

Effect of *CCR5-Δ32* Heterozygosity on the Risk of Perinatal HIV-1 Infection: A Meta-Analysis

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Summary: Several studies have investigated whether heterozygosity for a 32-basepair deletion in the CC chemokine receptor 5 gene (*CCR5-Δ32*) affects susceptibility to perinatal HIV-1 infection, but results have been inconclusive. We performed a meta-analysis of published data from 11 studies of HIV-1 perinatally exposed children who were genotyped for the *CCR5-Δ32* polymorphism. The crude overall HIV-1 infection rates, by simple data pooling, were 20% (one of five) among *CCR5-Δ32* homozygote children, 39% (131 of 335) among *CCR5-Δ32* heterozygote children, and 40% (1408 of 3526) among wild-type *CCR5* homozygote children. Compared with wild-type *CCR5* homozygotes, the random effects risk ratio for *CCR5-Δ32* heterozygotes was 1.04 (95% confidence interval [CI], 0.92–1.17) among all children ($N = 3861$) and 1.03 (95% CI, 0.90–1.17) among those of European descent ($n = 2890$). Results were similar when adjusted for the available data on the *CCR2-64I* polymorphism ($n = 1542$). The meta-analysis clarifies that perinatal infection is not significantly altered by heterozygosity for *CCR5-Δ32* in the child. **Key Words:** *CCR5-Δ32*—HIV-1—Perinatal infection.

Some beta chemokine receptors are coreceptors for the entry of human immunodeficiency virus type 1 (HIV-1) into target cells (1). Genetic variants for these receptors may offer protection against HIV-1 infection and retard disease progression. The most extensively studied polymorphism is in the gene that codes for CC chemokine receptor 5 (*CCR5*), the major coreceptor for transmission of HIV-1. People homozygous for a 32-basepair deletion in this gene (*CCR5-Δ32*) express no copies of the receptor, while people who inherited the *CCR5-Δ32* allele from one parent and a functional *CCR5* allele from the other parent (“*CCR5-Δ32* heterozygotes”) express, on

average, about half as much of the receptor as people with two normal *CCR5* alleles (“wild-type” subjects) (2,3). *CCR5-Δ32* heterozygosity is clearly associated with slower disease progression in HIV-1-infected adults (4), and adults homozygous for *CCR5-Δ32* are largely resistant to HIV-1 infection (5). The evidence for protection from HIV-1 infection among *CCR5-Δ32* heterozygotes is mixed. Among adults, some studies have found no evidence that *CCR5-Δ32* heterozygotes are protected against HIV-1 infection (5,6), but other studies suggest partial protection (7–9). The potential protective role of *CCR5-Δ32* heterozygosity against vertical transmission from HIV-1-infected mothers to their infants is also uncertain. Although many cohort studies (10–25) have investigated the effect of the child’s *CCR5* genotype on susceptibility to perinatal HIV-1 infection, the results have been largely inconclusive. If the magnitude

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of the protective effect against perinatal infection is similar to that demonstrated for disease progression in adults (a 25% risk reduction), a large number of mother–infant pairs is needed to have adequate statistical power to refute an effect. In fact, most perinatal cohorts have relatively small sample sizes, even when multicenter collaborations have been involved. Therefore, we performed a meta-analysis of the accumulated data to address this question definitively.

METHODS

Eligibility of Studies

We considered all studies that had obtained genotyping data for the *CCR5-Δ32* polymorphism on children born to HIV-1–infected mothers. Studies were eligible if they included at least five HIV-1–infected and five HIV-1–uninfected children with *CCR5* genotype ascertained with standard molecular methods. For study reports using identical or overlapping populations of children, only the larger and more complete report was considered to avoid duplication of data. Studies including only HIV-1–infected children without a control group of HIV-1–exposed but –uninfected children were excluded. Studies were eligible regardless of the ethnic background of the population.

Search Strategy

Investigations were identified through MEDLINE and EMBASE searches up to January 2002, using the key words *CCR5-Δ32*, polymorphism, HIV-1, and perinatal transmission in various combinations; perusal of references of retrieved articles; and communication with experts.

Data Extraction

The following data were extracted from each eligible study: author(s), year of publication, dates of birth (range), country or countries of recruitment, study design, total number of children enrolled in the study, total number of children genotyped for the *CCR5-Δ32* polymorphism, number of perinatally exposed children with genotype data who were eventually determined to be HIV-1–infected or –uninfected, distribution of *CCR5* genotypes in the HIV-1–infected and –uninfected children, maternal use of antiretroviral treatment, and racial descent of the infants. *CCR5-Δ32* is generally restricted to individuals of European descent (8). Studies of individuals of African descent may thus not be directly pertinent to the research question, although some African Americans or African-European subjects may have partial European genetic backgrounds and may thus carry the *CCR5-Δ32* polymorphism. Therefore, whenever possible, subjects were separated according to European and African descent. Finally we recorded the available data on other chemokine receptor polymorphisms in HIV-1–infected and –uninfected children, maternal viral load, and maternal chemokine receptor polymorphisms. Data were extracted independently by two observers. Minor discrepancies were resolved by consensus.

Primary Outcome

The primary outcome was HIV-1 perinatal infection as defined by the following criteria: 1) positive results on two separate occasions of one or more of the following assays: culture, polymerase chain reaction, or p24 antigen, provided that both tests were performed beyond 1 month of age and at least one test was performed beyond 3 months of age; or 2) for a child aged more than 18 months, repeatedly positive HIV-1 antibodies by enzyme immunoassay (EIA) and a confirmatory test. Children were considered uninfected if they fulfilled the following three conditions: two or more negative EIA HIV-antibody tests performed between 6 and 18 months of age, or one negative EIA test performed after 18 months; absence of other laboratory evidence of infection; and absence of an AIDS-defining condition (26).

Analysis

Crude infection rates, by simple data pooling, were calculated for *CCR5-Δ32* heterozygote children, *CCR5-Δ32* homozygote children, and wild-type *CCR5* homozygote children. The crude infection rates were calculated for all children, regardless of ethnic background, as well as for children of European descent only.

In the main analysis, infection rates were compared between *CCR5-Δ32* heterozygote children and wild-type *CCR5* homozygote children. The risk ratio (relative risk) was used as the metric of choice for the data synthesis since cohort studies were involved. Odds ratios are also given for the main comparisons. Between-study heterogeneity was examined using the Q statistic and was considered significant for $p < 0.10$ (27). Studies were weighted by the inverse of the variance, a measure of precision, and the data were combined using both fixed (Mantel–Haenszel) and random effects (DerSimonian and Laird) models (27). Fixed effects models assume that there is no genuine heterogeneity between the strength of the probed association across the various studies and, thus, the observed variability is due to chance. Random effects models allow for heterogeneity in the results of various studies by incorporating an estimate of the between-study variance in the calculations. When heterogeneity exists between studies, random effects calculations tend to give wider confidence intervals (CIs) than fixed effects calculations, but the two models coincide when there is no between-study heterogeneity.

The main analysis included all children, regardless of their ethnic background, and a secondary analysis was performed among children of European descent. We also assessed the effect of *CCR5-Δ32* after adjusting for the potential effect of *CCR2-64I* allele whenever data were available. Because the *CCR5-Δ32* and *CCR2-64I* polymorphisms are in strong linkage disequilibrium (they are never found on the same haplotype), it would be useful to exclude a potentially confounding effect of *CCR2-64I*. Therefore, we addressed whether *CCR5-Δ32* heterozygotes versus wild-type *CCR5* homozygotes have different infection rates when analyses were limited to wild-type *CCR2* homozygotes. An exploratory analysis was also performed for the effect of the child's *CCR2-64I* on perinatal transmission.

Finally, we examined meta-analysis diagnostics. Specifically, we evaluated whether the natural logarithm of the risk ratio was related to the standard error in each study in a regression weighted by the inverse of the variance (28). Such a relationship is suggestive of publication bias or latent heterogeneity (28). We also examined whether the summary risk ratio changed in the same direction over time using recursive cumulative meta-analysis (29).

Analyses were performed in SPSS 10.0 (SPSS, Inc., Chicago, IL) and in Meta-Analyst (Joseph Lau, Boston, MA). All p values were two-tailed.

RESULTS

Study and Population Characteristics

A total of 16 potentially eligible articles were identified that provided information on the risk of perinatal infection according to the child's genotype for the *CCR5-Δ32* polymorphism (10–25). Of these 16, three were excluded because all children had been included in a larger study (21–23); one was excluded because only two HIV-1-uninfected children were evaluated (24); and one was excluded because most of the infants had been included in another study and the data for the remaining eligible children ($n = 280$) could not be separated (25).

The remaining 11 independent, nonoverlapping studies included 3866 infants with known HIV-1 infection status and *CCR5* genotype data (Table 1). Studies were typically multicenter collaborations. Three studies (10, 13, 16) were prospective cohorts, three studies (11, 15, 19) combined prospective and retrospective referral cohorts, and five studies (12, 14, 17, 18, 20) were retrospective. Seven studies (10–12, 14–15, 17–18) included only children of European descent; one study (19) included only African American children; and three studies (13, 16, 20) included both children of European descent and children of African descent, two of which (13, 20) provided separate data for these subgroups. The studies with children of European descent had *CCR5-Δ32* allele frequencies ranging from 4.0% to 9.8% (Table 1). The distribution of genotypes was consistent with Hardy–Weinberg equilibrium in all studies. One cohort (19) of African American children had an allele frequency of 2.2%, presumably due to racial admixture. Also of note was the low overall

TABLE 1. Characteristics of the eligible studies included in the meta-analysis

| Author (year) | Race | Infants (n) | <i>CCR5-Δ32</i> allele (%) | Mother ART | Year of birth |
|------------------|--------------------|-------------|----------------------------|------------------|---------------|
| Ometto (2000) | E | 186 | 7.5 | 13% | 1991–1997 |
| Mangano (2000) | E | 882 | 4.0 | 25% ^a | 1986–1998 |
| Romiti (2000) | E | 426 | 4.2 | None | 1983–1995 |
| Bailey (1999) | E | 128 | 9.8 | Few ^b | 1991–1995 |
| | A | 11 | 0.0 | Few ^b | 1991–1995 |
| Villalba (1999) | E | 388 | 5.0 | None | 1981–1996 |
| Misrahi (1998) | E | 512 | 5.0 | Few ^b | 1983–1996 |
| Shearer (1998) | Mixed ^c | 831 | 2.6 | Few ^b | 1989–1995 |
| Mandl (1998) | E | 79 | 7.6 | Few ^b | 1985–1994 |
| Esposito (1998) | E | 208 | 5.0 | None | 1983–1996 |
| Rousseau (1997) | A | 93 | 2.2 | None | 1989–1994 |
| Edelstein (1997) | E | 86 | 8.7 | None | 1983–1995 |
| | A | 36 | 0.0 | None | 1983–1995 |

^a 10% with unknown maternal treatment status.

^b most infants were born before 1994.

^c 53% European descent, 43% African descent, 4% other.

E, European descent; A, African descent; ART, antiretroviral therapy; ND, no data.

TABLE 2. Perinatal transmission rates of HIV-1 according to the genotype of the child (HIV-1 infected children/total number of children)

| Author | All (%) | w/w | $\Delta32/w$ | $\Delta32/\Delta32$ |
|-----------|---------------------------|---------|--------------|---------------------|
| Ometto | 27/186 (15) | 23/158 | 4/28 | 0/0 |
| Mangano | 433/882 (49) | 397/812 | 36/69 | 0/1 |
| Romiti | 254/426 (60) | 234/392 | 19/32 | 1/2 |
| Bailey | 23/128 [E] (18) | 18/103 | 5/25 | 0/0 |
| | 1/11 [A] (9) | 1/11 | 0/0 | 0/0 |
| Villalba | 164/388 (42) | 151/349 | 13/39 | 0/0 |
| Misrahi | 276/512 (54) | 249/462 | 27/49 | 0/1 |
| Shearer | 130/831 ^a (34) | 127/788 | 3/43 | 0/0 |
| Mandl | 34/79 (43) | 32/68 | 2/10 | 0/1 |
| Esposito | 83/208 (40) | 75/187 | 8/21 | 0/0 |
| Rousseau | 42/93 (45) | 39/89 | 3/4 | 0/0 |
| Edelstein | 51/86 [E] (59) | 40/71 | 11/15 | 0/0 |
| | 22/36 [A] (61) | 22/36 | 0/0 | 0/0 |

^a 53% European descent, 43% African descent, 4% other.

E, European descent; A, African Descent; ND, no data; w, wild-type.

frequency of the *CCR5-Δ32* allele (2.6%) in a racially mixed US cohort composed of 53% children of European descent, 43% children of African descent, and 4% children of other races (16).

In five studies (12, 14, 18–20) the mothers had not received any antiretroviral treatment. In 2 studies (10–11) 13% and 25%, respectively, were given single-agent zidovudine treatment (30). Four studies (13, 15–17) provided no information on maternal treatment, but given the range of years of birth, antiretroviral treatment probably was given to relatively few women. Summary data on maternal viral load and maternal *CCR5* genotype for the *CCR5-Δ32* polymorphism were provided in only 2 studies (10, 16). Two studies (11, 25) provided additional information on transmission rates by the child's *CCR2-64I* genotypes.

Effect of Child's *CCR5* Genotype on Perinatal Infection Risk

HIV-1 infection rates overall and by child's *CCR5* genotype in each study are shown in Table 2. The infection rates ranged between 9% and 61% overall and between 9% and 34% in the prospective studies. The rates were substantially higher in purely retrospective studies and in studies with a retrospective component (42%–61%), presumably because of the selection of referred HIV-infected children.

The crude overall HIV-1 infection rates among all children ($N = 3866$, 11 studies) were 20% (one of five) among *CCR5-Δ32* homozygote children, 39% (131 of 335) among *CCR5-Δ32* heterozygote children, and 40% (1408 of 3526) among wild-type *CCR5* homozygote children. The risk ratio for transmission among *CCR5-*

Δ32 heterozygotes compared with wild-type *CCR5* homozygotes ($N = 3861$) was 1.04 (95% CI, 0.92–1.17) by random effects and 0.97 (95% CI, 0.85–1.11) by fixed effects (Fig. 1). The respective odds ratios estimates were 0.96 (95% CI, 0.75–1.24) by random effects and 0.94 (95% CI, 0.74–1.21) by fixed effects. There was no significant between-study heterogeneity ($Q = 10.12$ with 10 degrees of freedom, $p = .4$). The five *CCR5*-Δ32 homozygotes were too few to make meaningful inferences.

The results were similar when the analyses were restricted to children of European descent (2890 children, 9 studies). The crude infection rates were 20% (one of five) for *CCR5*-Δ32 homozygote children, 43% (125 of 288) for *CCR5*-Δ32 heterozygote children, and 47% (1219 of 2602) for wild-type *CCR5* homozygote children. The risk ratio comparing *CCR5*-Δ32 heterozygotes with wild-type *CCR5* homozygotes was 1.03 (95% CI, 0.90–1.17) by random effects and 0.99 (95% CI, 0.87–1.13) by fixed effects (Fig. 2). The respective odds ratios estimates were 0.99 (95% CI, 0.76–1.28) by random effects and 0.98 (95% CI, 0.76–1.27) by fixed effects. There was no significant between study heterogeneity ($Q = 5.25$ with 8 degrees of freedom, $p = .7$).

The results of more precise studies (those with smaller standard error) did not differ from the results of less precise studies ($p = .3$), and there was no consistent

evidence that the summary effect changed substantially over time (random effects risk ratio 1.36 in 1997, 1.06 in 1998, 1.02 in 1999, 1.04 in 2000).

CCR5 haplotype data had been obtained by one group of investigators (21) ($n = 649$, a subset of (11)). When the analysis was limited to children who were wild-type for *CCR2*, the crude infection rates were 63% (24 of 38) in *CCR5*-Δ32 heterozygote children, and 54% (245 of 451) in wild-type *CCR5* homozygote children (risk ratio, 1.16; 95% CI, 0.90–1.50). Two studies (11,25) had obtained *CCR2* genotypes on 1542 children. The crude overall infection rate by simple data pooling of these two studies was 28% (15 of 54) in *CCR2*-64I homozygote children, 35% (125 of 358) in *CCR2*-64I heterozygote children, and 36% (410 of 1130) in wild-type *CCR2* homozygote children. By random effects, the risk ratio for *CCR2*-64I homozygotes and heterozygotes versus wild-type *CCR2* homozygotes was 0.93 (95% CI, 0.76–1.14) without any significant between-study heterogeneity (fixed effects risk ratio, 0.93 [95% CI, 0.80–1.07]). Even when *CCR2*-64I was analyzed using a recessive model (*CCR2*-64I homozygotes vs. *CCR2*-64I heterozygotes and wild-type *CCR2* homozygotes) or a codominant model (*CCR2*-64I homozygotes vs. wild-type *CCR2* homozygotes), the effect of *CCR2*-64I was not found to be significant for perinatal infection (not shown).

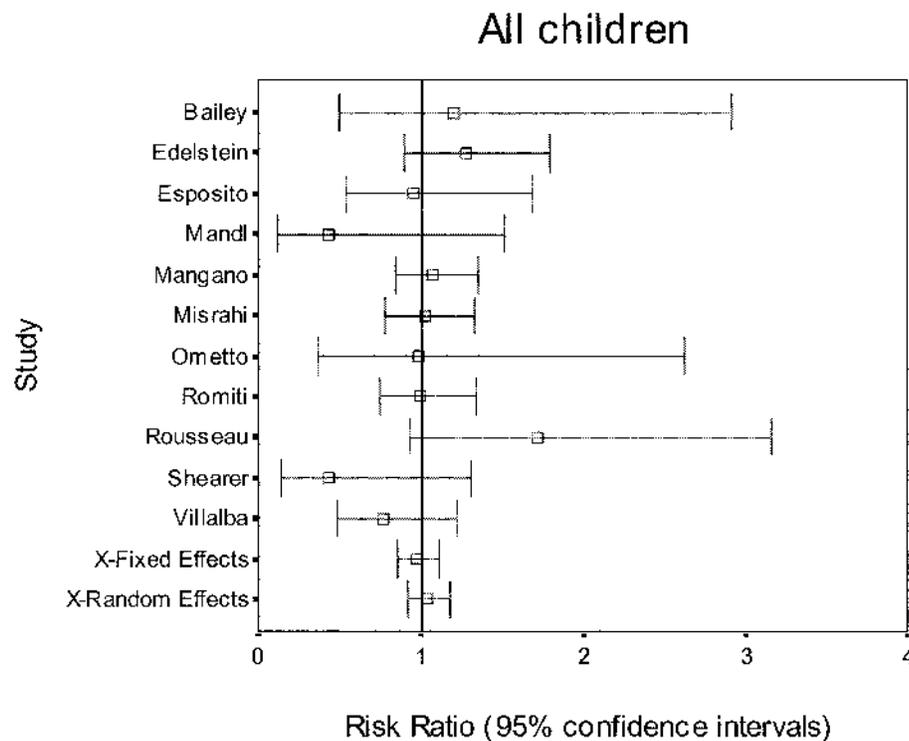


FIG. 1. Risk ratio of perinatal transmission of *CCR5*-Δ32 heterozygotes versus wild-type *CCR5* homozygotes. All children considered, regardless of race ($n = 3861$, 11 studies). Each study is shown by a square denoting the point estimate of the effect and whiskers denoting the 95% confidence intervals. Also shown are the summary effects (X) by fixed and random effects modeling.

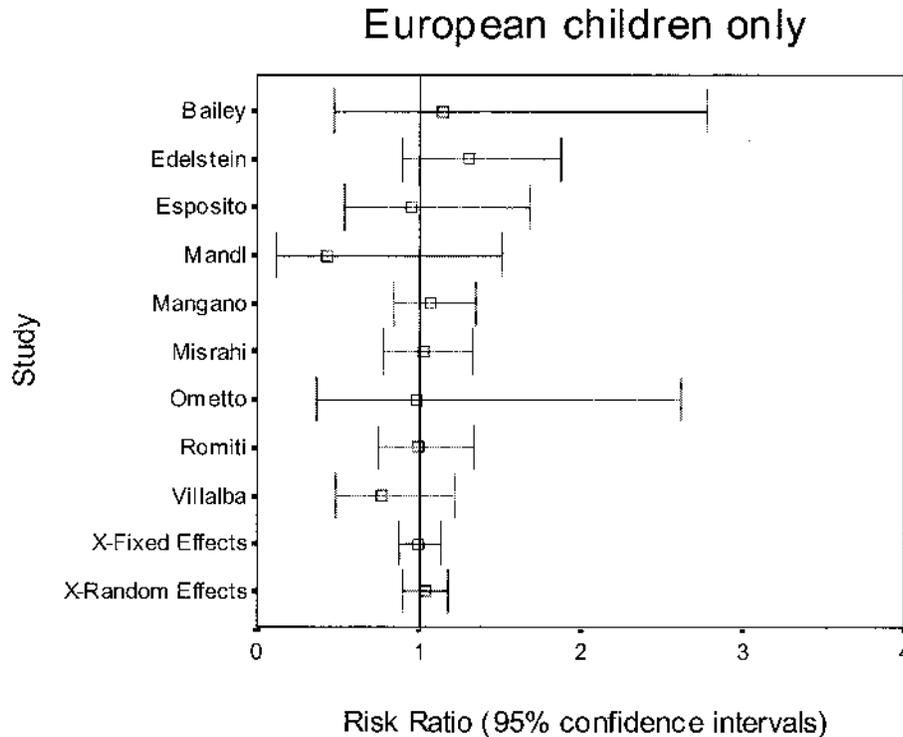


FIG. 2. Risk ratio of perinatal transmission of *CCR5-Δ32* heterozygotes versus wild-type *CCR5* homozygotes. Data are limited to children of European descent ($n = 2890$, 9 studies).

DISCUSSION

Meta-analysis offers a powerful method to synthesize information from genetic association studies (4,31–32). This meta-analysis refutes a clinically meaningful effect of a child's *CCR5-Δ32* heterozygosity on the risk of perinatal HIV-1 infection. We found no evidence that *CCR5-Δ32* heterozygosity in the child alters the risk of perinatal HIV-1 infection. With 3866 and 1542 children genotyped for *CCR5-Δ32* and *CCR2-64I*, respectively, the study had slightly over 90% power for each polymorphism to show a 25% relative risk reduction in the risk of perinatal transmission from 40% to 30% (at $\alpha = 0.05$ in the absence of between-study heterogeneity). Thus, we can exclude a 25% relative risk reduction, the magnitude of protection offered by *CCR5-Δ32* against HIV-1 disease progression in adults (4). The results were consistent whether we restricted the analysis to children of European descent or not. Given the dearth of *CCR5-Δ32* homozygotes in all the cohorts combined, we could not make meaningful conclusions regarding whether *CCR5-Δ32* homozygosity is protective in the perinatal setting, as in adults. The available data for *CCR2-64I* also revealed no role for this polymorphism in perinatal infection, similar to the lack of a protective effect for infection in adults (33).

Several factors may underlie the lack of an observed association between *CCR5-Δ32* heterozygosity and peri-

natal infection. First, expression of *CCR5* is influenced by factors other than *CCR5-Δ32* genotype as demonstrated by the fact that *CCR5* expression levels differ considerably among individuals with the same genotype for this locus (2–3). Also, occasionally perinatal transmission occurs via R5X4 or X4 strains that may establish infection via CXCR4, which is an alternative coreceptor for HIV-1 (34–36,10). Moreover, the route of infection may also be important for the lack of an observed association. Apart from transplacental HIV perinatal transmission during separation of the placenta from the uterine wall, some cases of perinatal infection may also occur via the mucosal route (37–38). Data are limited on the natural or inducible expression levels of chemokine receptors in neonatal cells from the gastrointestinal or respiratory tract. Furthermore, in such settings the importance of *CCR5* receptors remains unclear, especially if mechanisms such as viral “capture” by dendritic cells, in contrast to “infection,” are implicated (39–40). This possibility seems to be in accord with the finding that maternal-infant HLA concordance is a risk factor for perinatal infection (41). Finally, data are limited on whether chemokine receptors are expressed by the syncytiotrophoblast (42–43), which would affect in utero and transplacental infection.

Some limitations need to be acknowledged. While our meta-analysis rules out an effect of infant's heterozygosity for *CCR5-Δ32* on perinatal infection, it is uncertain

whether *CCR5-Δ32* affects transmission through breast-feeding and whether the mother's genotype may have an effect on one or more transmission routes. Only two studies (10,16) reported data on whether maternal *CCR5-Δ32* status affects perinatal transmission of HIV-1. Mothers with *CCR5-Δ32* generally have lower viral levels and, possibly, lower infectivity in the absence of antiretroviral treatment (44), but the evidence seems inconclusive. Finally, most studies in this meta-analysis included only women not receiving antiretroviral treatment. A small proportion of women had been treated, mostly with zidovudine. There is no reason to believe that maternal treatment might be confounding an infant's *CCR5-Δ32* effect. Moreover, there are no data on cohorts of women treated with the currently available highly active antiretroviral regimens. Nevertheless, in the current treatment era perinatal transmission rates are very low for developed countries, approximately 1% for women who achieve viral load levels less than 1000 copies/mL (45). Thus it is unlikely that, in these settings, studies would document any differences based on genotype.

In summary, our results suggest that perinatal infection rates are not strongly determined by the number of functional CCR5 receptors in the child. Therefore, other receptors and transmission mechanisms may play a more important role.

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