Effects of *CCR5-Δ32*, *CCR2-64I*, and *SDF-1 3′A* Alleles on HIV-1 Disease Progression: An International Meta-Analysis of Individual-Patient Data

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Background: **Studies relating certain chemokine and chemokine receptor gene alleles with the outcome of HIV-1 infection have yielded inconsistent results.**

Objective: **To examine postulated associations of genetic alleles with HIV-1 disease progression.**

Design: **Meta-analysis of individual-patient data.**

Setting: **19 prospective cohort studies and case–control studies from the United States, Europe, and Australia.**

Patients: **Patients with HIV-1 infection who were of European or African descent.**

Measurements: **Time to AIDS, death, and death after AIDS and HIV-1 RNA level at study entry or soon after seroconversion. Data were combined with fixed-effects and random-effects models.**

Results: **Both the *CCR5-Δ32* and *CCR2-64I* alleles were associated with a decreased risk for progression to AIDS (relative hazard among seroconverters, 0.74 and 0.76, respectively; $P = 0.01$ for both), a decreased risk for death (relative hazard among seroconverters, 0.64 and 0.74; $P < 0.05$ for both), and lower HIV-1 RNA levels after seroconversion (difference, -0.18 $\log_{10}$ copies/mL and -0.14 $\log_{10}$ copies/mL; $P < 0.05$ for both). Having the *CCR5-Δ32* or *CCR2-64I* allele had no clear protective effect on the risk for death after development of AIDS. The results were consistent between seroconverters and seroprevalent patients. In contrast, *SDF-1 3′A* homozygotes showed no decreased risk for AIDS (relative hazard for seroconverters and seroprevalent patients, 0.99 and 1.03, respectively), death (relative hazard, 0.97 and 1.00), or death after development of AIDS (relative hazard, 0.81 and 0.97; $P > 0.5$ for all).**

Conclusions: **The *CCR5-Δ32* and *CCR2-64I* alleles had a strong protective effect on progression of HIV-1 infection, but *SDF-1 3′A* homozygosity carried no such protection.**

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The burgeoning information on the human genome creates opportunities and challenges for studies of disease associations. Because genetic differences often produce modest effects, many patients must be studied to reach definitive conclusions. In the absence of a single large study, meta-analysis of individual-patient data (1–3) from smaller studies offers a way to assemble an adequate sample size. This approach is based on a unifying protocol that has standardized analytic definitions. When the protocol is applied to data contributed by most investigators working in a field, this method can provide more convincing results than a simple pooling of data or a meta-analysis of published reports (3). A meta-analysis of individual-patient data is also superior to a meta-analysis of published reports for examining differences in reported results.

Host genetic variability affects the risk for AIDS after infection with HIV-1, but the effect of specific alleles (that is, alternative forms of a gene that exist at a specific chromosomal location [locus]) has been inconsistent. C-C chemokine receptor 5 (CCR5) is a major co-receptor for HIV-1, but *CCR5-Δ32*, an allele that contains a 32–base pair deletion, codes for a nonfunctional co-receptor (4–6). *CCR5-Δ32* homozygotes (people who inherited the *CCR5-Δ32* allele from both parents) are highly resistant to HIV-1 infection (4–7). *CCR5-Δ32* heterozygotes (people who inherited the *CCR5-Δ32* allele from one parent and a functional *CCR5* allele from the other parent) are susceptible to HIV-1 infection; however, according to some reports (6, 8–20), they progress from HIV-1 infection to AIDS more slowly than persons with two normal *CCR5* alleles

(called wild-type individuals). CCR2b is a minor HIV-1 co-receptor. The gene that codes for this chemokine receptor has a variant allele (*CCR2-64I*) that may affect the risk for AIDS (21). Epidemiologic studies of *CCR2-64I* carriers have been inconsistent (18–26), and in vitro studies have identified no functional differences between cells from *CCR2-64I* carriers and those from wild-type patients (27, 28). Stromal cell–derived factor-1 (SDF-1) is the chemokine ligand of CXCR4, an important co-receptor for HIV-1 late in the disease course (29, 30). Homozygosity for the *SDF-1 3′A* allele has been reported to slow disease progression (31), but not in all studies (18, 19, 32–35). To address these inconsistencies, we conducted an international meta-analysis of individual-patient data on the *CCR5*, *CCR2*, and *SDF-1* alleles; data were contributed by 19 teams of investigators.

METHODS

Organization of the Meta-Analysis

All research teams investigating associations of genetic alleles with the course of HIV-1 disease progression were invited to contribute individual-patient data to the International Meta-Analysis of HIV Host Genetics. Collaborating teams were identified through MEDLINE searches, cited references of retrieved papers, abstracts of major HIV-related meetings, and communication with investigators working in the field. The meta-analysis was also announced in *Nature Medicine* (36), on the Web site of the International Cochrane Collaboration, and at HIV scientific meetings. A common protocol was developed in collaboration with research teams identified through these efforts. The meta-analysis database remained open until 12 February 1999 for the collection of *CCR5-Δ32* and *CCR2-64I* data; because most of the participating investigator teams evaluated *SDF-1 3′A* after they studied *CCR5-Δ32* and *CCR2-64I*, we collected data on *SDF-1 3′A* until 30 November 1999.

Selection of Databases

Prospective cohort studies of patients with HIV-1 infection were included in the analysis if they had collected information on the pertinent genotypes, as well as on the time from seroconversion or study entry to the development of AIDS and to death. We excluded studies if genetic data or time-to-event data were unavailable or if the participants were enrolled after 1 January 1996. We included case–control studies if they compared patients with rapid versus slower rates of progression. Case–control studies were analyzed separately from prospective cohort studies.

Definitions and End Points

The prospective cohort studies in our meta-analysis typically had follow-up visits every 6 months. Within each study, we divided the participants according to enrollment before (seroconverters) or after (seroprevalent patients) HIV-1 infection. For seroconverters, a negative result and a subsequent positive result on enzyme-linked immunosorbent assay (ELISA) and Western blot test were obtained after enrollment. We analyzed the data on a time scale that originated at the date of study entry for seroprevalent participants and at the estimated date of seroconversion (calculated as the midpoint between the last study visit at which the patient tested negative for HIV-1 and the first visit at which the patient tested positive for HIV-1) for the seroconverters. The cohorts differed little in the precision of the estimated date of seroconversion because semiannual data were typically available. Data for patients of European descent and data for patients of African descent (37) were considered separately.

Our analysis examined four major outcomes: 1) time from seroconversion (or study entry) to the development of AIDS, according to 1987 criteria by the U.S. Centers for Disease Control and Prevention (38); 2) time from seroconversion (or study entry) to death; 3) time from development of AIDS to death; and 4) serum or plasma HIV-1 RNA level, which was measured by using a consistent method within each study. For seroconverters, we used the first measurement of HIV-1 RNA level recorded since onset of chronic HIV-1 infection (range, 6 to 42 months after the estimated date of seroconversion); for seroprevalent patients, we used the first study measurement of HIV-1 RNA level. We censored data on follow-up after 1 January 1996 to minimize the effects of potent antiretroviral therapy. The average follow-up to AIDS development or to the point of censoring in the *CCR5-Δ32* and *CCR2-64I* analyses was 6.73 years for seroconverters and 6.37 years for seroprevalent patients; for the *SDF-1* analysis, the average

follow-up was 7.14 years for the seroconverters and 6.51 years for seroprevalent patients.

We specified our outcome variables a priori and asked all investigators to contribute data in a format consistent with the protocol. Investigators at the coordinating center, which was located at the National Cancer Institute in Rockville, Maryland, communicated with the contributing investigators to verify that the data from each study adhered to the common definitions of the meta-analysis. The contributed data sets also underwent logical tests to identify internal inconsistencies or incompatibilities. Any missing information or errors in logic that were identified at the coordinating center were referred to the contributing investigators; all identified errors were resolved.

Statistical Analysis

We used Cox regression to determine hazard ratios (relative hazards) for the times to events for all study cohorts and subgroups (39). The hazard ratio approximates the relative risk or incidence risk ratio. A $\log_{10}$ transformation was used for all analyses of HIV-1 RNA level. Differences in HIV-1 RNA level within studies were analyzed as differences for independent samples of continuous variables.

Pooled summary estimates of hazard ratios and differences of means were obtained by weighting estimates from each study by the inverse of its variance (1, 40). We estimated fixed effects and random effects (1, 40). Fixed-effects models assume that any differences in results among studies are simply due to chance, whereas random-effects models assume that there may be true differences in the results of different studies. We report random-effects estimates because these provide more conservative confidence intervals when the results are highly heterogeneous across cohorts. (In the absence of heterogeneity, fixed-effects and random-effects estimates coincide.)

We assessed heterogeneity by using the Q statistic, which we considered to be significant if the *P* value was less than 0.10 (1). However, some cohorts had few *SDF-1 3′A* homozygotes with clinical events. Therefore, we also calculated an efficient score test for heterogeneity on the basis of the appropriate interaction terms between genotype and cohort in a cohort-stratified proportional hazards model. Inferences were similar with both tests.

To model the effect of rare genotypes (*CCR2-64I* homozygotes or patients who were heterozygous for *CCR5-Δ32* and *CCR2-64I*), we fit Cox models to the pooled data from all cohort studies with stratification by study. For cohorts with no events among *SDF-1 3′A* homozygotes, we estimated log relative hazards β values on the basis of a penalized likelihood with a penalty term of $-0.5\,(\log(1 + \exp(\beta)) - \beta)$. Penalty terms shrink extreme β values (which also have large variances) toward zero. Because these extreme estimates have small weights, they contribute little to the overall results. Their exclusion yielded results similar to those of the main analysis.

All calculations were performed by using the MATLAB software package, version 5.3 (The MathWorks, Inc., Natick, Massachusetts).

RESULTS

We restricted the main analysis of *CCR5-Δ32* and *CCR2-64I* to patients of European or African descent with genotype data for both alleles (**Table 1**). Because *CCR5-Δ32* and *CCR2-64I* are in complete linkage of disequilibrium (nonrandom association of alleles that lie close together on a chromosome) (21), the *CCR5-Δ32* and *CCR2-64I* alleles are never found on the same paternal or maternal chromosome. Therefore, we compared patients with a variant allele to patients who were wild-type homozygotes for both *CCR5* and *CCR2*. Because the *CCR5-Δ32* allele is almost exclusively found in persons of European descent (4–6), the analysis of *CCR5-Δ32* was limited to such persons. The analysis of *SDF-1 3′A* was limited to persons of European descent because only two of the *SDF-1 3′A* homozygous patients were of African descent (**Table 2**).

Effect of *CCR5-Δ32* on AIDS, Survival, and HIV-1 RNA

CCR5-Δ32 heterozygotes progressed significantly more slowly to AIDS than patients with the wild-type *CCR5* genotype (**Figure 1A** and **1B**). The relative hazard for AIDS was 0.74 (95% CI, 0.56 to 0.97) among seroconverters and 0.70 (CI, 0.54 to 0.91) among seroprevalent patients. The hazard for death was also significantly lower among *CCR5-Δ32* heterozygotes in both the seroconverter (relative hazard, 0.64 [CI, 0.48 to

Table 1. **Database for Main Meta-Analysis of *CCR5*-Δ*32* and *CCR2-64I*, according to Study Cohort and Genotype***

Cohort	Alias	Seroconverters				Seroprevalent Patients			
		Patients	Follow-up	AIDS Events	Patients with HIV-1 RNA Data	Patients	Follow-up	AIDS Events	Patients with HIV-1 RNA Data
		n	*person-years*	←	*n*	→	*person-years*	*n*	
European descent†									
AIDS Research Initiative (Australia)	ARI	0	–	–	–	88	437	21	–
Amsterdam Cohort of Homosexual Men	ACHM	122	677	51	122	222	1287	129	214
Amsterdam Cohort of Intravenous Drug Users	AIVD	63	275	8	43	27	175	7	–
Copenhagen AIDS Cohort	CAC	0	–	–	–	100	731	62	94
District of Columbia Gay Cohort	DCG	45	335	26	40	60	412	47	59
Hemophilia Growth and Development Study	HGDS	0	–	–	–	147	725	42	146
Multicenter AIDS Cohort Study	MACS-Eur	405	2633	183	226	615	3702	509	53
Multicenter Hemophilia Cohort Study	MHCS-Eur	234	2337	106	159	347	2959	107	266
French Seroconverter Cohort	SEROCO	355	2199	113	324	47	247	11	42
San Francisco City Clinic Cohort	SFCC	22	162	4	–	138	973	54	49
San Francisco Men's Health Study	SFMHS	36	274	17	34	328	2256	222	314
Swiss HIV Cohort Study	SHCS	265	1795	36	–	–	–	–	–
African descent‡									
AIDS Link to the Intravenous Experience	ALIVE	134	578	17	–	541	2846	122	–
Multicenter AIDS Cohort Study	MACS-Afr	40	223	10	24	32	257	20	–
Multicenter Hemophilia Cohort Study	MHCS-Afr	25	269	10	–	66	607	22	55
Total patients		1746	11 757	581	972	2758	17 614	1375	1292
Genotype									
CCR5-+/+ and *CCR2*-+/+ (Homozygous for wild-type *CCR5* and *CCR2*)		1169	7604	409	649	1785	11 063	938	814
CCR5-+/Δ*32* and *CCR2*-+/+ (Heterozygous for *CCR5*-Δ*32* and homozygous for wild-type *CCR2*)		245	1804	78	156	361	2592	167	200
CCR5-+/+ and *CCR2*-+/*64I* (Homozygous for wild-type *CCR5* and heterozygous for *CCR2-64I*)		281	1963	80	137	527	3353	237	237
CCR5-+/Δ*32* and *CCR2*-+/*64I* (Heterozygous for *CCR5*-Δ*32* and heterozygous for *CCR2-64I*)		33	257	10	20	53	387	20	34
CCR5-+/+ and *CCR2-64I*/64I (Homozygous for wild-type *CCR5* and homozygous for *CCR2-64I*)		18	129	4	10	32	218	13	7

* For the *CCR5* and *CCR2* analysis, 15 cohort studies contributed data on patients with HIV-1 infection but not clinically defined AIDS (38) at enrollment (before 1 January 1996). The data shown are for the 13 cohorts with *CCR5*-Δ*32* or *CCR2-64I* information on ≥20 patients of European or African descent. Patient data from another study (17) that provided *CCR5*-Δ*32* data only were combined with the *CCR5*-Δ*32* data from other participating studies. The results of this analysis (not reported) were consistent with the findings from the main analysis. The final cohort study, the Spanish Earth Study, had too few eligible patients for analysis.
† Of the European descendants (seroconverter and seroprevalent patients combined, $n = 3672$), 16% were heterozygous for the *CCR5*-Δ*32* allele and homozygous for wild-type *CCR2*; 17% were heterozygous or homozygous for *CCR2-64I* and homozygous for wild-type *CCR5*.
‡ Among the patients of African ancestry ($n = 839$), 28% carried one or two copies of the *CCR2-64I* allele.

0.85]) and seroprevalent (relative hazard, 0.64 [CI, 0.52 to 0.79]) groups (data not shown in **Figure 1**). *CCR5*-Δ*32* heterozygosity was not clearly related to the risk for dying after development of AIDS (**Figure 1C** and **1D**). The relative hazard for death following AIDS development was 0.77 (CI, 0.55 to 1.06) in seroconverters and 1.00 (CI, 0.76 to 1.31) in seroprevalent patients.

We subsequently examined differences among genotypes in HIV-1 RNA level. Compared with the HIV-1 RNA level in wild-type patients, the HIV-1 RNA level for *CCR5*-Δ*32* heterozygotes was lower by 0.18 $\log_{10}$ copies/mL (CI, −0.05 to −0.32 $\log_{10}$ copies/mL) in seroconverters and by 0.21 $\log_{10}$ copies/mL in seroprevalent patients (CI, −0.03 to −0.39 $\log_{10}$ copies/mL) (**Figure 1E** and **1F**). The HIV-1 RNA level is the strongest known predictor of HIV-1 disease progression, and differences of about 0.20 $\log_{10}$ copies/mL are prognostically meaningful (41, 42). To evaluate how consideration of the HIV-1 RNA level changed the predictive value of genotype, we adjusted the relative hazard for early HIV-1 RNA level in a meta-analysis that was limited to cohorts with data available on HIV-1 RNA level. After adjustment for HIV-1 RNA level, the relative hazard for development of AIDS in *CCR5*-Δ*32* heterozy-

gotes compared with wild-type homozygotes was 0.82 (CI, 0.58 to 1.16) for seroconverters and 0.77 (CI, 0.52 to 1.16) for seroprevalent patients. Without adjustment for HIV-1 RNA level in the models, the corresponding values for the same subset of patients were 0.71 (CI, 0.51 to 0.98) and 0.65 (CI, 0.51 to 0.83), respectively. These findings suggest that the genotypic differences in early HIV-1 RNA levels explain some of the protective effect of the *CCR5-Δ32* allele.

Effect of *CCR2-64I* on AIDS, Survival, and HIV-1 RNA Level

Compared with patients who were wild type for both *CCR2* and *CCR5*, patients who were heterozygous or homozygous for the *CCR2-64I* allele progressed more slowly from HIV-1 infection to AIDS (**Figure 2A** and **2B**). The relative hazard for AIDS was 0.76 (CI, 0.60 to 0.96) among seroconverters and 0.88 (CI, 0.76 to 1.01) among seroprevalent patients. Similarly, the hazard for death following seroconversion was lower among both seroconverters (relative hazard, 0.74 [CI, 0.57 to 0.97]) and seroprevalent patients (0.87 [CI, 0.73 to 1.03]) with the *CCR2-64I* allele. In the seroprevalent patients, the findings for relative hazard for AIDS and for death were not statistically significant. The *CCR2-64I* allele showed no protection against death after AIDS had developed (**Figure 2C** and **2D**). The relative hazard for death after development of AIDS was 1.10 (CI, 0.69 to 1.76) in seroconverters and 1.00 (CI, 0.85 to 1.17) in seroprevalent patients. The effect of the *CCR2-64I* allele on risk for AIDS was similar between seroconverters of European descent (relative hazard, 0.75 [CI, 0.59 to 0.97]) and those of African descent (relative hazard, 0.81 [CI, 0.38 to 1.75]). The corresponding relative hazard among seroprevalent patients was 0.87 (CI, 0.75 to 1.01) in persons of European descent and 1.02 (CI, 0.56 to 1.83) in persons of African descent.

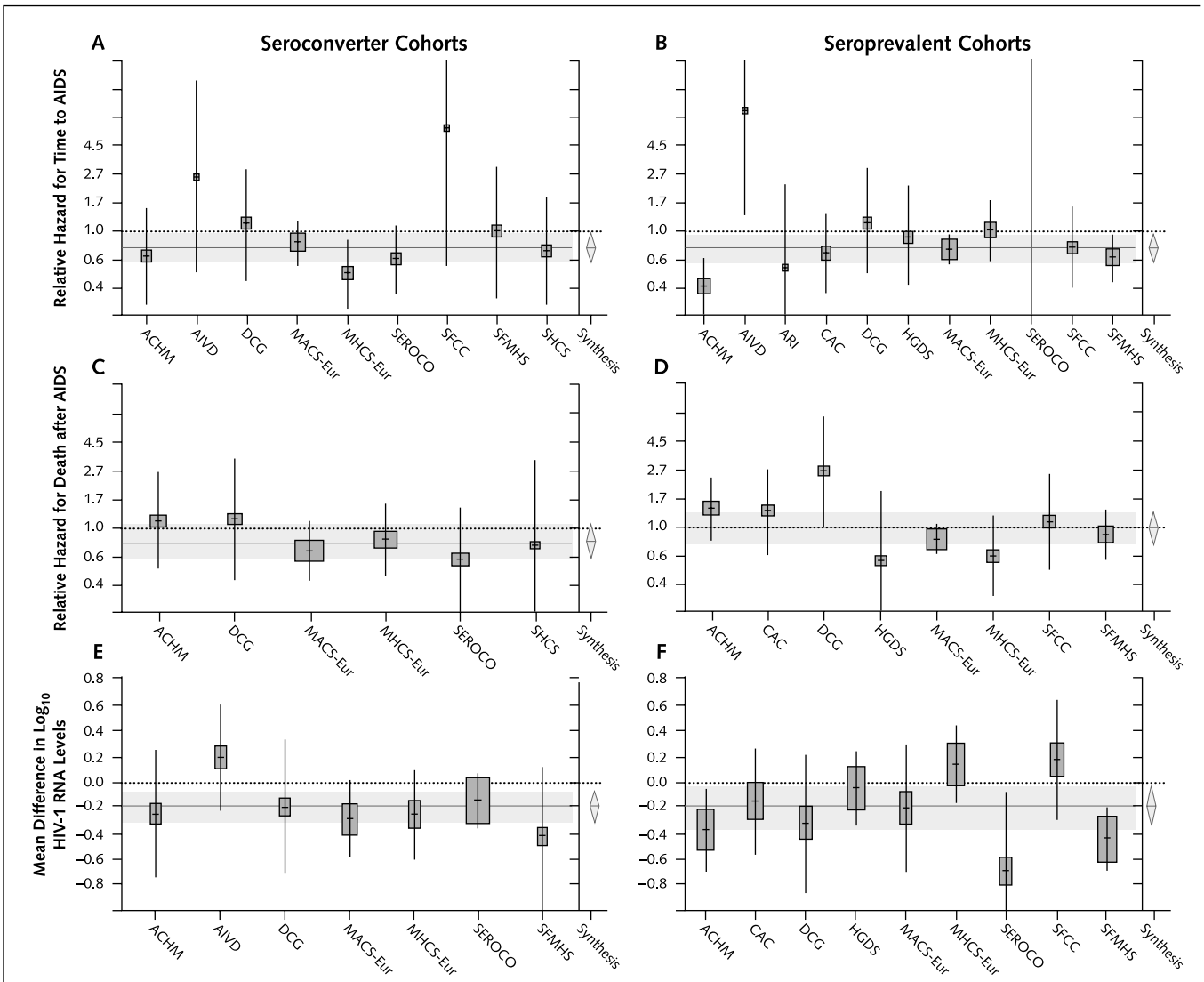
Levels of HIV-1 RNA during early chronic HIV-1

Table 2. **Database for the *SDF-1 3′A* Meta-Analysis***

Cohorts	Homozygous for *SDF-1 3′A*			Homozygous for Wild-Type *SDF-1 3′G* or Heterozygous for *SDF-1 3′A*		
	Patients	Deaths	Follow-up	Patients	Deaths	Follow-up
	n		*person-years*	*n*		*person-years*
Seroconverters†						
ACHM	3	2	18.2	119	46	747.0
MACS-Eur	13	0	116.4	357	137	2522.8
MHCS-Eur	11	5	112.8	292	120	3082.1
SEROCO	22	3	166.3	332	74	2208.3
SFMHS	2	0	16.0	42	11	317.0
SHCS	11	2	64.7	254	19	1794.8
Total	62	12	494.4	1396	407	10 672.0
Seroprevalent patients‡						
ACHM	9	6	72.5	213	112	1382.1
CAC	3	1	25.8	98	60	810.3
CHIC	8	3	26.9	198	74	627.5
DCG	4	2	43.2	54	40	411.5
HGDS	6	2	31.6	139	42	778.4
MACS-Eur	34	25	237.8	443	315	3415.2
MHCS-Eur	22	7	213.9	424	113	3791.5
SEROCO	4	1	26.9	42	5	233.7
SFCC	6	0	60.6	131	43	1031.4
SFMHS	13	8	106.2	235	132	2016.3
Total	109	55	845.4	1977	936	14 497.9

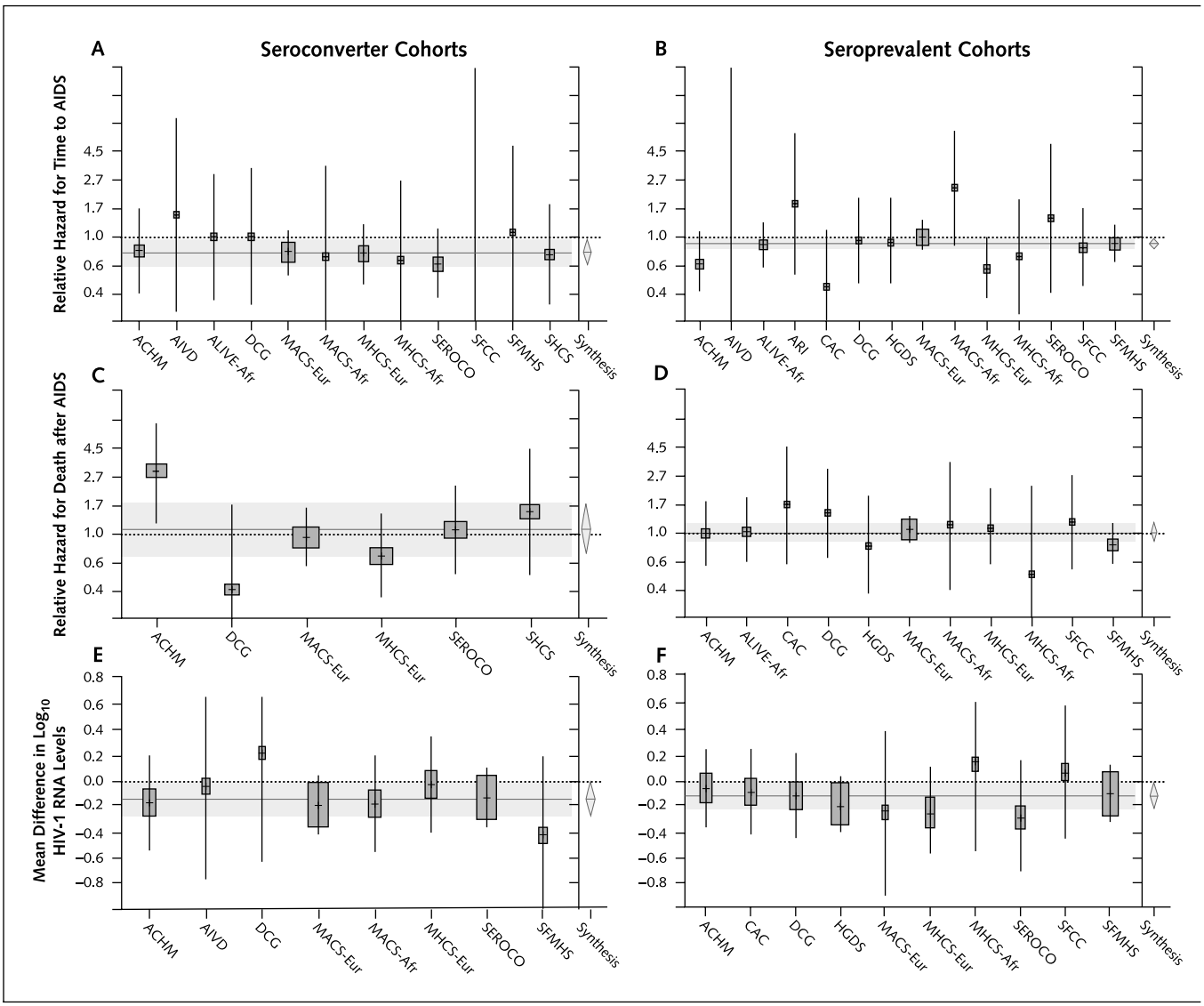
* For the *SDF-1 3′A* meta-analysis, 13 cohort studies contributed information on seroconverters (n = 1757) and seroprevalent patients (n = 2877) with HIV-1 infection who had undergone genotyping for *SDF-1 3′A*. Shown are the seroconverter and seroprevalent cohorts with ≥20 evaluable patients. African descendants were excluded from the meta-analysis because among the seroconverters (n = 225) and seroprevalent patients (n = 932) of African descent, only 2 were *SDF-1 3′A* homozygotes. The following cohorts were excluded because no patients were homozygous for *SDF-1 3′A*: among seroconverters, DCG (n = 45 patients who had genotyping for *SDF-1 3′A*), and SFCC (n = 22). ACHM = Amsterdam Cohort of Homosexual Men; CAC = Copenhagen AIDS Cohort; CHIC = Copenhagen HIV Immunology Cohort; DCG = District of Columbia Gay Cohort; HGDS = Hemophilia Growth and Development Study; MACS = Multicenter AIDS Cohort Study; MHCS = Multicenter Hemophilia Cohort Study; SEROCO = French Seroconverter cohort; SFCC = San Francisco City Cohort; SFMHS = San Francisco Men's Health Study; SHCS = Swiss HIV Cohort Study. Afr and Eur denote subgroups of African and European descent, respectively.
† Data on HIV-1 RNA level were available for 955 patients.
‡ Data on HIV-1 RNA level were available for 1404 patients.

Figure 1. **Meta-analysis of the effect of *CCR5-Δ32* heterozygosity on HIV-1 disease progression among patients of European descent.**



In each panel, patients who are heterozygous for *CCR5-Δ32* without *CCR2-64I* are compared with patients who are homozygous for wild-type *CCR5* and *CCR2*. Shown are the relative hazard for AIDS from seroconversion (*A*) or study entry (*B*); relative hazard for death following the development of AIDS (*C*, *D*); and mean difference in $\log_{10}$ HIV-1 RNA levels at 6 to 42 months after seroconversion (*E*) or at first study measurement (*F*). Hazard ratios in panels A through D are plotted on a natural log scale. Relative hazard = 1 (*dotted line*) indicates no difference in hazard rates; values less than 1 indicate relative protection for *CCR5-Δ32* carriers. For each cohort, point estimates (*boxes*) and 95% CIs (*bars*) are provided. Within panels, the areas of the boxes are proportional to the weights used in meta-analytic synthesis. The glyphs labeled "Synthesis" (*diamonds*) show the results of meta-analysis; the center lines indicate summary estimates, and the length of the diamonds spans the 95% CI, which was based on a random-effects model. Cohort-specific results are overlaid on a shaded line and band that correspond to the summary estimate and CI, respectively. Heterogeneity of the study-specific results was measured by using the Q statistic: A, $P > 0.2$; B, $P = 0.11$; C, $P > 0.2$; D, $P = 0.15$; E, $P > 0.2$; F, $P = 0.05$. Each Q statistic has a chi-square distribution with the degrees of freedom equal to one less than the number of cohorts in the analysis. Only seroconverter groups and seroprevalent groups with relevant data for at least 20 patients are shown. ACHM = Amsterdam Cohort of Homosexual Men; AIVD = Amsterdam Cohort of Intravenous Drug Users; ARI = AIDS Research Initiative (Australia); CAC = Copenhagen AIDS Cohort; DCG = District of Columbia Gay Cohort; HGDS = Hemophilia Growth and Development Study; MACS-Eur = patient subgroup of European descent in Multicenter AIDS Cohort Study; MHCS-Eur = patient subgroup of European descent in Multicenter Hemophilia Cohort Study; SEROCO = French Seroconverter Cohort; SFCC = San Francisco City Clinic Cohort; SFMHS = San Francisco Men's Health Study; SHCS = Swiss HIV Cohort Study.

Figure 2. **Meta-analysis of the effect of the *CCR2-64I* allele on HIV-1 disease progression.**



Each panel compares patients who are homozygous or heterozygous (but without the *CCR5*-Δ*32* allele) for *CCR2-64I* with patients who are homozygous for wild-type *CCR5* and wild-type *CCR2*. The panels are constructed as described in the legend for Figure 1. The Q statistic was used to calculate *P* values: A, $P > 0.2$; B, $P > 0.2$; C, $P = 0.10$; D, $P > 0.2$; E, $P > 0.2$; F, $P > 0.2$. Subgroups comprising patients of European (*Eur*) or African (*Afr*) ancestry are noted. Otherwise, cohorts are limited to patients of European descent. Only seroconverter and seroprevalent groups with relevant data for at least 20 patients are shown. ACHM = Amsterdam Cohort of Homosexual Men; AIVD = Amsterdam Cohort of Intravenous Drug Users; ALIVE = AIDS Link to the Intravenous Experience; ARI = AIDS Research Initiative (Australia); CAC = Copenhagen AIDS Cohort; DCG = District of Columbia Gay Cohort; HGDS = Hemophilia Growth and Development Study; MACS = Multicenter AIDS Cohort Study; MHCS = Multicenter Hemophilia Cohort Study; SEROCO = French Seroconverter Cohort; SFCC = San Francisco City Clinic Cohort; SFMHS = San Francisco Men's Health Study; SHCS = Swiss HIV Cohort Study.

infection were 0.14 $\log_{10}$ copies/mL lower (CI, −0.01 to −0.27 $\log_{10}$ copies/mL) in seroconverters with the *CCR2-64I* allele than in seroconverters without the allele (**Figure 2E**). Similarly, among seroprevalent patients with the *CCR2-64I* allele, the first HIV-1 RNA level obtained after study entry was also significantly lower (by 0.12 $\log_{10}$ copies/mL [CI, −0.01 to −0.23 $\log_{10}$ copies/mL]) (**Figure 2F**). The relative hazard for development of AIDS among patients with the *CCR2-64I* allele was somewhat attenuated after adjustment for

HIV-1 RNA level. The adjusted relative hazard was 0.86 (CI, 0.62 to 1.19) among seroconverters and 0.90 (CI, 0.65 to 1.25) among seroprevalent patients. Without adjustment in the models for HIV-1 RNA level, the corresponding values in the same subset of patients were 0.84 (CI, 0.60 to 1.16) for seroconverters and 0.79 (CI, 0.63 to 0.97) for seroprevalent patients.

Effect of Dual *CCR5* and *CCR2* Alleles on AIDS

Of 1555 seroconverters of European descent, 31 (2.0%) were heterozygous for both the *CCR5*-Δ*32* allele and the *CCR2-64I* allele. If these alleles have independent effects, the predicted relative hazard for AIDS development should equal the product of the individual estimated genetic effects ($0.74 \times 0.76 = 0.56$). In fact, the relative hazard for development of AIDS in the patients with these dual alleles compared with patients who were wild type for both genes was 0.66 (CI, 0.35 to 1.25). This relative hazard was 0.50 (CI, 0.31 to 0.79) in seroprevalent patients. Of 1509 seroconverters who lacked the *CCR5*-Δ*32* allele, 19 (1.3%) were homozygous for the *CCR2-64I* allele. The relative hazard for development of AIDS in this group was 0.43 (CI, 0.16 to 1.16) compared with wild-type patients and 0.55 (CI, 0.20 to 1.51) compared with *CCR2-64I* heterozygotes. A qualitatively consistent pattern was seen in seroprevalent patients. Although these results are not conclusive, they are consistent with the hypothesis that two protective alleles offer more protection than a single protective allele.

Effect of *SDF-1 3′A* Homozygosity on AIDS, Survival, and HIV-1 RNA

SDF-1 3′A homozygotes showed no consistent evidence of slow progression to AIDS (**Figure 3A** and **3B**) and no evidence of slow progression to death (**Figure 3C** and **3D**). The relative hazard for AIDS was 0.99 (CI, 0.44 to 2.23) among seroconverters and 1.03 (CI, 0.80 to 1.34) among seroprevalent patients. Similar results were obtained for the relative hazard for death following seroconversion (relative hazard in seroconverters, 0.97 [CI, 0.35 to 2.70]) or study entry (relative hazard in seroprevalent patients, 1.00 [CI, 0.76 to 1.32]). *SDF-1 3′A* homozygosity showed no significant or consistent association with risk for death after developing AIDS (**Figure 3E** and **3F**). The relative hazard for death following AIDS was 0.81 (CI, 0.25 to 2.60) in seroconverters and 0.97 (CI, 0.73 to 1.29) in seroprevalent patients. For all clinical end points, the seroconverter cohorts had statistically significant heterogeneity. For example, among the six seroconverter cohorts in the meta-analysis of AIDS risk (**Figure 3A**), one showed a significant deleterious effect, one showed a significant protective effect, and four showed no significant effect ($P = 0.02$, Q statistic for heterogeneity).

Among seroconverters, HIV-1 RNA levels were lower in *SDF-1 3′A* homozygotes than in other patients, but the difference was not statistically significant (mean difference, -0.20 $\log_{10}$ copies/mL [CI, -0.39 to 0.05 $\log_{10}$ copies/mL]). Among seroprevalent patients, HIV-1 RNA levels were similar regardless of *SDF-1 3′A* genotype (mean difference, -0.05 $\log_{10}$ copies/mL [CI, -0.23 to 0.14 $\log_{10}$ copies/mL]).

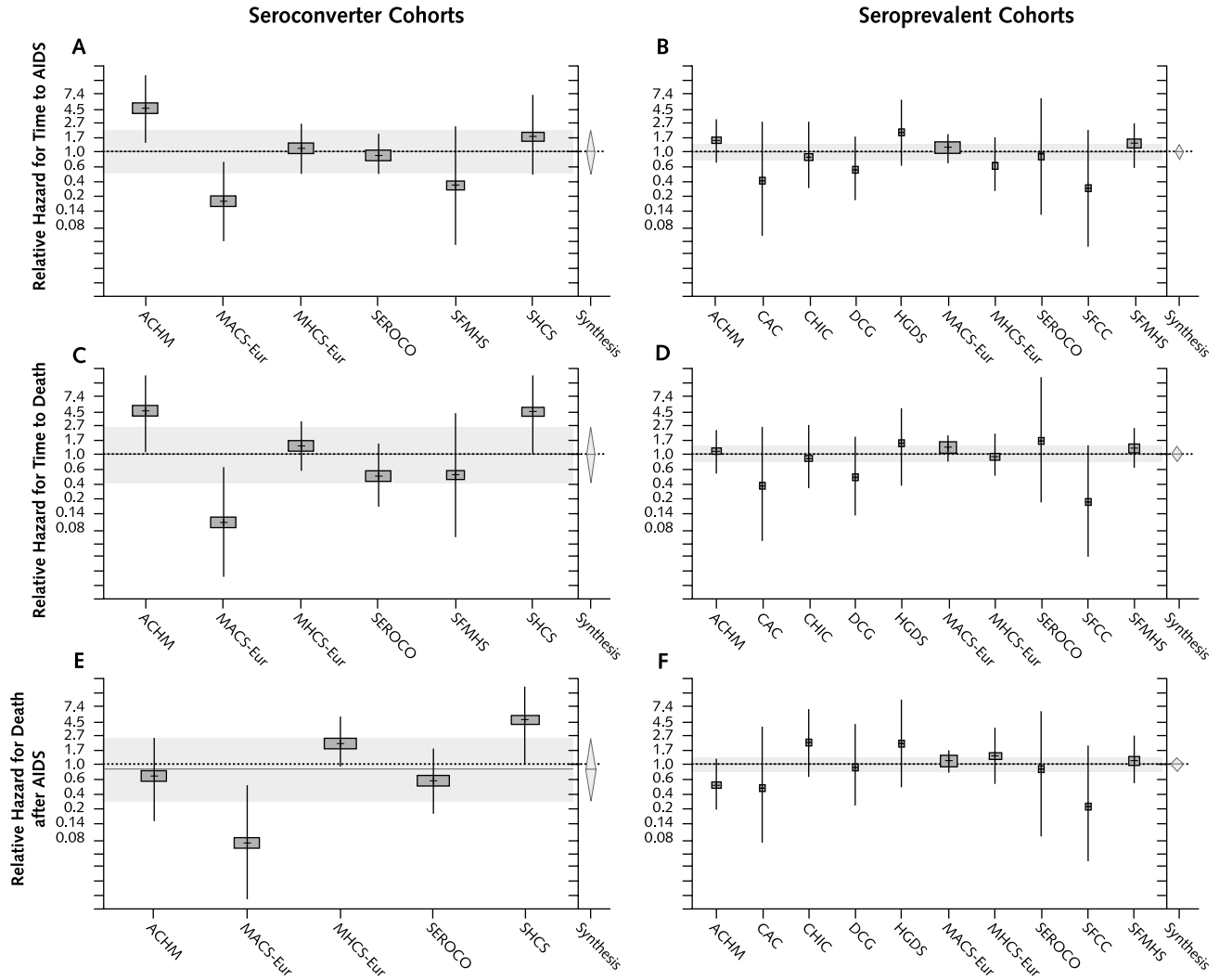
Case–Control Studies

Results from two case–control studies (15, 18) (410 participants total) were generally consistent with the results of the prospective cohort studies. These studies compared "nonprogressors" with CD4 cell counts greater than 0.500×10^9 cells/L who had no clinical disease more than 8 years after seroconversion with "rapid progressors" who had CD4 cell counts less than 0.300×10^9 cells/L within 3 years of seroconversion. Compared with patients who were wild type for both *CCR5* and *CCR2*, the pooled odds ratios for being a progressor rather than a nonprogressor were 0.12 (CI, 0.02 to 0.62) for *CCR5*-Δ*32* heterozygotes, 0.42 (CI, 0.22 to 0.81) for patients with the *CCR2-64I* allele, and 0.29 (CI, 0.06 to 1.49) for patients with both the *CCR5*-Δ*32* and *CCR2-64I* alleles. The Genetics of the Resistance to Infection by the Immunodeficiency Virus (GRIV) case–control study (18) also contributed data for the *SDF-1 3′A* analysis; *SDF-1 3′A* homozygotes were under-represented among rapid progressors (0 of 69) compared with nonprogressors (8 of 181), but the difference was not statistically significant ($P = 0.12$).

DISCUSSION

The main findings of the meta-analysis are summarized in **Table 3**. The meta-analysis confirmed that *CCR5*-Δ*32* heterozygotes have a reduced risk for progressing from initial HIV-1 infection to the development of AIDS. We also found that these patients have less viremia early in the course of their disease. The

Figure 3. **Meta-analysis of the effect of *SDF-1 3′A* homozygosity on HIV-1 disease progression among patients of European descent.**



Unless otherwise specified, the panels were constructed as described in the legend for Figure 1. Each panel compares patients homozygous for *SDF-1 3′A* with all other patients; the seroconverter and seroprevalent groups shown are those that contributed usable data on ≥20 patients. The six panels show the relative hazard for AIDS from seroconversion (*A*) or from study entry (*B*), the relative hazard for death (*C*, *D*), and, finally, the relative hazard for death following the development of AIDS (*E*, *F*). The *P* values for the Q statistics were: A, $P = 0.02$; B, $P > 0.2$; C, $P = 0.01$; D, $P > 0.2$; E, $P = 0.01$; F, $P > 0.2$. ACHM = Amsterdam Cohort of Homosexual Men; CAC = Copenhagen AIDS Cohort; CHIC = Copenhagen HIV Immunology Cohort; DCG = District of Columbia Gay Cohort; HGDS = Hemophilia Growth and Development Study; MACS-Eur = patient subgroup of European descent in Multicenter AIDS Cohort Study; MHCS-Eur = patient subgroup of European descent in Multicenter Hemophilia Cohort Study; SEROCO = French Seroconverter Cohort; SFCC = San Francisco City Clinic Cohort; SFMHS = San Francisco Men's Health Study; SHCS = Swiss HIV Cohort Study.

protective effect of *CCR5*-Δ*32* was most clearly evident before the development of AIDS. Co-receptor use may change with the evolution of HIV-1 infection in the host, and HIV-1 strains that use CXCR4 may become more common as disease advances (30). The lack of a strong protective effect among *CCR5*-Δ*32* heterozygotes following the development of AIDS is consistent with this model.

The effect of the *CCR2-64I* allele has been controversial, but we confirmed that progression from infection to AIDS or death was slower in persons with this allele. Among seroconverters of European descent, the magnitude of the protective effect among *CCR2-64I* heterozygotes and homozygotes combined—a 24% risk reduction—is almost identical to the effect of the *CCR5-Δ32* allele. The protective effect was more modest among seroprevalent patients, for whom the timing of HIV-1 infection was less well defined. As with *CCR5-Δ32* heterozygotes, persons with the *CCR2-64I* allele had lower HIV-1 RNA levels. This finding could explain the protective effect of *CCR2-64I*, but the reason that patients with this allele maintain lower viral levels remains to be determined. The protective *CCR5-Δ32* and *CCR2-64I* alleles are relatively common. In the studied populations, approximately one third of the patients of European descent carried at least one of the two protective alleles, and 28% of the patients of African descent carried the *CCR2-64I* allele.

Our meta-analysis indicates that *SDF-1 3′A* homozygosity does not retard HIV-1 disease progression, either early or late in the course of HIV-1 infection. All of the summary relative hazard estimates were close to the null value, and the 95% CIs, especially in the seroprevalent cohorts, seemed to rule out the possibility that *SDF-1 3′A* homozygosity confers any clinically meaningful protection. The finding in one previous study (31) of a protective effect for *SDF-1 3′A* homozygotes may have been due to chance.

To avoid bias, we attempted to include all active research teams in our meta-analysis, and we know of only one large study that did not participate. The nonparticipating study (19), which included 1090 patients of European and African descent with HIV-1 infection, previously reported a disease-retarding effect for *CCR5-Δ32* and for *CCR2-64I* and suggested an acceleration of disease progression (rather than protection) for *SDF-1 3′A* homozygotes. Because the results of that study are generally consistent with our meta-analytic findings, inclusion of the study in our meta-analysis probably would not have changed our conclusions.

Our meta-analysis comprised patients who acquired HIV-1 through various modes, including homosexual transmission, treatment with blood products, and drug injection, and this diversity enhances the generalizability of our findings. Most cohorts contained patients who were infected by a single mode of transmission. In general, we did not discern differences in the strength of the observed associations according to mode of transmission, but the protective effects for *CCR5-Δ32* and *CCR2-64I* were generally not observed in the cohorts of injection drug users. We cannot determine whether this reflects a genuine difference or a chance finding.

We obtained generally similar results between seroconverter and seroprevalent patients. Seroprevalent co-

Table 3. **Summary of Key Findings**

Genotype	Genotype Frequency (Ancestry), %	Relative Hazard for AIDS (95% CI)	
		Seroconverters	Seroprevalent Patients
CCR5-+/CCR5-Δ32	16 (European)	0.74 (0.56–0.97)	0.70 (0.54–0.91)
CCR2-+/CCR2-64I or *CCR2-64I/CCR2-64I*	17 (European)	0.75 (0.59–0.97)	0.87 (0.75–1.01)
	28 (African)	0.81 (0.38–1.75)	1.02 (0.56–1.83)
SDF-1 3′A/SDF-1 3′A	5 (European)	0.99 (0.44–2.23)	1.03 (0.80–1.34)

CCR5-Δ32 heterozygosity and *CCR2-64I* heterozygosity or *CCR2-64I* homozygosity were associated with delayed progression to AIDS in patients with HIV-1 infection. No consistent effect was seen for *SDF-1 3′A* homozygosity.

CCR5-Δ32 heterozygosity and *CCR2-64I* heterozygosity or *CCR2-64I* homozygosity were associated with delayed progression to death in patients with HIV-1 infection. The *CCR5-Δ32* and *CCR2-64I* alleles had no clear protective effect in protracting survival after the diagnosis of AIDS.

The effect of the *CCR5-Δ32* and *CCR2-64I* alleles may be mediated, at least in part, by their effect on HIV-1 replication (as reflected in a lower HIV-1 RNA level).

The following is a potential causal pathway for the effect of the *CCR5-Δ32* and *CCR2-64I* alleles:
favorable genotype → reduced HIV-1 replication (lower RNA level) → slower loss of CD4 cells → lower risk for AIDS and death

hort studies are most informative about events late in the course of HIV-1 disease (for example, survival after AIDS onset), such as the postulated effect of the *SDF-1 3′A* allele (31). However, seroprevalent cohort studies have two clear limitations. First, they tend to exclude rapid progressors and, therefore, fail to fully capture the early dynamics of the disease. Second, for several reasons, seroprevalent patients who undergo genotyping may differ from those who do not. In this regard, rapid progressors were overrepresented among seroprevalent patients who had undergone genotyping in the Multicenter AIDS Cohort Study (MACS) and were underrepresented among seroprevalent patients who had undergone genotyping in the Multicenter Hemophilia Cohort Study (MHCS). In MHCS, patients with rapid disease progression were less likely to undergo genotyping because they were less likely to have had an archived specimen suitable for DNA extraction. Conversely, in MACS, sampling for genotyping had been guided partly by preliminary case–control analyses in which case-patients were rapid progressors. Consequently, a greater number of rapid progressors underwent genotyping in that cohort. In cohorts of seroconverters, typically all available patients underwent genotyping. For that reason, seroconverter data are less likely to suffer from selective sampling.

The potential role for determining the host genotype in patients with HIV-1 infection in clinical practice remains to be determined. We have demonstrated that the effects of the *CCR5-Δ32* and *CCR2-64I* alleles appear to be mediated, at least in part, through the HIV-1 RNA level, which is obtained routinely in patients with HIV-1 infection to assess prognosis (41–43) and response to treatment. Preliminary evidence suggests that chemokine receptor alleles may also influence the response to antiretroviral therapy (44, 45). If those findings are confirmed, testing for chemokine receptor genetic alleles may prove useful for identifying patients at increased risk for viral suppression failure while receiving antiretroviral therapy.

The marriage of epidemiology and molecular genetics promises to be highly informative (46), but individual epidemiologic studies may lack the statistical power needed to firmly establish associations for genetic differences that have modest effects. Such genotypes are of interest because they may, in the aggregate, play an important role in many common diseases (47). On the other hand, the number of alleles in the human genome ensures that statistically significant associations sometimes will be found by chance, even in investigations restricted to biologically plausible candidates. Meta-analysis of individual-patient data offers a way to examine potentially important genetic associations for a wide range of diseases. The benefits of a meta-analysis of individual-patient data in genetic epidemiology include the ability to standardize databases and analyses, improve accuracy for time-to-event analyses, improve statistical adjustments for other variables, and promote international collaboration. The main disadvantage of a meta-analysis of individual-patient data is the considerable effort required to coordinate the study and create the database. In this meta-analysis, we have shown that alleles of two chemokine receptor genes have a strong, clinically meaningful protective effect against HIV-1 disease progression. In contrast, *SDF-1 3′A* homozygosity seems not to have a consistent protective or deleterious effect. Our study demonstrates that meta-analysis of individual-patient data may prove useful in the field of genetic epidemiology.

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