Stromal Cell–Derived Factor–1 Genotype, Coreceptor Tropism, and HIV Type 1 Disease Progression

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This study used a well characterized cohort of human immunodeficiency virus type 1 (HIV-1)–infected hemophiliacs to define the relationship between the *SDF1-3′A* allele, the plasma HIV-1 coreceptor tropism, and the natural history of HIV-1 disease. Subjects heterozygous or homozygous for the *SDF1-3′A* allele experienced higher rates of decline in $CD4^+$ T cell counts over time than did those without the allele ($P = .009$). Moreover, they had an increased risk of progression to acquired immunodeficiency syndrome and death, a relationship that persisted even when baseline plasma HIV-1 RNA levels and $CD4^+$ T cell counts or *CCR5Δ32* and *CCR2-64I* genotype were controlled for. This relationship was even stronger in a subgroup of subjects for whom tropism data were available. Subjects with the *SDF1-3′A* allele were also more likely to have detectable X4-tropic viruses ($P = .012$), and, when tropism was included in the survival analyses, the effect of the *SDF1-3′A* allele on disease progression was no longer significant. Therefore, the increased frequency of X4-tropic viruses in subjects carrying the *SDF1-3′A* allele may explain the observed adverse effect that this allele has on the natural history of HIV-1 disease.

The natural history of HIV-1 disease is heterogeneous and influenced by numerous virologic, immunologic, and host factors. HIV-1 infection is usually initiated by viruses that use the CCR5 coreceptor, referred to (on the basis of their biological phenotype) as non–syncytium-inducing viruses or (on the basis of their coreceptor tropism) as R5 viruses [1, 2]. During the course of infection, in approximately one-half of subjects, syncytium-inducing (SI) viruses—strains that use the CXCR4 coreceptor and are known as X4 viruses—will develop [1]. Although it is difficult to prove cause and effect, the emergence of SI or X4 viruses has been associated with both a precipitous decline in $CD4^+$ T cell counts and accelerated disease progression [3–7]. Little is known about why SI or X4 viruses develop in only a subset of individuals and what factors may contribute to the emergence of these strains.

During the last decade, there has been interest in the relationship between genetic factors and HIV-1 disease progression, which was recently summarized by O'Brien and Nelson [8]. Large deletions in *CCR5 (CCR5Δ32)*, a multisite allele of the *CCR5* promoter *(CCR5 P1)*, and a mutation in *CCR2, (CCR2-64I)* [9–12] have been associated with variable effects on HIV-1 disease progression. Homozygosity for *CCR5Δ32* provides near complete protection from infection [13], and heterozygosity has been associated with delayed disease progression. In contrast, *CCR5 P1* has been associated with accelerated disease progression in the absence of either *CCR5Δ32* or *CCR2-64I* [10]. Several studies have dem-

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onstrated that the *CCR2-64I* allele is also associated with delayed disease progression [11, 12], possibly as a result of the interaction between CCR2 and the CXCR4 receptor, resulting in reduced risk of development of SI or X4 viruses [14].

A polymorphism in the 3′ untranslated region of the gene encoding stromal cell–derived factor–1 (SDF-1), also known as CXCL12, is present at a variable frequency in different populations [15, 16]. SDF-1 is the natural ligand for CXCR4, and results of studies of the relationship between the presence of the *SDF1-3′A* allele and susceptibility to HIV-1 infection have varied: the largest study showed no protection [16], and another suggested a reduced risk of HIV-1 infection in Thai subjects [15]. Similarly, the effects on disease progression have been conflicting: some studies suggested that it is protective [16], others showed accelerated disease progression [17–20], and yet others did not detect any effect of the *SDF1-3′A* allele on the natural history of HIV-1 disease [21–23]. Finally, the effect that this polymorphism has on SDF-1 levels is not known: one early study proposed that levels may be increased [16], and another actually demonstrated lower levels in individuals homozygous for the *SDF1-3′A* allele [24]. The present study further evaluates the relationship between this polymorphism and plasma HIV-1 RNA levels, $CD4^+$ T cell counts, coreceptor tropism, and HIV-1 disease progression.

SUBJECTS AND METHODS

Study Population

The Hemophilia Growth and Development Study (HGDS) is a multicenter study in the United States that, between 1989 and 1990, enrolled a population-based cohort of 6–19-year-olds with hemophilia. The cohort included 207 HIV-1–infected study subjects who acquired HIV-1 infection through exposure to blood products, in most cases between 1982 and 1983, 6–8 years before study enrollment. Participants were followed for 7 years, up to ~15 years from the time of infection. The details of recruitment and the characteristics of this cohort have been reported elsewhere [25, 26]. The human-subjects committees of collaborating institutions approved the HGDS, informed consent was obtained from parents or legal guardians, and informed consent or assent was obtained from all participants, in compliance with the human-experimentation guidelines of the US Department of Health and Human Services.

The ethnic composition of the cohort—72% European American, 15% Hispanic, 11% African American, and 2% other—resembled that of the general hemophiliac population in the United States [27]. During the 7 years of follow-up, 0.48% of the HIV-1–infected cohort was lost to vital status follow-up. Although the study did not enroll individuals who died before recruitment, there is little other evidence of an introduced selection bias. At baseline and 6-month intervals, an assessment of medical history, physical examinations, and $CD4^+$ T cell counts were performed. Blood samples were processed within 24 h, for cryopreservation of cells, plasma, and serum. Antiretroviral therapy during the course of follow-up was prescribed at the discretion of the primary providers. Since only 9 subjects included in the analysis had been exposed to protease inhibitor–containing triple-drug therapy, and then only 3 had been exposed for >6 months, the effect of treatment on disease progression was minimal in this cohort.

Plasma HIV-1 RNA Level, *SDF1* Genotype, and Coreceptor Tropism

Plasma HIV-1 RNA levels were measured at baseline and annually, from stored specimens, at a central laboratory by use of the branched DNA assay (version 2.0; Versant HIV-1 RNA; Bayer Healthcare Diagnostics). Samples with undetectable levels of virus (<500 copies/mL) were retested by use of version 3.0 (lower limit of detection, 50 copies/mL) [28]. The *SDF1-3′A* allele was detected by use of a polymerase chain reaction (PCR) restriction fragment–length polymorphism assay that has been described elsewhere [16]. Presence of the *SDF1* genotype was determined for 204 of the 207 HIV-1–infected subjects in the cohort; results were not available for the remaining subjects, because of a lack of host DNA.

Plasma samples obtained closest to baseline, with HIV-1 RNA levels >500 copies/mL, were sent to ViroLogic for analysis of coreceptor tropism. The HIV-1 envelope coreceptor tropism assay was developed by modifying the phenotypic drug susceptibility assay initially developed for protease and reverse-transcriptase (RT) inhibitors [29, 30]. Pseudotyped HIV-1 viruses were generated by use of a genomic vector carrying a luciferase reporter gene together with expression vectors containing patient virus envelope genes amplified (by RT-PCR) from plasma HIV-1 RNA. Coreceptor tropism is defined as the ability of the recombinant viruses to infect U87 cells that have been engineered to express CD4 with either CCR5 or CXCR4. CCR5-tropic (R5), CXCR4-tropic (X4), and mixed or dual tropic (R5/X4) designations were verified by blockade of coreceptor-mediated infection by use of specific antagonists, with no distinction made between dual and mixed tropism.

Coreceptor tropism data were available for 126 of the 207 subjects in the cohort, with all but 1 having *SDF1* genotype data available as well ($n = 125$). Results of tropism studies were not available for the remainder of subjects, for a variety of reasons—including plasma HIV-1 RNA levels <500 copies/mL ($n = 23$), below which the tropism assay cannot be performed; inadequate stored specimens ($n = 18$); and the inability to amplify the envelope gene, for technical reasons, such as degraded RNA template leading to failed first-strand synthesis during RT-PCR, failure of primer annealing because of a mutation in one of the primer binding sites, and generation of an internal restriction site in the amplicon that subsequently gets cleaved

Table 1. Baseline characteristics of subjects from the Hemophilia Growth and Development Study (HGDS) cohort for whom *SDF1* genotype data were available and those for whom both *SDF1* genotype and coreceptor tropism data were available.

Characteristic	HGDS cohort for whom *SDF1* genotype date were available (n = 204)	Subset of HGDS for whom *SDF1* genotype and coreceptor tropism data were available (n = 125)
Age, mean (SD), years	13.1 (3.1)	13.0 (2.9)
SDF1-3′A allele frequency, %	18.4	18.8
$CD4^+$ T cell count, mean (SD), cells/μL	428 (319.6)	409 (310.4)
Plasma HIV-1 RNA level, mean (SD), $\log_{10}$ copies/mL	3.4 (0.77)	3.6 (0.63)

during the digestion step of the assay (n = 40). The tropism assay was performed on samples obtained as close to the date when the baseline specimen was obtained, as availability allowed; these samples were obtained during the first 12 months of enrollment for 79% of the subjects for whom tropism data were available.

Study Variables

$CD4^+$ T cell counts were measured every 6 months, and plasma HIV-1 RNA levels were measured annually. The baseline plasma HIV-1 RNA level represents the value at the time of the first available plasma sample from time of entry into the cohort. Participants were categorized as having progressed to AIDS if they met the 1987 Centers for Disease Control definition [31]. Of the 204 subjects for whom *SDF1* genotype data were available, 20 (9.8%) had an AIDS-defining condition at entry and were not included in the AIDS survival analysis. Ten (8.0%) of the 125 subjects for whom coreceptor tropism and *SDF1* genotype data were available had received a diagnosis of AIDS at the time of enrollment and were similarly not included in the analysis.

Statistical Analysis

SDF1 *genotype, plasma HIV-1 RNA level, $CD4^+$ T cell count, and coreceptor tropism.* Since there were few subjects homozygous for *SDF1-3′A*, analyses compared subjects with wild-type *(wt) SDF1* with subjects either heterozygous or homozygous for *SDF1-3′A*. The repeated measurements of plasma HIV-1 RNA levels and $CD4^+$ T cell counts were modeled by use of random-coefficient regression models [32]. Each subject's plasma HIV-1 RNA level and $CD4^+$ T cell count were modeled as linear functions of the time-varying age variable, with each subject having a different intercept and slope. The relationship between *SDF1* genotype and baseline plasma HIV-1 RNA level and $CD4^+$ T cell counts, as well as plasma HIV-1 RNA level and $CD4^+$ T cell count rate of change, was examined by use of approximate F tests in the regression models. In all the models, plasma HIV-1 RNA levels were $\log_{10}$ transformed, and absolute $CD4^+$ T cell counts were square-root transformed, to better comply with the model assumptions. In the subset of subjects for whom tropism data were available, Fisher's exact test was used to assess the relationship between *SDF1* genotype and the presence of X4 viruses.

SDF1 *genotype and clinical progression.* Cox proportional hazards models were used to examine the effects of *SDF1* genotype on progression to clinical AIDS and death in the presence of AIDS [31]. Both unadjusted and adjusted effects were assessed to examine the value of predicting survival on the basis of *SDF1* genotype alone and after baseline plasma HIV-1 RNA levels and $CD4^+$ T cell counts were controlled for, as well as for the presence of the *CCR5Δ32* and *CCR2-64I* mutations, which have previously been shown to be related to disease progression in the cohort, and coreceptor tropism [26]. Kaplan-Meier curves were also plotted, to provide a graphical comparison of time to progression to AIDS and death, by *SDF1* genotype.

RESULTS

The baseline characteristics of the subset of subjects for whom coreceptor tropism data were available were similar to those of the overall cohort (table 1), except that subjects with tropism, compared with those without tropism, had lower $CD4^+$ T cell counts (P = .28) and higher plasma HIV-1 RNA levels (P < .001). This is consistent with the fact that tropism data were often not available because plasma HIV-1 RNA levels were too low for successful amplification in the tropism assay. Overall, the *SDF1-3′A* allele frequency was 18.4%, with 7 subjects homozygous and 61 subjects heterozygous for this variant. Compared with the overall cohort, the proportion of subjects homozygous and heterozygous and the allele frequency were essentially the same in the subgroup for whom tropism data were available, as was the use of antiretroviral therapy. In the subset of subjects tested for plasma HIV-1 coreceptor tropism for whom *SDF1* genotype results were also available, there were 50 (40%) with R5/X4 viruses, 75 (60%) with only R5 viruses, and none with only X4 viruses. There was an increased fre-

quency (56%) of R5/X4 viruses in subjects with the *SDF1-3′A* allele, compared with those without it (32%) ($P = .012$).

The relationship between the presence of the *SDF1-3′A* allele and $CD4^+$ T cell counts and plasma HIV-1 RNA levels at baseline and change over time was assessed for the entire cohort, as well as for the subset for whom coreceptor tropism data were available (table 2). For the subset of subjects for whom tropism data were available, those with and without the variant allele were no different with regard to baseline $CD4^+$ T cell counts or antiretroviral use. However, there was a trend toward higher baseline plasma HIV-1 RNA levels in subjects carrying the *SDF1-3′A* allele ($P = .096$), albeit with no significant difference in the change in this measure over time. In contrast, there was a significantly greater rate of decline in $CD4^+$ T cell counts in subjects with the polymorphism ($P = .009$). Similar relationships for decline in $CD4^+$ T cell counts were seen in the subjects for whom coreceptor tropism data were available ($P = .006$); among these subjects, baseline plasma HIV-1 RNA levels were significantly higher in those with the *SDF1-3′A* allele than in the those with *wt SDF1* ($P = .023$) (table 2). When the model was adjusted for tropism in these subjects, there was a marked reduction in the significance of the relationship between the presence of the *SDF1-3′A* allele and baseline plasma HIV-1 RNA level ($P = .22$), as well as for decline in $CD4^+$ T cell count, with the *P* value decreasing from .006 to .045, which was seen even when antiretroviral use was controlled for or when only heterozygous subjects were analyzed.

There was an increased risk of progression to AIDS and death for subjects with the *SDF1-3′A* allele, as determined by Kaplan-Meier analysis (figure 1). By use of Cox proportional hazards models, we found that the hazard ratio (HR) for progression to AIDS in subjects with the *SDF1-3′A* allele was 1.75 (95% confidence interval [CI], 1.04–2.96; $P = .037$) and was minimally affected by the incorporation of baseline plasma HIV-1 RNA levels and $CD4^+$ T cell counts into the model (table 3). Since both *CCR5Δ32* and *CCR2-64I* polymorphisms have been shown to influence the natural history of HIV-1 disease, we also incorporated these variables into the model. This analysis demonstrated no significant change in the relationship between *SDF1* genotype and progression to AIDS and death. Once again, the results were minimally changed when the analyses were limited to subjects heterozygous for *SDF1-3′A* and when antiretroviral use was included in the model with plasma HIV-1 RNA levels and $CD4^+$ T cell counts (data not shown). The Kaplan-Meier analyses and Cox proportional hazard models performed in the subgroup for whom coreceptor tropism data were available also showed an increased risk of progression to AIDS and death; HRs in subjects with the *SDF1-3′A* allele were 2.75 (95% CI, 1.48–5.10; $P = .001$) and 2.01 (95% CI, 1.14–3.52; $P = .015$), respectively (figures 1 and 2 and table 3). This relationship was minimally changed by the inclusion of *CCR5* and *CCR2* genotypes into the model for progression to AIDS and death. Similarly, the relationship with progression to AIDS

Table 2. Baseline and change in $CD4^+$ T cell counts and plasma HIV-1 RNA levels in the entire Hemophilia Growth and Development Study (HGDS) cohort as well as in the subset for whom coreceptor tropism data were available, by the presence or absence of the *SDF1-3′A* allele.

Measure	Wild-type *SDF1*, mean (95% CI)[a]	*SDF1-3′A*,[b] mean (95% CI)[a]	*P*[c]
HGDS cohort ($n = 204$)			
$CD4^+$ T cell count, cells/μL			
Baseline[d]	347 (297–402)	364 (292–444)	.72
Percentage change from baseline per year	−7.4 (−5.9 to −8.8)	−10.8 (−8.7 to −13.0)	.009
Plasma HIV-1 RNA level, $\log_{10}$ copies/mL			
Baseline	3.31 (3.20–3.42)	3.48 (3.32–3.64)	.096
Change in $\log_{10}$ copies/mL/year	0.055 (0.032–0.078)	0.064 (0.029–0.098)	.69
HGDS subset for whom coreceptor tropism data were available ($n = 125$)			
$CD4^+$ T cell count, cells/μL			
Baseline[d]	352 (289–421)	309 (228–402)	.45
Percentage change from baseline per year	−8.1 (−6.3 to −10.0)	−12.8 (−10.0 to −15.6)	.006
Plasma HIV-1 RNA level, $\log_{10}$ copies/mL			
Baseline	3.48 (3.36–3.60)	3.70 (3.54–3.85)	.023
Change in $\log_{10}$ copies/mL/year	0.053 (0.023–0.082)	0.083 (0.034–0.13)	.27

[a] Mean baseline and rate of change of plasma HIV-1 RNA levels and $CD4^+$ T cell counts are the estimated intercept and slope in the random coefficient model, with modeling plasma HIV-1 RNA levels and $CD4^+$ T cell counts through time as a linear function of age and adjustment for *CCR2* and *CCR5* chemokine receptor genotype. CI, confidence interval.

[b] This includes subjects who were either heterozygous or homozygous for the *SDF1-3′A* allele.

[c] Value of the approximate *F* test comparing baseline and rate of change in plasma HIV-1 RNA levels and $CD4^+$ T cell counts between *SDF1* genotype group.

[d] Estimates obtained by back-transforming (i.e., squaring) the original estimates, which were in the square-root scale.

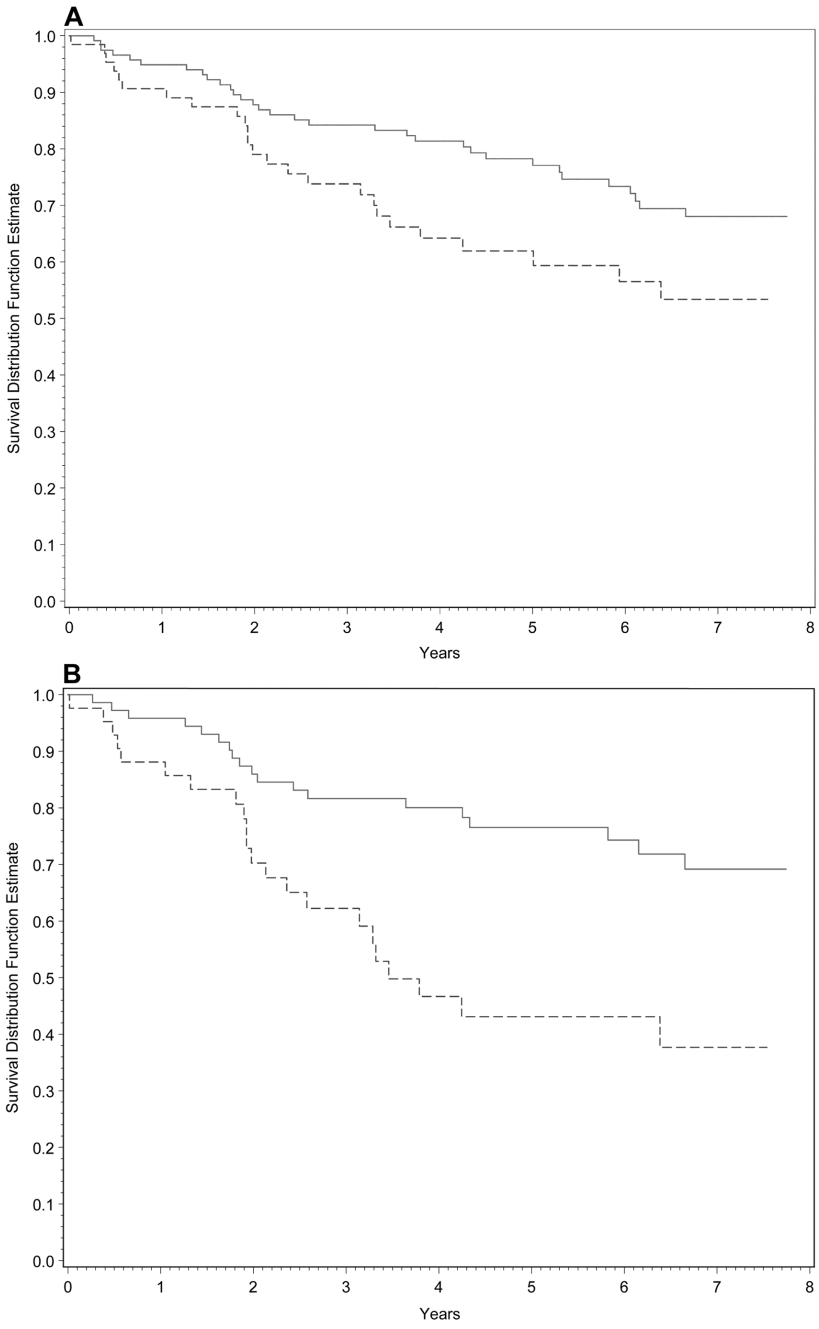

Figure 1. Kaplan-Meier analysis for progression to clinical AIDS by *SDF1* genotype in subjects who had not received a diagnosis of AIDS at baseline in the Hemophilia Growth and Development Study cohort ($n = 184$) *(A)* and the subset of study participants for whom coreceptor tropism data were available ($n = 115$) *(B). Dotted line,* wild-type *SDF1; broken line,* subjects homozygous or heterozygous for the *SDF1-3′A* allele.

persisted when baseline plasma HIV-1 RNA levels and $CD4^+$ T cell counts were included in the models (table 3).

Since subjects with the *SDF1-3′A* allele appeared to be at an increased risk of disease progression and since this group has a higher frequency of R5/X4-tropic viruses, compared with the group with *wt SDF1*, it was of interest to assess how differences in tropism influenced the effect of *SDF1-3′A* on disease progression. In fact, similar to what was seen for decline in $CD4^+$ T cell counts, after adjustment for tropism was made, the relationship weakened: the HR for progression to AIDS by *SDF1* genotype decreased from 2.75 to 1.68, and the relationship was no longer statistically significant ($P = .115$) (table 3). Again, none of the results related to disease progression were changed when antiretroviral use at baseline was included in the models or when the analyses were limited to subjects heterozygous for the *SDF1-3′A* allele (data not shown).

Table 3. Cox proportional hazard models for *SDF1* genotype, predicting progression to clinical AIDS and death in the presence of AIDS.

Group, model	Progression to AIDS		Progression to death	
	HR (95% CI)	*P*	HR (95% CI)	*P*
HGDS cohort, no. of subjects	184[a]		204[b]	
Unadjusted model	1.75 (1.04–2.96)	.037	1.68 (1.05–2.68)	.031
Model adjusted for baseline HIV-1 RNA levels and $CD4^+$ T cell counts	1.71 (0.99–2.93)	.053	1.64 (1.01–2.66)	.047
HGDS tropism, no. of subjects	115[c]		125[d]	
Unadjusted model	2.75 (1.48–5.10)	.001	2.01 (1.14–3.52)	.015
Model adjusted for baseline HIV-1 RNA levels and $CD4^+$ T cell counts	2.22 (1.16–4.23)	.016	1.48 (0.83–2.64)	.186
Model adjusted for coreceptor tropism	1.68 (0.88–3.21)	.115	1.37 (0.77–2.43)	.283

NOTE. CI, confidence interval; HGDS, Hemophilia Growth and Development Study; HR, hazard ratio.

[a] Subjects for whom *SDF1* genotype data were available and who did not meet the 1987 Centers for Disease Control (CDC) case definition for AIDS at baseline.

[b] Subjects for whom *SDF1* genotype data were available.

[c] Subjects for whom both *SDF1* genotype and coreceptor tropism data were available and who did not meet the 1987 CDC case definition for AIDS at baseline.

[d] Subjects for whom both *SDF1* genotype and coreceptor tropism data were available.

DISCUSSION

There has been divergence in the results of studies assessing the effect that the *SDF1-3′A* allele has on HIV-1 disease [16–23, 33]. Although the present study has focused on only one of many host genetic factors that might influence the natural history of HIV-1 disease, it has shown that, in the HGDS cohort, this allele (in heterozygous and homozygous subjects) was associated with more-rapid decline in $CD4^+$ T cell counts and accelerated disease progression. Moreover, this genetic variant was associated with an increased likelihood of having detectable X4 viruses, and the results have suggested that much of the effect of *SDF1-3′A* on disease progression may be related to the presence of this virus population.

A limitation of all cohort studies is the numerous confounding variables, such as differences in the characteristics of the study populations, the duration of follow-up, and the influence of antiretroviral therapy. In fact, a possible explanation for the divergent results, compared with those from other studies, may relate to the observation that the protective effect on disease progression occurs early [16]. Since the HGDS enrolled hemophiliacs in 1989 and 1990 who had been infected ~6–8 years before, early protective effects of the *SDF1-3′A* allele could have been missed, although an effect to accelerate disease progression that may predominate later during the course of disease might be more apparent. Therefore, cohorts with large seroincident groups may show protection, whereas cohorts that include a mix of subjects during the early and later years of infection may show no overall effect on disease progression. Consistent with this is the fact that, in the present study, increased risk of disease progression associated with the *SDF1-3′A* allele became evident only after the first few years of follow-up, ~9–10 years after the time of infection (figures 1 and 2).

Potential biological explanations for the effect of the *SDF1-3′A* allele on the natural history of HIV-1 disease has been explored by several groups. One study showed that subjects with the *SDF1-3′A* allele had decreased SDF-1 levels [24]; another showed that lower plasma SDF-1 levels were associated with an increased frequency of SI viruses [34]. Therefore, the *SDF1-3′A* allele may either causally or through positive linkage disequilibrium with causal alleles in or near *SDF1* result in decreased SDF-1 expression that may either facilitate the emergence or enhance the pathogenicity of SI or X4 viruses. If true, this effect is likely to be most prominent during the later years of infection, when X4 viruses tend to emerge, and less relevant during the early years, when R5 viruses drive much of disease pathogenesis. Although most studies have not demonstrated a relationship between the *SDF1* genotype and the presence of SI viruses [17, 18, 35–38], all have been relatively small, have used biological phenotypes predominantly from cell-associated virus cultured in vitro, and had varied patient populations. In contrast, in our study, we detected tropism by use of molecular methods on plasma virus in subjects during the later years of infection, when X4 viruses may have a greater influence on the natural history of HIV-1 disease. The importance of our observation is further supported by the data showing that the inclusion of tropism in the models resulted in a marked decrease in the HR for progression to AIDS and death (table 3). These results suggest that the effect that the *SDF1* genotype has on the presence of X4 virus in plasma may well be driving the observed increased risk of disease progression. If presence of the *SDF1-3′A* allele is associated with lower plasma SDF-1 levels, delayed disease progression during early infection may relate to the in vitro observation by Marechal et al. [39] that SDF-1 increases *tat* transactivation of R5 viruses, viruses that predominate during the early years of infection.

There are several limitations of the present study, including that antiretroviral assignment was at the discretion of the provider and tropism data were not available for all subjects. Al-

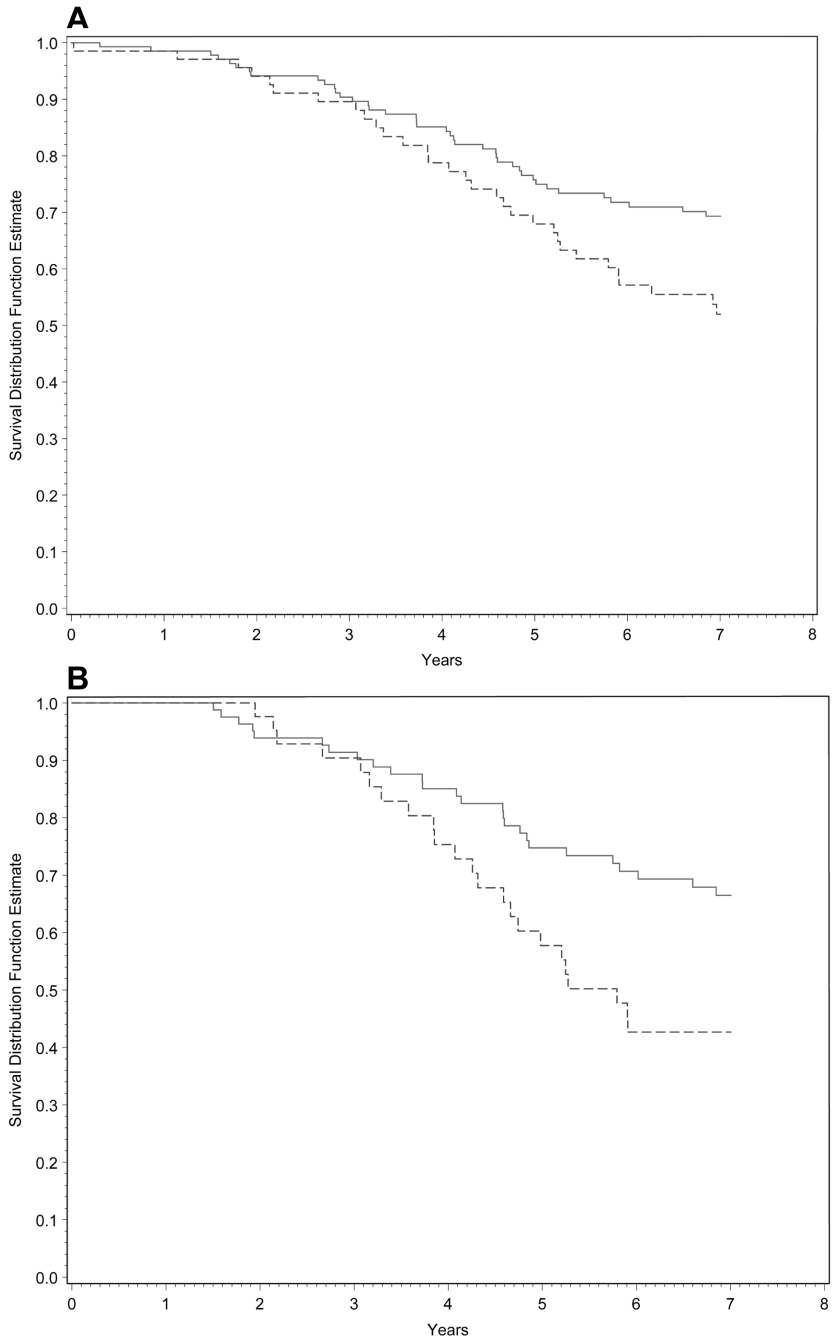

Figure 2. Kaplan-Meier analysis for progression to death in the presence of AIDS by *SDF1* genotype in the Hemophilia Growth and Development Study cohort ($n = 204$) *(A)* and the subset of study participants for whom coreceptor tropism data were available ($n = 125$) *(B). Dotted line,* wild-type *SDF1; broken line,* subjects homozygous or heterozygous for the *SDF1-3′A* allele.

though an effect of antiretroviral therapy cannot be excluded, it seems unlikely, in light of the limited use of therapy at baseline and of potent therapy over time. Furthermore, the results were not changed when antiretroviral use was included in the models of HIV-1 disease progression (data not shown). The lack of tropism data would not have influenced the observations relating *SDF1* genotype to HIV-1 disease progression seen in the entire cohort. In contrast, the analyses suggesting that the *SDF1* genotype's effect on disease progression is mediated by its relationship with tropism could have been influenced by the lack of data on the entire cohort. Nevertheless, this too seems unlikely, since subjects for whom tropism data were available were quite similar to subjects for whom tropism data were not available, including the use of antiretroviral therapy and the *SDF1-*

3′A allele frequency. Moreover, multiple-imputation analysis was applied to impute the missing tropism data by use of baseline plasma HIV-1 RNA levels, $CD4^+$ T cell counts, antiretroviral use, *SDF1* genotype, and other variables. The imputed tropism values were then included in the analysis of decline of $CD4^+$ T cell counts and disease progression, with little change seen in the outcome of the analyses (data not shown).

The strength of the present observation is that it comes from a single, well-characterized cohort, and the relationship between *SDF1* genotype and longitudinal decline in $CD4^+$ T cell counts (table 2) was consistent with the survival data (figures 1 and 2 and table 3). Moreover, the tropism data provide a plausible biological explanation for the clinical observations. Although most previous studies have focused on the effect that *SDF1-3′A* homozygosity has on the natural history of HIV-1 disease, the present study has demonstrated a significant association between heterozygosity for the *SDF1-3′A* allele and accelerated disease progression. A potential explanation for this is that the HGDS cohort was restricted to subjects in the later years of disease, which excludes the early effects of this allele on disease progression and enrichment for subjects who would experience enhanced disease progression associated with the *SDF1-3′A* allele. Finally, these observations add to other data suggesting that genetic markers that might influence levels of the natural ligand for coreceptors might influence the natural history of HIV-1 disease [40]. Further studies to define how cytokines and cytokine expression might influence the natural history of HIV-1 disease could lead to novel therapeutic strategies in the future.

HEMOPHILIA GROWTH AND DEVELOPMENT STUDY

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