmilk are associated with mother-to-child HIV-1 transmission. Current HIV Research. 2005; 3:361. [PubMed: 16250882]

Ferbas J, Giorgi JV, Amini S, Grovit-Ferbas K, Wiley DJ, Detels R, et al. Antigen-specific production of RANTES, macrophage inflammatory protein (MIP)-1alpha and MIP-1beta in vitro is a correlate of reduced human immunodeficiency virus burden in vivo. Journal of Infectious Diseases. 2000; 182:1247. [PubMed: 10979927]

Fernandez RM, Borrego S, Marcos I, Rubio A, Lissen E, Antinolo G. Fluorescence resonance energy transfer analysis of the RANTES polymorphisms −403G --> A and −28G --> C: evaluation of both variants as susceptibility factors to HIV type 1 infection in the Spanish population. AIDS Research and Human Retroviruses. 2003; 19:349. [PubMed: 12803993]

Garzino-Demo A, Moss RB, Margolick JB, Cleghorn F, Sill A, Blattner WA, et al. Spontaneous and antigen-induced production of HIV-inhibitory beta-chemokines are associated with AIDS-free status. Proceedings of the National Academy of Sciences of the USA. 1999; 96:11986. [PubMed: 10518563]

Iqbal SM, Ball TB, Kimani J, Kiama P, Thottingal P, Embree JE, et al. Elevated T cell counts and RANTES expression in the genital mucosa of HIV-1-resistant Kenyan commercial sex workers. Journal of Infectious Diseases. 2005; 192:728. [PubMed: 16088822]

John-Stewart GC, Mbori-Ngacha D, Payne BL, Farquhar C, Richardson BA, Emery S, et al. HIV-1-specific cytotoxic T lymphocytes and breast milk HIV-1 transmission. Journal of Infectious Diseases. 2009; 199:889. [PubMed: 19434932]

John GC, Bird T, Overbaugh J, Nduati R, Mbori-Ngacha D, Rostron T, et al. CCR5 promoter polymorphisms in a Kenyan perinatal human immunodeficiency virus type 1 cohort: association with increased 2-year maternal mortality. Journal of Infectious Diseases. 2001; 184:89. [PubMed: 11398114]

John GC, Nduati RW, Richardson BA, Panteleeff D, Mwatha A, Overbaugh J, et al. Correlates of Mother-to-Child Human Immunodeficiency Virus Type 1 (HIV-1) Transmission: Association with

Maternal Plasma HIV-1 RNA Load, Genital HIV-1 DNA Shedding, and Breast Infections. Journal of Infectious Diseases. 2001; 183:206. [PubMed: 11120927]

John GC, Rousseau C, Dong T, Rowland-Jones S, Nduati R, Mbori-Ngacha D, et al. Maternal SDF1 3′A polymorphism is associated with increased perinatal human immunodeficiency virus type 1 transmission. Journal of Virology. 2000; 74:5736. [PubMed: 10823884]

Kaur G, Mehra N. Genetic determinants of HIV-1 infection and progression to AIDS: susceptibility to HIV infection. Tissue Antigens. 2009; 73:289. [PubMed: 19317737]

Koizumi Y, Kageyama S, Fujiyama Y, Miyashita M, Lwembe R, Ogino K, et al. RANTES −28G delays and DC-SIGN −139C enhances AIDS progression in HIV type 1-infected Japanese hemophiliacs. AIDS Research and Human Retroviruses. 2007; 23:713. [PubMed: 17530998]

McDermott DH, Beecroft MJ, Kleeberger CA, Al-Sharif FM, Ollier WE, Zimmerman PA, et al. Chemokine RANTES promoter polymorphism affects risk of both HIV infection and disease progression in the Multicenter AIDS Cohort Study. AIDS. 2000; 14:2671. [PubMed: 11125885]

Pedersen BR, Kamwendo D, Blood M, Mwapasa V, Molyneux M, North K, et al. CCR5 haplotypes and mother-to-child HIV transmission in Malawi. PLoS ONE. 2007; 2:e838. [PubMed: 17786209]

Piacentini L, Biasin M, Fenizia C, Clerici M. Genetic correlates of protection against HIV infection: the ally within. Journal of Internal Medicine. 2009; 265:110. [PubMed: 19093964]

Scala E, D'Offizi G, Rosso R, Turriziani O, Ferrara R, Mazzone AM, et al. C-C chemokines, IL-16, and soluble antiviral factor activity are increased in cloned T cells from subjects with long-term nonprogressive HIV infection. Journal of Immunology. 1997; 158:4485.

Shieh B, Yan YP, Ko NY, Liau YE, Liu YC, Lin HH, et al. Detection of elevated serum beta-chemokine levels in seronegative Chinese individuals exposed to human immunodeficiency virus type 1. Clinical Infectious Diseases. 2001; 33:273. [PubMed: 11438889]

Singh KK, Hughes MD, Chen J, Phiri K, Rousseau C, Kuhn L, et al. 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. 2008; 49:259. [PubMed: 18845960]

Soriano A, Martinez C, Garcia F, Plana M, Palou E, Lejeune M, et al. Plasma stromal cell-derived factor (SDF)-1 levels, SDF1-3′A genotype, and expression of CXCR4 on T lymphocytes: their impact on resistance to human immunodeficiency virus type 1 infection and its progression. Journal of Infectious Diseases. 2002; 186:922. [PubMed: 12232832]

Sriwanthana B, Hodge T, Mastro TD, Dezzutti CS, Bond K, Stephens HA, et al. HIV-specific cytotoxic T lymphocytes, HLA-A11, and chemokine-related factors may act synergistically to determine HIV resistance in CCR5 delta32-negative female sex workers in Chiang Rai, northern Thailand. AIDS Research and Human Retroviruses. 2001; 17:719. [PubMed: 11429112]

Suresh P, Wanchu A, Sachdeva RK, Bhatnagar A. Gene polymorphisms in CCR5, CCR2, CX3CR1, SDF-1 and RANTES in exposed but uninfected partners of HIV-1 infected individuals in North India. Journal of Clinical Immunology. 2006; 26:476. [PubMed: 16865553]

Torimiro JN, Wolfe ND, Thomas A, Martin MP, Mpoudi-Ngole E, Tamoufe U, et al. Frequency of CCR5 variants among rural populations with low HIV-1 prevalence in Cameroon. AIDS. 2007; 21:527. [PubMed: 17301575]

Tresoldi E, Romiti ML, Boniotto M, Crovella S, Salvatori F, Palomba E, et al. Prognostic value of the stromal cell-derived factor 1 3′A mutation in pediatric human immunodeficiency virus type 1 infection. Journal of Infectious Diseases. 2002; 185:696. [PubMed: 11865429]

Vidal F, Peraire J, Domingo P, Broch M, Cairo M, Pedrol E, et al. Polymorphism of RANTES chemokine gene promoter is not associated with long-term nonprogressive HIV-1 infection of more than 16 years. Journal of Acquired Immune Deficiency Syndromes. 2006; 41:17. [PubMed: 16340468]

Vidal F, Peraire J, Domingo P, Broch M, Knobel H, Pedrol E, et al. Lack of association of SDF-1 3′A variant allele with long-term nonprogressive HIV-1 infection is extended beyond 16 years. Journal of Acquired Immune Deficiency Syndromes. 2005; 40:276. [PubMed: 16249700]

Wichukchinda N, Nakayama EE, Rojanawiwat A, Pathipvanich P, Auwanit W, Vongsheree S, et al. Protective effects of IL4-589T and RANTES-28G on HIV-1 disease progression in infected Thai females. AIDS. 2006; 20:189. [PubMed: 16511411]

Zhao XY, Lee SS, Wong KH, Chan KC, Ma S, Ya WC, et al. Effects of single nucleotide polymorphisms in the RANTES promoter region in health and HIV-infected indigenous Chinese. European Journal of Immunogenetics. 2004; 31:179. [PubMed: 15265023]

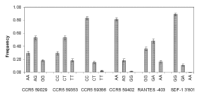

Figure 1.
CCR5, RANTES, and SDF-1 polymorphism genotype frequencies among pregnant HIV-1-seropositive Kenyan women attending greater Nairobi antenatal clinics

Table 1

Mother-to-child HIV-1 transmission and breastmilk chemokine concentrations by maternal CCR5, RANTES, and SDF-1 polymorphism genotype

Polymorphism	*Genotype*	*N*	*Number HIV-1 Infected (%)*	*Hazard Ratio (95% CI)*[a]	*Median Chemokine Concentrations (IQR)*[b]
Overall		286	66 (23%)		
CCR5 59029	AA	76	20 (26%)	1.04 (0.72-1.50)	-
	AG	138	29 (21%)		
	GG	49	14 (29%)		
CCR5 59353	CC	82	18 (22%)	1.13 (0.80-1.62)	-
	CT	150	34 (23%)		
	TT	52	14 (27%)		
CCR5 59356	CC	236	54 (23%)	0.90 (0.52-1.58)	-
	CT	44	12 (27%)		
	TT	6	0 (0%)		
CCR5 59402	AA	229	54 (24%)	1.08 (0.62-1.90)	-
	AG	53	10 (19%)		
	GG	3	2 (67%)		
RANTES-403	GG	102	22 (22%)	1.15 (0.82-1.62)	190 (78-399)
	GA	136	31 (23%)		182 (86-381)
	AA	47	13 (28%)		153 (79-311)
SDF-1 3′ 801	GG	255	58 (23%)	1.10 (0.54-2.23)	287 (18-554)
	GA	30	8 (27%)		300 (18-497)
	AA	1	0 (0%)		n/a

[a] Hazard ratios and associated 95% confidence intervals were calculated using Cox proportional hazards with exact marginal likelihoods assuming an allele-dose model.

[b] In pg/ml. Breastmilk RANTES concentrations are presented for the RANTES −403 polymorphism and breastmilk SDF-1 concentrations for the SDF-1 3′801 polymorphism. Relationships between breastmilk concentrations of RANTES, SDF-1, MIP-1α, and MIP-1β were assessed for all 6 polymorphisms; no significant associations were found (p>0.05 for all).