Open access • Journal Article • DOI:10.1097/00002030-199809000-00001

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Published on: 18 Jun 1998 - AIDS (Lippincott Williams and Wilkins)

Topics: Simian immunodeficiency virus and Virus

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DOI
10.1097/00002030-199809000-00001

Publication date
1998

Published in
AIDS

The role of a stromal cell-derived factor-1 chemokine gene variant in the clinical course of HIV-1 infection

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Background: A G-to-A transition in the 3′ untranslated region (UTR) of stromal cell-derived factor (SDF)-1 gene (*SDF1*-3′A) has recently been described, which in the homozygous state was associated with delayed disease progression.

Objective: To analyse the effect of the SDF-1 polymorphism on AIDS-free survival and survival after AIDS diagnosis, also in relation to viral phenotype.

Design: Retrospective longitudinal study among 344 homosexual HIV-1-infected men.

Results: A more rapid progression to AIDS (Centers for Disease Control and Prevention 1993 definition) was observed in *SDF1*-3′A/3′A subjects than in wild-type (*SDF1*-wt/wt) subjects (relative hazard, 1.75; $P = 0.07$). Using death as an endpoint, accelerated progression was no longer observed (relative hazard, 0.93; $P = 0.84$), suggesting a late protective effect of the *SDF1*-3′A/3′A genotype. Indeed, survival after AIDS diagnosis was significantly delayed in *SDF1*-3′A/3′A subjects (relative hazard, 0.40; $P = 0.02$). No effect of the *SDF1*-3′A/wt genotype on disease progression was observed. Interestingly, a higher frequency of Kaposi's sarcoma was observed as the AIDS-defining event among *SDF1*-3′A/3′A (40.0%) and *SDF1*-3′A/wt (30.6%) subjects than in *SDF1*-wt/wt subjects (17.0%). At the end of the study the total frequency of syncytium-inducing (SI) HIV-1 variants was lower in *SDF1*-3′A/3′A subjects (22.2%) than in *SDF1*-3′A/wt (32.5%) and *SDF1*-wt/wt subjects (40.5%), although not significantly. SDF-1 genotype did not influence the rate of evolution to SI HIV-1. Progression to AIDS after the emergence of SI HIV-1 was accelerated in *SDF1*-3′A/3′A subjects compared with the *SDF1*-wt/wt genotypic group (relative hazard, 4.04; $P = 0.06$).

Conclusions: In our study group, homozygosity for a G-to-A transition in the 3′ UTR of SDF-1 is associated with an accelerated progression to AIDS but a subsequent prolonged survival after AIDS diagnosis.

AIDS 1998, **12**:F85–F90

Keywords: HIV-1, stromal cell-derived factor-1, disease progression, Kaposi's sarcoma, viral phenotype, CD4 T cells

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Sponsorship: This study was financially supported by The Netherlands Foundation for Preventive Medicine (grant no. 28-2547), and was performed as part of the Amsterdam Cohort Studies on AIDS, a collaboration between the Municipal Health Service, the Academic Medical Centre, and the Central Laboratory of The Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands.

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Date of receipt: 18 February 1998; revised: 17 March 1998; accepted: 25 March 1998.

Introduction

G-protein-coupled seven-transmembrane receptors have been identified as coreceptors for HIV-1. Syncytium-inducing (SI) T-cell line-adapted HIV-1 variants utilize CXC-chemokine receptor (CXCR)-4, macrophage-tropic non-SI (NSI) HIV-1 variants use CC-chemokine receptor (CCR)-5, and primary SI HIV-1 variants can use both receptors to enter human cells [1–6]. Other chemokine receptors including CCR-2b and CCR-3 can function as coreceptors for a minority of viruses [4,5,7]. A 32 base-pair deletion (Δ32) in the *CCR-5* gene has been associated with reduced HIV-1 transmission risk and delayed disease progression [8–14]. In addition, a Val→Ile switch in the first transmembrane domain of CCR-2b (CCR-2b 64I) has also been associated with a delayed disease progression [15] (unpublished data).

The natural ligands for CCR-5, the β-chemokines RANTES, macrophage inflammatory protein (MIP)-1α, and MIP-1β, can inhibit replication of NSI HIV-1 variants [16]. Stromal cell-derived factor (SDF)-1, the natural ligand for CXCR-4 [17,18], can interfere with infection of SI HIV-1 [17–19]. Recently, a polymorphism in an evolutionary conserved segment of the 3′ untranslated region (3′UTR) of the SDF-1 structural gene transcript (*SDF1*-3′A) was described. Persons homozygous for this mutation had a significantly delayed progression to AIDS and were even more strongly protected from death [20]. It was hypothesized that the *SDF1*-3′A mutation could result in increased SDF-1 production, resulting late in infection in strong competition with SI HIV-1 variants at the CXCR-4 receptor level.

Here, we analysed the effect of the *SDF1*-3′A polymorphism in 344 participants of the Amsterdam cohort on AIDS-free survival and survival after AIDS diagnosis, also in relation to the presence or absence of SI HIV-1 variants. In addition, we studied the prevalence and the rate of evolution to SI HIV-1 variants.

Subjects and methods

Study population

The study population was the same as described previously [14]. Briefly, between October 1984 and March 1986, 961 asymptomatic homosexual men were enrolled in a prospective study on the prevalence and incidence of HIV-1 infection and the risk factors for AIDS. In the first serum sample taken, 728 men tested negative for HIV-1 antibodies; 131 of these men underwent seroconversion during the study. The remaining 238 men were positive for HIV antibodies at entry between October 1984 and April 1985; five of these men refused to participate further, leaving 233 seroprevalent study cases. All participants were Caucasian. Epidemiological studies on the incidence of HIV-1 infection have shown that infection in seroprevalent homosexual men must have occurred on average 1.5 years before entry in the Amsterdam Cohort Studies. Therefore, the time of seroconversion for seroprevalent men was set at 1.5 years before study entry and 131 persons with a documented seroconversion and 233 seroprevalent individuals were studied as one study group (n = 364).

By 1 January 1996 (the censor date), 189 men had developed AIDS (median follow-up, 5.9 years; range, 0.6–12.3 years). From one of these subjects no DNA was available for SDF-1 genotyping, 94 men had not developed AIDS (median follow-up, 10.1 years; range, 0.3–13.7 years), and 81 men were lost to follow-up (median follow-up, 2.0 years; range, 0.6–12.5 years).

SDF-1 genotyping

DNA was available for SDF-1 genotyping for 344 (94%) of out 364 men. Genomic DNA was isolated from cryopreserved peripheral blood mononuclear cells (PBMC; Qiagen blood kit, Qiagen, Hilden, Germany), and 100 ng of DNA was analysed by PCR with primers SDF 3′UTR-F (sense, 5′-CAGTCAAC CTGGGCAAAGCC-3′) and SDF 3′UTR-R2 (antisense, 5′-CCTGAGAGTCCTTTTGCGGG-3′). The G→A transition in *SDF1*-3′A alleles eliminates a *Msp*I site allowing the use of a PCR restriction fragment length polymorphism assay for rapid detection of SDF-1 genotypes [20]. Samples were amplified with 1 U *Taq* polymerase (Promega, Madison, Wisconsin, USA) in the buffer provided, with a final $MgCl_2$ concentration of 2 mmol/l. Conditions of PCR comprised 5 min denaturation at 94°C, 35 cycles of 1 min at 94°C, 1 min at 50°C, and 1 min at 72°C, and 5 min elongation at 72°C in a Biometra Uno II thermocycler (Biometra, Göttingen, Germany). PCR products were subjected to restriction analysis with *Msp*I for 2 h at 37°C (Gibco BRL, Gaithersburg, Maryland, USA) and analysed on a 1.5% agarose gel, yielding a 101- and a 193-base-pair product in the case of a SDF-1 wild-type allele (*SDF1*-wt) and a 294 base-pair product in the case of *SDF1*-3′A.

Immunological and virological assays

Enumeration of CD4+ T cells was performed every 3 months using flow cytofluorometry. Cocultivation of HIV-1-positive PBMC with MT-2 cells was performed to detect SI HIV-1 variants [21]. Time of SI conversion was the calculated midpoint between the last SI-negative and first SI-positive sample.

Statistical analysis

Kaplan–Meier and Cox proportional hazard analyses were performed to study the effect of SDF-1 genotype on disease progression in HIV-1-infected individuals.

The following were considered endpoints for analysis: (i) AIDS according to the 1987 Centers for Disease Control and Prevention (CDC) definition [22], (ii) AIDS according to the 1993 CDC definition, thus including CD4+ T-cell counts below 200×10^6/l as an AIDS-defining event [23], and (iii) death. Kaplan–Meier analyses were also used to estimate the cumulative incidence of conversion to SI HIV-1 in relation to *SDF-1 genotype. The duration of AIDS*-free survival in relation to SDF-1 genotype for the period during which only NSI HIV-1 variants were present (conversion to SI HIV-1 was used as a censor criterion), or for the period after the emergence of SI variants, were analysed separately. Significance in survival analysis was determined by the log-rank and log-likelihood tests.

The Mann–Whitney U test was used to compare CD4 T-cell decline and CD4 T-cell count. Fisher's exact test was used to compare the frequency of SI HIV-1 and the frequency of Kaposi's sarcoma among the SDF-1 genotypic groups. All analyses were performed using SPSS release 7.5 (SPSS, Inc. Chicago, Illinois, USA).

Results

SDF-1 genotype distribution

The *SDF1*-3′A polymorphism was studied in 344 subjects enrolled in the Amsterdam Cohort Studies. In this study group, 12 (3.5%) subjects were homozygous (*SDF1*-3′A/3′A) and 95 (27.6%) subjects were heterozygous (*SDF1*-3′A/wt) for the SDF-1 3′A mutation. The remaining 237 (68.9%) subjects had a SDF-1 wild-type (*SDF1*-wt/wt) genotype, resulting in an allelic frequency of 0.173. Genotype distribution was comparable for the seroincident and seroprevalent cases.

SDF-1 genotype and clinical course of HIV-1 infection

Kaplan–Meier and Cox proportional hazard analysis were used to examine the role of the SDF-1 polymorphism in the clinical course of HIV-1 infection, using AIDS [22,23] or death as an endpoint. In contrast to the reported protective effect associated with the *SDF1*-3′A/3′A genotype, progression to AIDS was accelerated in *SDF1*-3′A/3′A subjects compared with *SDF1*-wt/wt subjects in our study group: relative hazard (RH) was 1.75 ($P = 0.07$) for AIDS according to the 1993 CDC definition (Fig. 1a; Table 1) and 1.30 ($P = 0.42$) for AIDS according to the 1987 CDC definition (Fig. 1b; Table 1). Comparable results were obtained when seroprevalent and seroincident cases were analysed separately (data not shown).

In agreement with a more rapid progression to AIDS, the group of *SDF1*-3′A/3′A carriers had a more rapid (although not significant) CD4+ T-cell decline (median decline, 80×10^6/l per year versus 57 and 69×10^6/l per year for *SDF1*-3′A/wt and *SDF1*-wt/wt genotypic groups, respectively) and a somewhat higher mean CD4+ T-cell count at AIDS diagnosis (according to the 1987 CDC definition; 240, 125, and 191×10^6/l for *SDF1*-3′A/3′A, *SDF1*-3′A/wt and *SDF1*-wt/wt carriers, respectively).

Kaposi's sarcoma is an AIDS-defining event that can occur at relatively high CD4+ T-cell counts. Interestingly, we observed a higher frequency of Kaposi's sarcoma as the AIDS-defining event among *SDF1*-3′A/3′A (40.0%, n = 10; $P = 0.09$) and *SDF1*-3′A/wt subjects (30.6%, n = 49; $P = 0.06$) than in *SDF1*-wt/wt subjects (17.0%, n = 129).

We no longer observed an accelerated progression associated with the *SDF1*-3′A/3′A genotype when death was used as an endpoint in our analysis (RH, 0.93; $P = 0.84$; Fig. 1c; Table 1), indicating that a

Table 1. Survival analysis for relative progression to different AIDS outcomes and conversion to syncytium-inducing (SI) HIV-1 variants by stromal cell-derived factor (SDF)-1 genotype using the Cox proportional hazard analysis.

			SDF1-3′A/wt versus *SDF1*-wt/wt		*SDF1*-3′A/3′A versus *SDF1*-wt/wt	
Endpoint	n	Events	RH (95% CI)	*P**	RH (95% CI)	*P**
AIDS						
CDC 1993	344	232	0.84 (0.63–1.14)	0.26	1.75 (0.95–3.22)	0.07
CDC 1987	344	188	0.84 (0.61–1.17)	0.30	1.30 (0.68–2.48)	0.42
Death	344	166	0.89 (0.63–1.26)	0.53	0.93 (0.45–1.90)	0.84
Death after AIDS						
CDC 1993	225†	164	0.88 (0.62–1.25)	0.47	0.40 (0.19–0.84)	0.02
CDC 1987	173†	164	0.99 (0.69–1.40)	0.94	0.49 (0.23–1.07)	0.07
SI conversion	279	106	0.73 (0.47–1.14)	0.17	0.46 (0.11–1.86)	0.28
AIDS						
Only non-SI present	267	79	1.08 (0.67–1.76)	0.75	2.52 (1.08–5.89)	0.03
After SI conversion	103‡	74	1.00 (0.58–1.73)	1.00	4.04 (0.95–17.17)	0.06

*Log-likelihood *P* value. †Lost to follow-up after AIDS diagnosis explains the discrepancy between the number of subjects in this analysis and the number of events in the analysis using AIDS as an endpoint. ‡Three subjects developed SI HIV-1 after AIDS diagnosis and were excluded from this analysis. wt/wt, wild-type; 3′A/wt, 3′A heterozygote; 3′A/3′A, 3′A homozygote; CDC, Centers for Disease Control and Prevention definition [22,23].

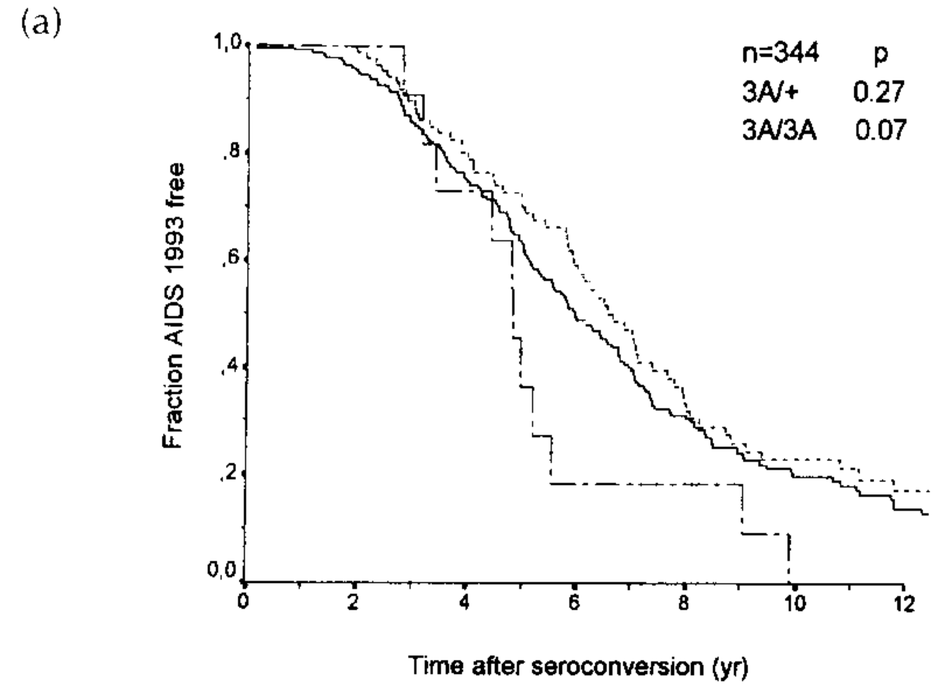

Fig. 1. Survival analyses for progression to AIDS and death. Kaplan–Meier plots are shown for time in years after seroconversion to (a) AIDS according to the Centers for Disease Control and Prevention (CDC) 1993 definition [23], (b) AIDS according to the CDC 1987 definition [22], and (c) death. Kaplan–Meier plots are shown for time in years to death after AIDS diagnosis according to (d) the 1993 CDC definition, and (e) the 1987 CDC definition. Number of patients and *P* values based on the log-rank test for survival of *SDF1*-3′A/wt (3A/+) and *SDF1*-3′A/3′A (3A/3A) subjects compared with *SDF1*-wt/wt subjects are shown. Solid lines indicate *SDF1*-wt/wt subjects, dotted lines indicate *SDF1*-3′A/wt subjects, and dashed lines indicate *SDF1*-3′A/3′A subjects.

late-stage protective effect associated with the *SDF1*-3′A/3′A genotype may compensate for the more rapid progression in the earlier phase of infection. To analyse this possibility, we examined the role of SDF-1 genotype on survival after AIDS diagnosis. Subjects carrying the *SDF1*-3′A/3′A genotype showed a significantly prolonged survival after AIDS diagnosis: from AIDS according to the 1993 CDC definition to death, RH was 0.40 ($P = 0.02$; Fig. 1d; Table 1), and from AIDS according to the 1987 CDC definition, RH was 0.49 ($P = 0.07$; Fig. 1e; Table 1). No effect on survival after AIDS diagnosis was observed for the *SDF1*-3′A/wt genotype (Fig. 1d, e; Table 1).

SDF-1 genotype and HIV-1 biological phenotype

At the end of the study, the total frequency of SI HIV-1 was lower in *SDF1*-3′A/3′A carriers (22.2%, n = 9) than in *SDF1*-3′A/wt carriers (32.5%, n = 80) or *SDF1*-wt/wt carriers (40.5%, n = 190), although this was not significant. Kaplan–Meier analysis with the emergence of SI HIV-1 as an endpoint criterion did

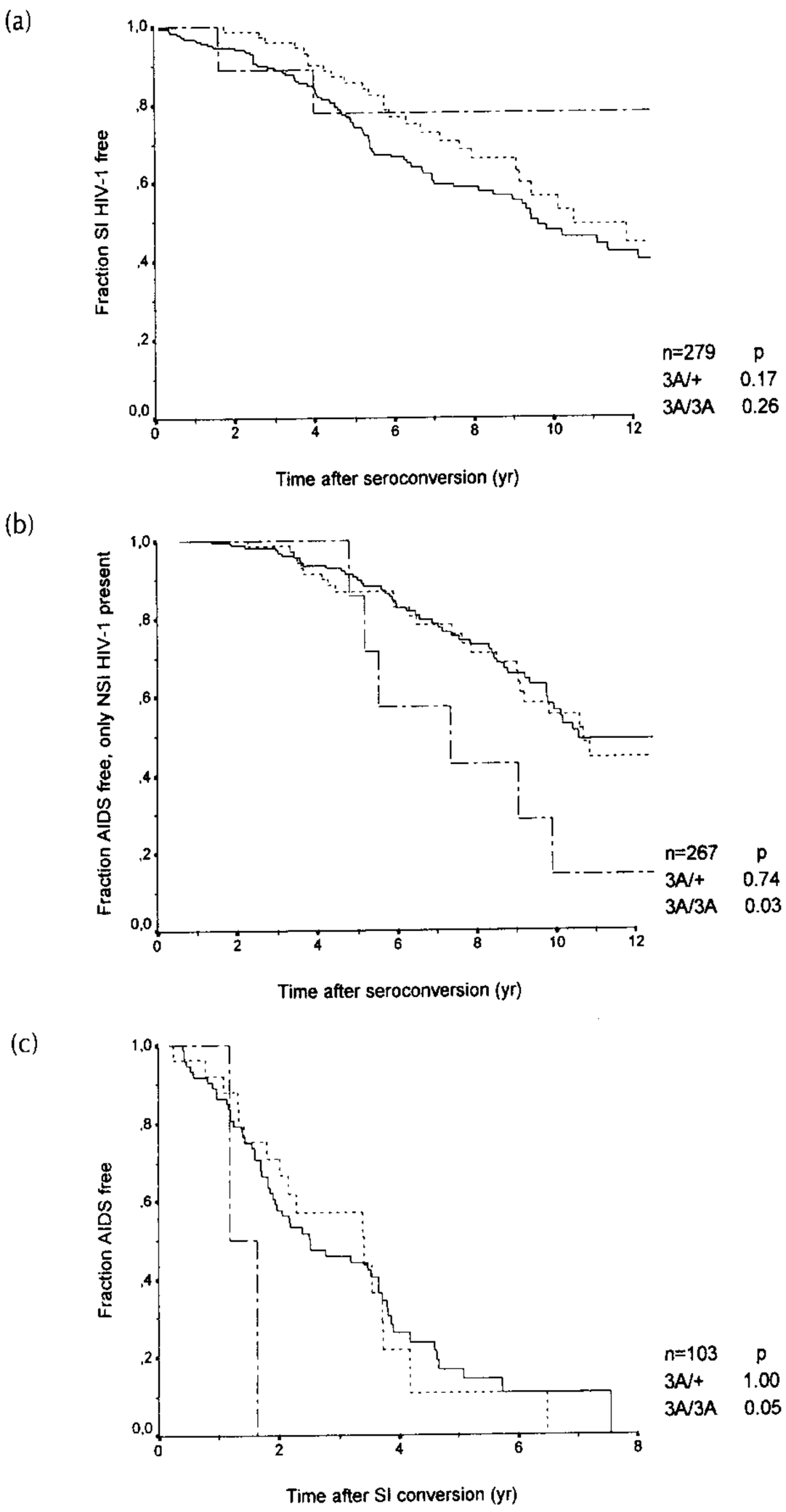

Fig. 2. Survival analysis for progression to syncytium-inducing (SI) HIV-1 and AIDS (Centers for Disease Control and Prevention 1987 definition) in the presence of non-SI (NSI) or SI HIV-1 variants. Kaplan–Meier plots are shown for time in years to (a) the emergence of SI HIV-1 variants, (b) AIDS diagnosis in the presence of only NSI HIV-1 variants (conversion to SI HIV-1 as a censor criterion), and (c) AIDS diagnosis after the emergence of SI HIV-1 variants. Number of patients and *P* values based on the log-rank test for survival of *SDF1*-3′A/wt (3A/+) and *SDF1*-3′A/3′A (3A/3A) subjects compared with *SDF1*-wt/wt subjects are shown. Solid lines indicate *SDF1*-wt/wt subjects, dotted lines indicate *SDF1*-3′A/wt subjects, and dashed lines indicate *SDF1*-3′A/3′A subjects.

not reveal a significant difference in the rate of evolution to SI HIV-1 in relation to SDF-1 genotype (*SDF1*-3′A/3′A: RH, 0.46; $P = 0.28$; *SDF1*-3′A/wt: RH, 0.73; $P = 0.17$; Fig. 2a; Table 1).

AIDS-free survival (AIDS according to the 1987 CDC definition) in the presence of only NSI HIV-1 variants, using SI conversion as a censor criterion, was significantly reduced for *SDF1*-3′A/3′A carriers compared with the *SDF1*-wt/wt genotypic group (RH, 2.52; $P = 0.03$; Fig. 2b; Table 1). The same phenomenon was observed when the period after SI conversion was analysed, with a more rapid disease progression for *SDF1*-3′A/3′A carriers (RH, 4.04; $P = 0.06$; Fig. 2c; Table 1). AIDS-free survival in *SDF1*-3′A/wt and *SDF1*-wt/wt carriers was indistinguishable, irrespective of the phenotype of the HIV-1 variants present (Fig. 2b, c). Survival after AIDS diagnosis was prolonged for *SDF1*-3′A/3′A carriers (Fig. 1d, e), and not restricted to the biological phenotype of the HIV-1 variants present (data not shown). However, a more detailed analysis in a larger study group may be required to obtain conclusive evidence on the role of *SDF1*-3′A polymorphism in relation to SI phenotype in the course of HIV-1 infection.

Discussion

Homozygosity for the G→A transition in the 3′UTR of the SDF-1 gene has been previously shown to be associated with delayed disease progression in HIV-1 infection [20]. In contrast to this observation, our results seem to show a more rapid progression to AIDS at a higher CD4+ T-cell count in individuals with a *SDF1*-3′A/3′A genotype, subsequently followed by an elongated survival time after AIDS diagnosis. Interestingly, we did observe a higher frequency of Kaposi's sarcoma as an AIDS-defining event among *SDF1*-3′A/3′A and *SDF1*-3′A/wt carriers, which makes it tempting to speculate that increased SDF-1 levels associated with a *SDF1*-3′A/3′A genotype may promote the development of Kaposi's sarcoma, thereby only expediting the moment of AIDS diagnosis.

The basis for the discrepancy in the influence of the *SDF1*-3′A/3′A genotype in the period from seroconversion to AIDS diagnosis between the study by Winkler *et al.* [20] and our study is unclear. The MACS cohort in their study, which showed an even stronger relative hazard for the *SDF1*-3′A/3′A genotype compared with their combined cohort study, contained an almost identical number of participants with a comparable estimate of the time of seroconversion to our study group. Moreover, the protective effect mediated by CCR-5 Δ32 heterozygosity and the CCR-2b 64I genotype as analysed in previous studies was the same for these cohorts [10,14,15] (unpublished data). Since the protective effect associated with SDF-1 genotype is most pronounced in a relatively late stage of infection one would not expect that an inaccurate estimation of the time of seroconversion of the

seroprevalent individuals included in our study group would influence the outcome of the survival analyses.

Even in a nested case–control study comparing HIV-1-infected progressors and long-term survivors (AIDS-free survival and stable CD4 cell counts above 400×10^6/l for more than 9 years) [14], we did not observe an increased frequency of the *SDF1*-3′A/3′A genotype in the long-term survivor group (data not shown), whereas in the study by Winkler *et al.* [20] the recessive protective effect of *SDF1*-3′A was more pronounced in individuals infected with HIV-1 for longer periods of time. Still, the low frequency of *SDF1*-3′A/3′A carriers in both studies may be responsible for the observed difference in the pre-AIDS period. Furthermore, studies in cohorts were different routes of transmission may apply are needed before general conclusions on the effect of SDF-1 genotype in the clinical course of HIV-1 infection are justified.

It was hypothesized that the *SDF1*-3′A/3′A genotype may upregulate SDF-1 expression, which at the CXCR-4 level could select against the emergence of T-cell-tropic SI HIV-1 strains in infected patients [21], but increased levels of SDF-1 may also compete for CXCR-4 with these SI variants after their appearance. Due to the low numbers of subjects, we could not exclude the possibility that evolution to SI HIV-1 variants was delayed in the *SDF1*-3′A/3′A genotypic group. However, since an accelerated disease progression was observed even in the *SDF1*-3′A/3′A carriers with SI variants, and prolonged survival after AIDS diagnosis was not restricted to carriers of SI HIV-1, competition for CXCR-4 coreceptor availability between SDF-1 and HIV-1 does not seem a likely explanation for the observed protection after AIDS diagnosis.

Revealing the mechanism responsible for prolonged survival after AIDS diagnosis will be necessary, especially when the accelerated progression to AIDS in the same individuals is considered, as observed in our study, in order to decide whether SDF-1 can form the basis for new therapeutics for application in AIDS patients.

Acknowledgements

The authors thank S. O'Brien for communication of unpublished results and F. Miedema and A. van't Wout for critical reading of the manuscript.

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