Published in final edited form as:
J Acquir Immune Defic Syndr. 2008 November 1; 49(3): 259–265. doi:10.1097/QAI.0b013e318186eaa4.

Associations of Chemokine Receptor Polymorphisms With HIV-1 Mother-to-Child Transmission in Sub-Saharan Africa: Possible Modulation of Genetic Effects by Antiretrovirals

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Abstract

Background—HIV-1 mother-to-child transmission (MTCT) remains an important route of infection in sub-Saharan Africa.

Methods—Genetic variants in *CCR*5 promoter, *CCR*2, *CX*$_3$*CR*1, and Stromal cell-derived factor-1 (*SDF*-1) genes were determined in 980 infants from sub-Saharan Africa using real-time polymerase chain reaction to determine association with MTCT.

Results—In antiretroviral-naive mother–infant pairs (n = 637), *CCR*5 promoter polymorphisms at positions 59029: A allele vs. G/G [odds ratio (OR): 1.61, 95% confidence interval (CI): 1.04 to 2.48; *P* = 0.032] and 59356: T allele vs. C/C (OR: 0.63, 95% CI: 0.41 to 0.96; *P* = 0.033) and *CCR*2-180: G allele vs. A/A (OR: 3.32, 95% CI: 1.13 to 9.73; *P* = 0.029) were associated with risk of MTCT. Treatment of HIV-1–infected mothers and infants with single-dose nevirapine or perinatal zidovudine altered but did not eliminate the association of genetic variants with MTCT.

Conclusions—*CCR*5 promoter, *CCR*2, and *CX*$_3$*CR*1 polymorphisms were associated with risk of MTCT likely through their role as an HIV-1 coreceptor or by modulating the early immune response. Host genetics may continue to alter MTCT when short-course interventions that only partially suppress virus are used. These findings will need to be confirmed in validation cohorts with a large number of infected infants.

Keywords

mother-to-child transmission; HIV-1; chemokine/chemokine receptor genotypes; antiretrovirals

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Presented in part at the XIVth Conference on Retroviruses and Opportunistic Infections, February 25–28, 2007, Boston, MA. (Poster no. 766).

The authors do not have a commercial or other association that might pose a conflict of interest except that during course of this study.

INTRODUCTION

The introduction of highly active antiretroviral therapy has transformed HIV-1 infection from a progressive, deadly disease to a chronic, manageable infection in developed countries including the United States and Europe. Additionally, much progress has been made in the development and implementation of strategies designed to interrupt mother-to-child transmission (MTCT). However, in countries where access to antiretroviral (ARV) medication is limited, such as sub-Saharan Africa, many women are not identified as HIV-1 infected during pregnancy leading to a growing number of children infected with HIV-1 worldwide.

Although high viral load in the mother is an important predictor of MTCT, not all infants born to women with high viral loads become infected, and some women infect their infants despite having low levels of circulating virus. Similarly, it is likely that the response to an effective vaccine for preventing HIV-1 transmission will differ in infants compared with older children and adults and among individuals. Therefore, the identification of genetic markers linked with transmission can help to define additional risk factors associated with MTCT and provide new insights into HIV-1 pathogenesis that can help in the development of an effective HIV-1 vaccine.

MTCT of HIV-1 occurs predominantly with macrophage-tropic (M-tropic), nonsyncytium-inducing viruses that use *CCR*5 as a coreceptor.[1,2] Additionally, upregulation of *CCR*5 expression in the placenta is associated with vertical transmission. [3] However, the role of chemokines and their receptors is complex, and a decrease in *CCR*5 expression could negatively affect immunologic function in newborns and alter the risk of MTCT.[4] Moreover, the 32 base pair *CCR*5 deletion that has been found to alter disease progression in children and adults is absent in most African populations.[5] Hence, other genetic variants that alter the expression or function of *CCR*5 or other HIV-1 coreceptors or modulators of innate immunity might alter the risk of MTCT.

The objective of this research was to examine the impact of genetic variants in chemokine and chemokine receptors including *CCR*5 promoter, *CCR*2, CX_3CR1, and *SDF*-1 polymorphisms on the risk of HIV-1 MTCT in 3 sub-Saharan African cohorts of infants. We hypothesized that the presence of genetic variants modulating the expression and/or function of HIV-1 coreceptors or their chemokine ligands would affect MTCT. Furthermore, we hypothesized that short-course ARVs when given to pregnant women and their infants might modify genetic associations for the risk of early MTCT because of their potential effects on such expression or function.

SUBJECTS AND METHODS

Study Subjects

Malawian Cohort—The Malawian study population consisted of ARV-naive pregnant women and their infants (n = 322 dried blood spots) who were involved in a vitamin A intervention trial to reduce MTCT from November 1995 through December 1996 (see Semba et al[6] for study details). The vitamin A intervention failed to alter MTCT.

South African Cohort—The mother–infant pairs enrolled were from Durban, South Africa, who participated in a vitamin A intervention trial to reduce the rate of MTCT of HIV-1 between July 1995 and April 1998 (see Coutsoudis et al[7] for study details). Peripheral blood mononuclear cells from 300 South African children born to ARV-naive HIV-1–infected mothers were evaluated. The vitamin A intervention failed to alter MTCT.[8]

Ugandan Cohort (HIV Network for Prevention Trials 012)—HIV-1–infected pregnant women (n = 358 dried blood spots) were enrolled at Mulago Hospital in Kampala, Uganda, from November 1997 to April 1999.[9] Mothers were randomly assigned nevirapine (NVP) 200 mg orally at onset of labor and 2 mg/kg to babies within 72 hours of birth, or zidovudine (ZDV) 600 mg orally to the mother at onset of labor, and 300 mg every 3 hours until delivery and 4 mg/kg orally twice daily to babies for 7 days after birth; placebo groups were also enrolled briefly for both treatment arms (see Guay et al[9] for study details). NVP given to mother and baby significantly reduced MTCT compared with the ZDV intervention.

Early transmission of HIV-1 in infants was defined as transmission within 6 weeks of birth as confirmed by HIV-1 RNA polymerase chain reaction or culture. All transmissions included both early and late (after 6 weeks of birth) MTCT. Overall, 21.4% of infants were determined to be HIV-1 infected; 20.2% of infants were from Malawi, 24.7% from South Africa, and 19.8% from Uganda.

This study followed the human experimentation guide-lines of the US Department of Health and Human Services and was approved by respective local ethics committees and review boards.

Genomic DNA Extraction and Genotyping

Genomic DNA extracted from dried blood spots or frozen peripheral blood mononuclear cells using QIAamp DNA Mini Kit (Qiagen, Valencia, CA) was genotyped for *CCR*5-59353-T/C, *CCR*5-59356-C/T, *CCR*5-59029-G/A, *CCR*2-G/A, *SDF*-1-G/A, and *CX*$_3$CR1-745-G/A, *CX*$_3$*CR*1-849-C/T polymorphisms using real-time polymerase chain reaction (LightCycler; Roche, Indianapolis, IN) as described previously.[10,11]

Statistical Methods

The Fisher exact test and the Kruskal–Wallis test were used to compare categorical and continuous variables, respectively, between cohorts. Logistic regression was used to evaluate the association of genotypes with risk of HIV transmission adjusted for cohort and randomized intervention separately among ARV-naive and ARV-exposed mother–infant pairs. Furthermore, multivariate analyses adjusted for maternal CD4 count and $\log_{10}$ HIV-1 RNA, and, among ARV-exposed pairs, compared the associations between prophylaxes (NVP or ZDV) by including an interaction term for prophylaxis and polymorphism adjusted for prophylaxis received. All *P* values are 2 tailed and are unadjusted for multiple comparisons. However, when controlled for multiple tests, some of the results would not remain significant. For *CCR*5, only promoter variants suspected to affect HIV-1–related disease progression were evaluated for their association with MTCT and the effects of ARVs; hence, *CCR*5 haplotypes were not done. For most of the polymorphisms considered, the frequency of 1 or more genotypes was low (<5%) and the number of infections was small. Therefore, we used a dominant model in which infants with the wild-type homozygote were used as the reference category. For *CCR*5-59029 and *CCR*5-59353, we used the most frequent homozygote category as the reference category.

RESULTS

Study Population and Distribution of Genotypes

The median $CD4^+$ lymphocyte counts per microliter for pregnant women from Malawi, South Africa, and Uganda were 399, 440, and 447 ($P = 0.049$), respectively. The median viral loads of each of the 3 cohorts of pregnant women were comparable with a median of 4.37 $\log_{10}$ copies per milliliter for all women studied (Table 1). Of the genotypes studied, the distributions of the *CCR*5-59029 variants differed significantly among the 3 cohorts of infants ($P = 0.004$),

with the G/G variant (associated with lower *CCR*5 expression)[12] occurring most commonly in infants from South Africa. There were also differences in the occurrence of *CCR*2-180 and *CCR*5-59353 polymorphisms among the different cohorts (Table 2).

Association of Chemokine Receptors and Chemokine Polymorphisms With the Risk of All HIV-1 MTCT in ARV-Naive Mother–Infant Pairs

Among ARV-naive mother–infant pairs studied, the Ugandan cohort (HIV Network for Prevention Trials 012) contributed only a small number (n = 15) of the infants to the analyses, and all infants in the Malawian and South African cohorts were ARV naive.

***CCR*5-59029-G/A—**For infants with the variant A allele, there was a 25% transmission rate compared with 17% among infants who were wild-type G/G homozygotes (associated with the least *CCR*5 expression) [odds ratio (OR): 1.61, 95% confidence interval (CI): 1.04 to 2.48; $P = 0.032$; adjusted for study and randomized intervention; Table 3]. This difference persisted in further analyses when adjusted for maternal $CD4^+$ cell count (OR: 1.79; $P = 0.013$) and plasma HIV-1 RNA (OR: 1.77; $P = 0.060$) in the subset of women for whom viral load measurements were available. Results for *CCR*5-59353-T/C variants were similar to *CCR*5-59029-G/A polymorphisms, reflecting the strong linkage disequilibrium between these 2 sets of polymorphisms (data not shown). For *CCR*5-59029 polymorphism, transmission rates were 29% and 16% for the A allele and G/G genotype in the South African cohort, and 21% and 18% in the Malawian cohort, respectively.

***CCR*5-59356-C/T—**The presence of the variant T allele was associated with MTCT with a transmission rate of 17% compared with 25% among infants who were wild-type C/C homozygotes (OR: 0.63, 95% CI: 0.41 to 0.96; $P = 0.033$) (Table 3). This difference persisted in analyses when adjusted for maternal $CD4^+$ cell count (OR: 0.55; $P = 0.010$) but lost significance when adjusted also for maternal HIV-1 RNA (OR: 0.66; $P = 0.16$). For *CCR*5-59356 polymorphisms, transmission rates were 16% and 29% for T allele and C/C genotype in the South African cohort and 18% and 21% in the Malawian cohort, respectively.

***CCR*2-180-G/A (64-V/I)—**For the *CCR*2-180-G/A polymorphism, there was no significant association of transmission with the variant A allele. However, there was 50% transmission for the A/A genotype compared with 22% for infants with the wild-type G allele (OR: 3.32, 95% CI: 1.13 to 9.73; $P = 0.029$) (Table 3). This difference remained significant when adjusted for maternal $CD4^+$ cell count (OR: 3.67; $P = 0.018$) but showed no significant difference when adjusted also for maternal HIV-1 RNA (OR: 1.51; $P = 0.64$). For the *CCR*2-180-G/A polymorphism, transmission rates were 24% and 56% for the G allele and A/A genotype in the South African cohort and 20% and 50% in the Malawian cohort, respectively.

No significant effects of CX_3CR1-745-G/A (249-V/I), CX_3CR1-849-C/T (280-T/M), or *SDF*-1-801-G/A genetic variants were observed for the risk of MTCT in ARV-naive children.

Association of Chemokine Receptors and Chemokine Polymorphisms With the Risk of Early HIV-1 MTCT in ARV-Exposed Mother–Infant Pairs

The HIV Network for Prevention Trials 012 studies demonstrated that mothers and infants receiving single-dose NVP were at lower risk of MTCT when compared with those receiving perinatal ZDV. Because NVP is known to result in a rapid decline in viral load and to have a prolonged half-life, we hypothesized that perinatal NVP exposure would alter the association of genetic variants with early MTCT (infection established at <6 weeks after birth), whereas less of an effect would be found with ZDV exposure. For the ARV-naive mother–infant pairs, early MTCT risks did not differ notably from the risk of overall transmission (data not shown).

***CCR*5-59029-G/A—**The *CCR*5-59029 effect on MTCT was dramatically altered for mother–infant pairs receiving NVP. Whereas ARV-naive infants with the variant A allele had a 1.51 OR for early transmission compared with the wild-type G/G group, infants with the A allele and exposed to NVP had a 0.14 OR for being infected. In contrast, the ZDV-exposed infants with the A allele had a 2.98 OR of being infected. The difference in the association of *CCR*5-59029 genotypes with MTCT between NVP and ZDV exposure was highly significant ($P = 0.004$; Table 4). This difference remained significant after adjusting for maternal $CD4^+$ lymphocyte count and viral load. There was a very similar difference in the association comparing infants with the variant *CCR*5-59353-C allele compared with wild-type T/T genotype and risk of MTCT according to NVP vs. ZDV exposure, reflecting the strong linkage disequilibrium between *CCR*5-59029-G/A and *CCR*5-59353-T/C polymorphisms (data not shown).

***CCR*5-59356-C/T—**For 59356 variants in ARV-naive infants, the variant T allele was associated with a decreased risk of early transmission compared with the wild-type C/C group (OR of 0.71). Similarly, for the ZDV-exposed mother–infant pairs, the relative risk of transmission for infants with the T allele vs. the C/C genotype was 0.42. The corresponding OR for MTCT for infants exposed to NVP was 1.83; however, there was no significant difference in the association according to ZDV or NVP exposure in unadjusted or adjusted analyses ($P = 0.12$ and 0.058, respectively; Table 4).

***CX*$_3$*CR*1-745-G/A (249-V/I) *and CX*$_3$*CR*1-849-C/T (280-T/M)—**In contrast to our findings of no association for risk of MTCT between infants with the variant *CX*$_3$*CR*1-745-A allele and those with the wild-type G/G genotype among ARV-naive mother–infant pairs (OR for early transmission of 1.12), infants with the *CX*$_3$*CR*1-745-A allele were at greater risk for infection compared with those with the G/G genotype for mother–infant pairs receiving NVP (OR: 5.64, 95% CI: 1.40 to 22.78; $P = 0.015$) and those receiving ZDV (OR: 5.02, 95% CI: 1.71 to 14.68; $P = 0.003$), respectively (Table 4). These effects remained significant even after adjusting for maternal $CD4^+$ lymphocyte count and log HIV-1 RNA. The numbers of children with *CX*$_3$*CR*1-849-C/C, *CX*$_3$*CR*1-849-C/T, and *CX*$_3$*CR*1-849-T/T genotypes were 355, 2, and 0, respectively; 70 of 355 with the wild-type C/C genotype were infected. Because of small numbers, no analyses of the associations with the risk of HIV-1 MTCT were possible.

No significant effects of *CCR*2-180-G/A (64-V/I) or *SDF*-1-801-G/A genetic variants were observed for the risk of MTCT in ARV-exposed children.

DISCUSSION

This study examined the impact of the genetics of HIV-1–exposed infants on MTCT in sub-Saharan Africa. Our findings suggest that: (1) an infant's genetics modifies the risk for HIV-1 infection, (2) chemokine receptors that alter HIV-1 entry into cells can modulate the risk for transmission, and (3) ARV therapy that reduces maternal viral load may modify the impact of host genetics on MTCT, and this may depend on the degree of viral suppression.

Although considerable research has examined the impact of the *CCR*5-wt/Δ32 genotype on MTCT, this variant is rare in Africa, and there remains controversy as to whether other *CCR*5 promoter variants alter the risk for perinatal infection.[1,13–21] The reported associations of MTCT risk with the *CCR*5-59029-G/A and *CCR*5-59353-T/C polymorphisms in ARV-naive mother–infant pairs and potential modulation by ARVs are novel for populations in sub-Saharan Africa. Our findings establish a link between *CCR*5 promoter variants at positions 59029 and 59353 in infants and the risk for perinatal infection. ARV-naive infants with the 59029-A allele had a higher risk of MTCT vs. G/G infants. The exposure to ARVs modified the impact of these genetic variants on MTCT. Children with the *CCR*5-59029-A allele, which

has been associated with higher expression of *CCR*5,[22] were less likely to be infected when exposed to NVP. However, this same variant was associated with a higher risk of MTCT when ZDV was given perinatally. Because *CCR*5-59029 and *CCR*5-59353 are in linkage disequilibrium, the associations between each of these polymorphisms and risk of transmission were similar. We speculate that the difference observed for MTCT between NVP-exposed and ZDV-exposed mother–infant pairs relates to the long half-life of NVP and its ability to rapidly decrease viral load. The effect of ZDVon viral load was likely less than that of NVP and combined with its shorter half-life resulted in similar associations for ZDV-treated mother–infant pairs as for ARV-naive infants. An alternative explanation for the effects observed with NVP and ZDV on MTCT could be an unidentified differential modulation of the expression of chemokines or chemokine receptors that alter the risk for transmission[23] or effect of other genetic factors[24]; however, more research is needed to understand these relationships that are likely to be complex. An additional possibility to consider is the timing of transmission. NVP decreases peripartum but not in utero transmission, whereas longer ZDV regimens can decrease both. Because the basic biology and thus the genetic determinants of these 2 routes of transmission may differ, it would be interesting to assess the timing of transmission in larger cohorts. A recent study reported the potential protective effects of *CCR*5-59029-G and *CCR*5-593563-T alleles against MTCT in Malawian children with lower maternal viral load[25]; however, this effect was lost in children with higher maternal viral load.

For the *CCR*5-59356-C/T promoter variant (having an unknown effect on *CCR*5 expression), infants with the T allele had a lower rate of transmission than infants with the C/C genotype. Our findings with respect to the *CCR*5-59356 variants differ from those of Kostrikis et al[26] who reported that the presence of the T/T genotype was associated with a higher rate of MTCT in untreated mother–infant pairs in the United States. Although this may reflect geographic differences as Kostrikis et al[26] evaluated mother–infant pairs from the United States and we studied the children cohorts from sub-Saharan Africa, this seems unlikely to be the explanation. In a smaller cohort of Kenyan infants, John et al[27] also found a trend toward decreased transmission associated with the 59656-T allele.

In contrast to our findings with *CCR*5, the association of CX_3CR1 genetic variants with MTCT is more complex. In earlier studies of HIV-1–infected children, we found that CX_3CR1 variants significantly alter HIV-1 disease progression including the development and severity of neurocognitive impairment.[12] These effects persisted after adjustment for both $CD4^+$ lymphocyte count and plasma HIV-1 RNA. Based on these findings, we hypothesized that the role of CX_3CR1 on HIV-1 disease progression was not through its role as a minor HIV-1 coreceptor but rather through its role as a chemokine modulator of the immune system.[28] In the current study, no significant effect of CX_3CR1 genotypes on MTCT was observed in ARV-naive mother–infant pairs. However, ARV-exposed infants carrying the CX_3CR1-745-A allele, related to expression of a mutant CX_3CR1 protein with impaired binding to its ligand fractalkine,[28] had a significantly higher rate of early transmission compared with infants with the G/G genotype. These findings did not differ significantly for MTCT associated with NVP and ZDV exposure. One possible explanation is that there may be a threshold level of maternal viral load below which the immunologic benefit mediated by CX_3CR1 becomes important. Additional studies are needed to examine this hypothesis.

The role of the *CCR*2-A/A genotype in MTCT remains controversial. Whereas Mangano et al[20] observed protective effects of this genotype in Argentinean children born to HIV-1–infected mothers, Teglas et al[29] and Brouwer et al[30] failed to find any impact of the *CCR*2 genotype on perinatal transmission in cohorts of children from France and Western Kenya, respectively. In the current study, the *CCR*2-A/A genotype was associated with higher risk of transmission vs. G allele carriers, suggesting a modest effect of *CCR*2 genotypes on MTCT in

mother–infant pairs in sub-Saharan Africa. The reasons for these differences remain unclear and suggest that the effect of *CCR*2 variants on transmission is modest.

The presence of *SDF*-1-G/A genotype in mothers was shown to be associated with increased perinatal transmission of HIV-1 in Kenya in an earlier study[31]; however, in the current study, the presence of the *SDF*-1-A allele in infants was rare and no impact on MTCT could be identified.

A strength and a limitation to our study is the different cohorts studied from 3 sub-Saharan countries. The consistency between the findings for the cohorts of ARV-naive mothers and ARV-naive infants from Malawi and South Africa provides additional support that our results are reflective of the effects of genetic variants on MTCT. However, we recognize that the differences in associations between genotypes and MTCT in ARV-naive infants vs. ARV-exposed mother–infant pairs could be confounded by geographic location of the cohorts studied (Uganda vs. Malawi/South Africa). It is possible that factors including population background, genetic differences, and differences in viral subtypes could affect the associations observed. Additionally, although no effects of vitamin A on chemokine receptor expression have been documented, it could also be a potential confounder. Because we evaluated associations between multiple genetic variants and risk of MTCT, it is also possible that our findings might be affected by the increased risk of false-positive results due to multiple comparisons. However, among ARV-naive mother–infant pairs, 4 of the 7 associations evaluated were significant with a hypothesis-driven unadjusted *P* value of less than 0.05, and this is higher than what might be expected by chance. In addition, although we found fewer significant associations among ARV-exposed mother–infant pairs, these associations tended to be more significant in unadjusted analyses and so less likely to be chance findings. It should also be noted that this study may lack power to identify associations that might be clinically important as evidenced by the wide CIs for some of the non-significant associations. Nevertheless, because of these issues, our findings require confirmation ideally in studies in which large numbers of both ARV-naive and ARV-exposed mother–infant pairs are evaluated in the same geographic locations.

In summary, our results suggest that the polymorphisms in the promoter region of *CCR*5 alter the risk of MTCT likely through the role of *CCR*5 as the dominant coreceptor used by HIV-1 for primary infection of infants. In contrast, polymorphisms that alter the expression of CX_3CR1 likely affect MTCT by modulating the early immunologic response to viral exposure. Our findings further suggest that the use of ARV therapy at delivery that is partially effective in reducing HIV-1 MTCT may significantly alter but not eliminate the role of host genetics on transmission.

Acknowledgments

Supported by Grants from the National Institute of Allergy and Infectious Diseases, the International Maternal Pediatric Adolescent AIDS Clinical Trials Network, and (AI-069536, AI-36214) Virology Core, University of California San Diego Center for AIDS Research. Dr. M.D.H. received grant support from Roche and had honoraria or consultancies with Abbott, Boehringer Ingelheim, Bristol Myers Squibb, Chiron, Roche, Tibotec, and Virionyx who are all manufacturers of antiretroviral therapy.

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TABLE 1

Characteristics of Mothers and Infants from Malawi, South Africa, and Uganda

Characteristics	Malawian Cohort (n = 322)	South African Cohort (n = 300)	Ugandan Cohort (n = 358)	Total (N = 980)	Comparison of 3 Cohorts*
Infant sex: female, n (%)	176 (54.7)	130 (43.3)	188 (52.5)	494 (50.4)	0.027
Mother's CD4 count (cells/μL) at delivery:	399 (174, 733)	440 (188, 720)	447 (148, 910)	428 (170, 802)	0.049
median (10th, 90th percentiles)	(n = 306)	(n = 285)	(n = 354)	(n = 945)	
Mother's HIV-1 RNA (log10 copies/mL)	4.33 (3.31, 5.15)	4.46 (3.49, 5.47)	4.38 (3.36, 5.37)	4.37 (3.36, 5.30)	0.090
at delivery: median (10th, 90th percentiles)	(n = 314)	(n = 105)	(n = 340)	(n = 759)	
HIV-1–infected infants, n (%)	65 (20.2)	74 (24.7)	71 (19.8)	210 (21.4)	0.29

* *P* values are for Fisher exact test for categorical variables and the Kruskal–Wallis test for continuous variables.

TABLE 2

Frequencies of *CCR*5, *CX*$_3$*CR*1, *CCR*2, and *SDF*-1 Genotypes of Infants from Malawi, South Africa, and Uganda

Genotypes Studied		Malawian Cohort (n = 322) (%)	South African Cohort (n = 300) (%)	Ugandan Cohort (n = 358) (%)	Total (N = 980) (%)	Comparison of 3 Cohorts*
*CCR*5-59029	A/A	72 (22)	48 (16)	99 (28)	219 (23)	0.004
	G/A	157 (49)	144 (49)	172 (48)	473 (49)	
	G/G	93 (29)	101 (34)	86 (24)	280 (29)	
*CCR*5-59356	T/T	9 (3)	14 (5)	8 (2)	31 (3)	0.43
	C/T	86 (27)	85 (29)	101 (28)	272 (28)	
	C/C	227 (70)	197 (67)	248 (69)	672 (69)	
*CCR*5-59353	C/C	72 (22)	64 (22)	110 (31)	246 (25)	0.030
	T/C	159 (49)	139 (47)	160 (45)	458 (47)	
	T/T	91 (28)	93 (31)	86 (24)	270 (28)	
CX$_3$*CR*1-745	A/A	2 (1)	4 (1)	3 (1)	9 (1)	0.44
	G/A	45 (14)	54 (18)	51 (14)	150 (15)	
	G/G	275 (85)	238 (80)	303 (85)	816 (84)	
CX$_3$*CR*1-849	T/T	0 (0)	0 (0)	0 (0)	0 (0)	0.10
	C/T	0 (0)	4 (1)	2 (1)	6 (1)	
	C/C	322 (100)	292 (99)	355 (99)	969 (99)	
*CCR*2-180	A/A	4 (1)	9 (3)	22(7)	35 (4)	0.001
	G/A	120 (37)	85 (29)	128 (38)	333 (34)	
	G/G	198 (61)	204 (68)	206 (61)	608 (62)	
SDF-1-801	A/A	0 (0)	0 (0)	0 (0)	0 (0)	0.11
	G/A	5 (2)	0 (0)	3 (1)	8 (1)	
	G/G	317 (98)	297 (100)	348 (99)	962 (99)	

Percentages are of nonmissing results for each genotypic variant and may not sum to 100% because of rounding.

*P values are for the Fisher exact test.

TABLE 3

Associations of Chemokine Receptor Variants With All HIV-1 MTCT in ARV-Naive Malawian and South African Mother–Infant Pairs

Genotypes	Percent Transmission	OR (95% CI) Adjusted for SRI	OR (95% CI) Adjusted for SRI, Mother's CD4 Count, and log HIV-1 RNA
CCR5-59029-G/A	n = 630	n = 630	n = 404
G/G	17.4 (34/195)	1.00 (reference)	1.00 (reference)
G/A or A/A (higher *CCR5* levels)	25.3 (110/435)	0.61 (1.04 to 2.48)	1.77 (0.98 to 3.20)
P	0.032	0.032	0.060
CCR5-59356-C/T	—	n = 633	n = 407
C/C	25.2 (110/437)	1.00 (reference)	1.00 (reference)
C/T or T/T (*CCR5* expression unknown)	17.4 (34/196)	0.63 (0.41 to 0.96)	0.66 (0.38 to 1.17)
P	0.033	0.033	0.16
CX_3CR1-745-G/A (V249I)	—	n = 633	n = 407
G/G	22.2 (116/523)	1.00 (reference)	1.00 (reference)
G/A or A/A (impaired CX_3CR1 function)	25.5 (28/110)	1.15 (0.71 to 1.86)	1.25 (0.65 to 2.40)
P	0.58	0.58	0.50
CCR2-180-G/A (V64I)*	—	n = 635	n = 409
G/G or G/A	22.1 (137/621)	1.00 (reference)	1.00 (reference)
A/A (*CCR2* effect mechanism unknown)	50.0 (7/14)	3.32 (1.13 to 9.73)	1.51 (0.27 to 8.53)
P	0.022	0.029	0.64

*For the *CCR2*-180-G/A polymorphism, there was no significant association of transmission with the variant A allele when compared with infants with the homozygote G/G as the reference category.

SRI, study and randomized intervention.

TABLE 4

Associations of Chemokine Receptor Variants With Early HIV-1 MTCT in ARV (NVP or ZDV)-Exposed Ugandan Mother–Infant Pairs

Genotypes	Percent Transmission	OR (95% CI) Adjusted for SRI	OR (95% CI) Adjusted for SRI, Mother's CD4 Count, and log HIV-1 RNA
CCR5-59029		n = 630	n = 404
NVP-exposed pairs		n = 170	n = 160
G/G	14.6 (6/41)	1.00 (reference)	1.00 (reference)
A/A or G/A	2.3 (3/129)	0.14 (0.03 to 0.58)	0.12 (0.03 to 0.55)
P	—	0.007	0.006
ZDV-exposed pairs		n = 169	n = 160
G/G	4.7 (2/43)	1.00 (reference)	1.00 (reference)
A/A or G/A	12.7 (16/126)	2.98 (0.66 to 13.53)	2.68 (0.57 to 12.52)
P	—	0.16	0.21
P (NVP vs. ZDV)*	—	0.004	0.005
CCR5-59356		n = 633	n = 407
NVP-exposed pairs		n = 170	n = 160
C/C	4.3 (5/117)	1.00 (reference)	1.00 (reference)
C/T or T/T	7.6 (4/53)	1.83 (0.47 to 7.10)	2.30 (0.56 to 9.35)
P	—	0.38	0.25
ZDV-exposed pairs		n = 169	n = 160
C/C	12.8 (15/117)	1.00 (reference)	1.00 (reference)
C/T or T/T	5.8 (3/52)	0.42 (0.12 to 1.51)	0.30 (0.07 to 1.40)
P	—	0.18	0.13
P (NVP vs. ZDV)*	—	0.12	0.058
CX_3CR1-745-G/A (V249I)		n = 633	n = 407
NVP-exposed pairs		n = 170	n = 160
G/G	3.4 (5/146)	1.00 (reference)	1.00 (reference)
A/A or G/A	16.7 (4/24)	5.64 (1.40 to 22.78)	4.48 (1.07 to 18.78)
P	—	0.015	0.040
ZDV-exposed pairs		n = 169	n = 160
G/G	7.6 (11/145)	1.00 (reference)	1.00 (reference)
A/A or G/A	29.2 (7/24)	5.02 (1.71 to 14.68)	5.84 (1.86 to 18.31)
P	—	0.003	0.003
P (NVP vs. ZDV)*	—	0.90	0.77

Early transmission of HIV-1 in infants was defined as transmission within 6 weeks of birth, as evaluated by HIV-1 DNA polymerase chain reaction.

**P* value (NVP vs. ZDV) is for testing that association between risk of MTCT and genetic variant that differs between NVP- and ZDV-exposed mother–infant pairs.

SRI, study and randomized intervention.