

Prevalence of SEN Viruses among Injection Drug Users in the San Francisco Bay Area

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SEN viruses (SENVs) are newly discovered bloodborne viruses that may play a role in liver disease. SENV strain prevalence was examined in a race/ethnicity-stratified sample of 531 injection drug users (IDUs) from the San Francisco Bay area. Weighted prevalences were as follows: SENV-A, 45.7%; SENV-C/H, 35.6%; and SENV-D, 10.3%. Infection was associated with a longer duration of injection drug use. SENV-A was more common in black subjects (adjusted odds ratio [OR_a], 4.37; 95% confidence interval [CI], 2.65–7.21) and Hispanic subjects (OR_a, 2.30; 95% CI, 1.38–3.85) than in white and non-Hispanic subjects, and the pattern was similar for SENV-C/H. For SENV-D, prevalence was similar in black and white subjects, but lower in Hispanic subjects; infection was less common among women than men (OR_a, 0.32; 95% CI, 0.15–0.71) and more common among men with at least 1 recent male sex partner than among heterosexual men (OR_a, 7.05; 95% CI, 2.62–18.95). SENV strains are common among San Francisco Bay area IDUs, and prevalence varies demographically within this group.

Recently, a novel single-stranded DNA virus of ~3800 nt was discovered in the serum of a human immunodeficiency virus type 1 (HIV-1)-infected injection drug user (IDU) from Italy [1–3]. This virus was designated “SEN virus” (SENV) on the basis of the initials of this patient. Phylogenetic analysis has shown the existence of 8 SENV strains, designated SENV-A to SENV-H [3]. These viruses belong to the *Circoviridae* family.

SENV strains appear to be common among people who are exposed to blood, but infrequent among those who are not. The prevalence of SENV-D or SENV-H among blood transfusion recipients in the United States was 30%, compared with 2%–3% among control subjects and blood donors [4]. Prevalence increased with the number of units transfused, and donor-recipient linkage demonstrated sequence homology for SENV. In

a recent study of IDUs from Baltimore, SENV-D was present in 32.7% of the subjects, and SENV-H was present in 37.5% [5].

Infection with SENV can be chronic. SENV-specific RNA (a possible replicative intermediate) has been recovered from liver tissue [4], and SENV has been shown to persist for up to 12 years in blood transfusion recipients. Reinfection with SENV strains also occurs. Wilson et al. [5] retested specimens from SENV-infected subjects after a median of 9.3 years. SENV-D was still present in 61.0% of subjects, although a nucleotide difference of 15% was present in ~75% of these IDUs, which indicated that they had become infected with a different strain of SENV-D. Similarly, about half the subjects who were repeatedly positive for SENV-H DNA had a different strain present after repeat testing [5].

The clinical impact of SENV infection is uncertain. In a study of blood transfusion-associated non-A–E hepatitis, 11 (92%) of 12 transfusion recipients who developed hepatitis had become infected with SENV after transfusion, compared with 55 (24%) of 225 recipients who did not develop hepatitis [6]. A study of Japanese patients found that SENV was more common in patients with acute or chronic liver diseases than in

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blood donors, although the investigators could not establish a causal relationship [7]. Therefore, it is possible that SENV causes acute hepatitis in some people who become infected with this virus. One study found that persons infected with SENV are less likely to respond to treatment for hepatitis C virus (HCV) [8], but this finding has not been confirmed [9]. Umemura et al. [9] found no evidence that SENV infection affected the severity or persistence of coexistent HCV infection.

Because there have been few epidemiologic studies of SENV strains, we evaluated the prevalence of SENV-A, SENV-D, and SENV-C/H strains in a diverse population of street-recruited IDUs from the San Francisco Bay area. We examined demographic associations and explored potential modes of transmission of these viruses.

SUBJECTS AND METHODS

Subjects. Subjects were IDUs enrolled in the Urban Health Study (UHS) during 1998–2000. Every month, UHS enrolls 200–225 IDUs from 1 of 6 inner-city San Francisco Bay area neighborhoods on a rotating basis [10]. Participants are interviewed (including questions about drug use and sexual behavior), provide a blood specimen, and are reimbursed. Overall, 2369 study participants were enrolled during 1998–2000, of whom 49% were black, 38% were white, and 7% were Hispanic; most of the remainder were Asian or Native American. In the present study, a stratified random sample of 531 participants was selected for SENV testing. Sampling was stratified by race/ethnicity to provide sufficient data for analysis in each of the 3 most common racial/ethnic groups. All Hispanic subjects were studied because only 131 were enrolled in the UHS sample, and 200 black subjects and 200 non-Hispanic white subjects were randomly selected (RANUNI SAS 8.0 [11]). The sampling was restricted to subjects who provided a plasma specimen of at least 4 mL. Plasma specimens were stored at -70°C until used.

Detection of SENV DNA. DiaSorin previously identified universal primers, NEW BCD 1S (sequence ID no. 115) and L 2AS (sequence ID no. 71), from sequences that are conserved among SENV strains [1]. To improve sensitivity, we developed modified primers designated NEW BCD 1S-2 [CCCAAAC(T/G/A)TTTGAAGAC(C/A)A(C/G)TGGTA] and NEW L 2AS [CC-TCGGTT(G/T)(C/G)AAA(G/T)GT(C/T)TGATAGTG]. Polymerase chain reactions (PCRs) were performed with a 50- μL mixture containing template, 160 μL of DNA extracted from 100 μL of plasma using QIAamp blood kit (Qiagen), gold PCR buffer with MgCl_2 , and 0.4 $\mu\text{mol/L}$ of each PCR primer, a 200- $\mu\text{mol/L}$ concentration of each deoxyribonucleoside triphosphate (dATP, dGTP, dCTP, and dTTP; Boehringer), and 1.25 U of AmpliTaq Gold DNA polymerase (Applied Biosystems). The reaction was performed in the GeneAmp PCR System 9700 (Applied Biosystems) without mineral oil. PCR consisted of a

preheating at 94°C for 10 min, 55 cycles of 94°C for 1 min, 55°C for 1 min, and 72°C for 1 min, followed by a terminal incubation period at 72°C for 9 min. PCR products were analyzed on 2% agarose gels.

PCR products were hybridized with SENV type-specific 5'-end biotinylated probes specific for conserved regions of each SENV strain that we examined. The SENV-A and SENV-H probes were slightly modified from the sequences in the DiaSorin patent. The NEW C probe was initially developed for this study to improve specificity and sensitivity, compared with that of the probe used in previous studies. The 4 probes we used were as follows: SENV-A, 5'-CCCCATGAAAGGGGAAGAGGCCTACACTGACTTT-3'; SENV-D, 5'-ATGATAGGCTTCCCYTTTAACTATAACCCA-3'; NEW C probe, 5'-CCCCTCCAGGTATTGCATGAAGAGTAT-TAC-3'; and SENV-H, 5'-CCAGTAATAGGCACTTCTGCTTTA-GAACAG-3'.

Streptavidin-coated black ELISA plates (Roche Molecular Biochemicals) were incubated overnight at 4°C with each biotinylated probe. The plates were washed, and 90 μL of hybridization solution and 10 μL of PCR amplified products denatured at 95°C for 5 min were added. The hybridization was performed for 1 h at 50°C for SENV-A and SENV-D probes or at 45°C for NEW C and SENV-H probes. The ELISA plates then were washed again, and antidigoxigenin antibodies conjugated to alkaline phosphatase were added. The mixture was incubated for 30 min at 37°C . Reactivity was detected by use of 0.25 mmol/L disodium 3-(4-methoxy-1,2-dioxetane-3,2'-(5'-chloro)tricyclo[3.3.1.1^{3,7}]decan}-4-yl)phenyl phosphate (CSPD) as substrate in 0.1 mol/L Tris-HCl and 0.1 mol/L NaCl (pH 9.5). The reaction was incubated at 37°C for 15 min. Chemiluminescence was measured by use of the 1450 Micro Beta PLUS scintillation counter (Wallac).

The cutoff points used to classify subjects for SENV infection status were determined by a 2-component normal mixture model method that has been described in detail elsewhere [12]. For each SENV strain, we calculated the mean of 2 measurements for the first 300 subjects who were tested. A mean of repeated measurements, rather than a single measurement, was used to reduce random error, but the repeated measurements were limited to the first 300 subjects on the presumption that the same magnitude of error was present for all observations. These mean values were log transformed and entered into a 2-component mixture model with constant mixing probabilities. The mixing proportions of the model correspond to the probability that the true, unknown infection status of a person is either "0" (uninfected) or "1" (infected). The cutoff for each assay was the point that minimized the overall misclassification rate, as determined from the fitted model. The cutoff points for the chemiluminescence readings were 4.75 for SENV-A, 4.54 for SENV-D, and 4.64 for SENV-C/H. On the basis of the dilution series of plasmid DNA containing an SENV PCR target

insert, the estimated lowest detection level for SENV DNA in these assays was 5 copies, which is the equivalent of 800 copies/mL in the original plasma specimen.

Serological assays. The presence of antibodies to hepatitis B virus (HBV) core antigen, HCV, and HIV-1 was determined by commercially available EIAs, as was the presence of HBV surface antigen.

Data analysis. To estimate the overall prevalence of each SENV strain in the UHS cohort, we weighted the race/ethnicity specific prevalence estimates by the sampling fraction for each group. To assess whether various demographic and behavioral risk factors influenced the prevalence of infection with the different SENV strains, we computed odds ratios (ORs) by fitting logistic regression models for infection status (PROC GENMOD; SAS 8.0) [11]. We calculated these ORs in 3 ways. Unadjusted odds ratios (ORs) were calculated for each of the 3 racial ethnic groups. Race/ethnicity-weighted unadjusted ORs, which were based on the initial sampling scheme so that they properly reflected risk in the overall UHS cohort, were calculated for other variables. We also calculated adjusted ORs (OR_a) that controlled for race/ethnicity, sex, neighborhood, age, and duration of injection drug use. In some separate models, we included sexual orientation and other factors, and stratified the analysis by sex. We also used logistic regression models to test for trends for duration of injection drug use and age. We classified as “homosexual/bisexual” any subject who either reported “homosexual” or “bisexual” as his or her sexual orientation or reported ever having a sex partner of the same sex.

RESULTS

Table 1 shows demographic and other descriptive variables for the 531 subjects. Overall, about three-fourths of the subjects were men. The participants’ age ranged from 19 to 82 years, with a median of 44 years (interquartile range [IQR], 37.5–49 years). Non-Hispanic white subjects were younger than Hispanic subjects, who tended to be younger than the black subjects. A similar pattern was seen for the duration of injection drug use, with non-Hispanic white subjects reporting the shortest time since onset of injection drug use. Nonetheless, almost two-thirds of the subjects had injected drugs for >20 years, and the median duration of drug injection was 24 years (IQR, 31–41 years). Most participants were exclusively heterosexual, but 38.1% of women and 18.7% of men met our definition of homosexual/bisexual. A high proportion of participants had evidence of HCV (92.8%) and HBV (76.0%) infection, and 10.0% were infected with HIV-1.

SENV-A DNA was present in specimens from 249 of the 531 samples, corresponding to a race/ethnicity-weighted prevalence of 45.7% (SD, 1.9%). The prevalence of SENV-A infection was similar in men and women (table 2), but the virus was more

Table 1. Demographic and other characteristics among injection drug users in the San Francisco Bay area, 1998–2000, by race/ethnicity.

Variable	White, non-Hispanic (n = 2200)	Black (n = 200)	Hispanic (n = 2131)
Neighborhood			
Bayview	13 (6.50)	23 (11.50)	4 (3.05)
Mission	35 (17.50)	23 (11.50)	61 (46.56)
Richmond	24 (12.00)	27 (13.50)	16 (12.21)
Tenderloin	70 (35.00)	36 (18.00)	28 (21.37)
Western Addition	51 (25.50)	25 (12.50)	11 (8.40)
West Oakland	7 (3.50)	66 (33.00)	11 (8.40)
Sex			
Female	55 (27.50)	53 (26.50)	26 (19.85)
Male	144 (72.00)	147 (73.50)	105 (80.15)
Age, years			
<30	35 (17.50)	5 (2.50)	15 (11.45)
30–39	63 (31.50)	25 (12.50)	29 (22.14)
40–49	75 (37.50)	113 (56.50)	55 (41.98)
≥50	27 (13.50)	57 (28.50)	32 (24.43)
Duration of IDU, years			
≤10	39 (19.70)	23 (11.79)	20 (16.00)
11–20	54 (27.27)	29 (14.87)	26 (20.80)
21–30	66 (33.33)	73 (37.44)	41 (32.80)
>30	39 (19.70)	70 (35.90)	38 (30.40)
Homosexual/bisexual^a			
Female	26 (47.27)	17 (33.33)	7 (28.0)
Male	41 (28.76)	16 (10.96)	16 (15.84)
Viral infections			
HBV	142 (71.00)	159 (79.90)	102 (77.86)
HCV	180 (90.00)	189 (94.97)	123 (93.89)
HIV-1	13 (6.50)	32 (16.00)	8 (6.11)

NOTE. Data are no. (%) of subjects. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV-1, human immunodeficiency type 1; IDU, injection drug use.

^a Subject stated “homosexual” or “bisexual” as sexual orientation or reported having had a sex partner of the same sex.

frequent in black subjects (62.5%) than in Hispanic subjects (47.3%), and more frequent in Hispanic subjects than in non-Hispanic white subjects (31.0%). The frequency of SENV-A infection tended to increase with duration of injection drug use ($P = .01$, unadjusted test for trend). Among men and women, the prevalence of SENV-A varied little by sexual orientation. Infection with other bloodborne viruses (HBV, HCV, HIV-1, SENV C/H, and SENV D) was more common in subjects who were infected with SENV-A than in those who were not.

We performed an adjusted analysis to determine whether confounding variables might explain these differences in SENV-A prevalence by race/ethnicity and duration of injection drug use. We included race/ethnicity and duration of injection drug use together with sex, age, and neighborhood in a single model.

Table 2. Weighted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for differences in prevalence of SENV virus (SENV) strains among injection drug users in the San Francisco Bay area (1998–2000), by selected characteristics.

Variable	SENV-A		SENV-C/H		SENV-D	
	Weighted ^a OR (95% CI)	Adjusted ^b OR (95% CI)	Weighted ^a OR (95% CI)	Adjusted ^b OR (95% CI)	Weighted ^a OR (95% CI)	Adjusted ^b OR (95% CI)
Sex						
Male	1.00 (referent)					
Female	1.11 (0.73–1.67)	1.09 (0.69–1.71)	1.11 (0.73–1.67)	0.91 (0.57–1.45)	0.26 (0.12–0.56)	0.32 (0.15–0.71)
Race/ethnicity						
White, non-Hispanic	1.00 (referent)					
Hispanic	2.00 (1.27–3.15)	2.30 (1.38–3.85)	1.63 (0.99–2.67)	1.70 (0.99–2.90)	0.57 (0.28–1.16)	0.43 (0.19–0.95)
Black	3.71 (2.45–5.61)	4.37 (2.65–7.21)	3.51 (2.28–5.42)	3.00 (1.82–4.92)	1.42 (0.84–2.38)	1.68 (0.90–3.13)
Age, years						
<30	1.00 (referent)					
>30–39	1.43 (0.87–2.35)	1.53 (0.67–3.48)	1.35 (0.80–2.28)	1.88 (0.76–4.67)	1.05 (0.55–2.00)	1.78 (0.50–6.20)
>40–49	1.41 (0.94–2.13)	1.22 (0.50–2.96)	1.27 (0.83–1.95)	1.46 (0.55–3.86)	0.80 (0.46–1.39)	1.10 (0.28–4.33)
≥50	1.41 (0.94–2.13)	0.94 (0.35–2.51)	1.27 (0.83–1.95)	1.16 (0.40–3.35)	0.80 (0.46–1.39)	1.42 (0.33–6.18)
Duration of IDU, years						
≤10	1.00 (referent)					
>11–20	2.93 (1.55–5.54)	2.90 (1.44–5.86)	1.46 (0.75–2.84)	1.23 (0.59–2.55)	1.00 (0.40–2.52)	0.97 (0.35–2.72)
>21–30	2.23 (1.24–4.01)	2.57 (1.22–5.39)	1.77 (0.97–3.24)	1.65 (0.78–3.49)	1.50 (0.67–3.36)	1.59 (0.56–4.52)
>30	2.79 (1.52–5.11)	3.65 (1.61–8.30)	1.80 (0.97–3.35)	1.86 (0.81–4.24)	2.10 (0.93–4.72)	1.93 (0.62–6.10)
Sexual orientation						
Female						
Heterosexual	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Homosexual/bisexual	1.64 (0.76–3.52)		1.10 (0.50–2.43)		0.42 (0.10–2.64)	
Male						
Heterosexual	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Homosexual/bisexual	0.88 (0.51–1.52)		0.85 (0.48–1.52)		1.73 (0.92–3.25)	
Viral markers						
HIV-1	2.71 (1.42–5.18)		2.17 (1.19–3.95)		1.71 (0.86–3.41)	
HCV	6.03 (2.27–16.00)		1.89 (0.83–4.31)		1.20 (0.45–3.18)	
HBV	2.30 (1.48–3.56)		1.25 (0.80–1.95)		2.00 (1.04–3.84)	
SENV-A	—		3.26 (2.21–4.83)		1.56 (0.95–2.33)	
SENV-C/H	3.27 (2.21–4.83)		—		1.41 (0.86–2.33)	
SENV-D	1.56 (0.95–2.58)		1.41 (0.86–2.33)		—	

NOTE. Test for trend: SENV-A (age: weighted, $P = .1$; adjusted, $P = .5$; and duration of IDU: weighted, $P = .01$; adjusted, $P = .01$); SENV-C/H (age: weighted, $P = .4$; adjusted, $P = .3$; and duration of IDU: weighted, $P = .05$; adjusted, $P = .07$); SENV-D (age: weighted, $P = .04$; adjusted, $P = .6$; and duration of IDU: weighted, $P = .02$; adjusted, $P = .2$). HBV, hepatitis B virus; HCV, hepatitis C virus; HIV-1, human immunodeficiency type 1; IDU, injection drug use.

^a Weighted by race/ethnicity on the basis of the initial sampling scheme; ORs for the racial/ethnic groups were unadjusted for in this analysis.

^b Adjusted for race/ethnicity, sex, neighborhood, age, and duration of IDU.

After adjustment for the other variables, the strength of the association between SENV-A and Hispanic and black race/ethnicity increased slightly, which indicated that these differences were not explained by these other demographic or behavioral factors. The effect of duration of injection drug use also persisted in the adjusted analysis ($P = .01$, test for trend).

SENV-C/H was less common than SENV-A (weighted prevalence, 35.6%; SD, 1.5%), but the 2 strains had some similarities in their distributions (table 2). SENV-C/H prevalence did not

differ significantly by sex, but was more common in black subjects (50.5%) and Hispanic subjects (32.1%) than in non-Hispanic white subjects (22.5%). SENV-C/H was somewhat more common in residents of the East Bay neighborhoods in West Oakland and Richmond than in the 4 other neighborhoods, all of which are located in San Francisco. In the race/ethnicity-weighted analysis, SENV-C/H was more frequent among subjects who had a longer duration of injection drug use ($P = .05$, test for trend), and who were infected with other

bloodborne viruses. Differences observed for SENV-C/H by race/ethnicity in the unadjusted analysis were consistent in the multivariate analysis. The pattern for duration of drug injection in the adjusted analysis was similar to that observed in the weighted analysis ($P = .07$, test for trend).

SENV-D (weighted prevalence, 10.3%; SD, 1.9%) was less prevalent than SENV-A or SENV-C/H, and its distribution differed from the other strains (table 2). SENV-D was much less common in women than men (OR, 0.26; 95% CI, 0.12–0.56), in contrast to SENV-A and SENV-C/H. Although black subjects (20.0%) were more likely to be infected with SENV-D than non-Hispanic white subjects (15.0%), the difference was less than for SENV-A or SENV-C/H. SENV-D was least common in Hispanic subjects (9.2%), in contrast to the intermediate rates for this group observed for SENV-A and SENV-C/H. Homosexual/bisexual men tended to have a higher prevalence than heterosexual men, which we had not observed for the other SENV strains. Older age was not associated with SENV-D prevalence in the weighted or adjusted analyses ($P = .6$, adjusted test for trend). Similar to the pattern for SENV-A and SENV-C/H, SENV-D prevalence increased with longer duration of injection drug use ($P = .02$, unadjusted test for trend). SENV-D infection was more common in participants who were infected with other viruses, but those relationships tended to be weaker than for SENV-A or C/H.

In the multivariate analysis, the association between SENV-D prevalence and sex was unchanged. After adjusting for other variables in an analysis restricted to men, those who met our definition of homosexual/bisexual men were ~70% more likely than heterosexual men to be infected with SENV-D (OR_s, 1.70; 95% CI, 0.87–3.33). When we compared the 31 men reporting at least 1 male sex partner in the past 6 months to the heterosexual men, this difference became much greater (OR_s, 7.05; 95% CI, 2.62–18.95).

DISCUSSION

SENV strains constitute a newly discovered group of viruses that have been implicated in blood transfusion-associated hepatitis. The potential role of these strains in chronic liver disease or other conditions remains to be elucidated. Among IDUs from the San Francisco Bay area, we found that infection with SENV strains was common and strongly associated with longer duration of injection drug use, which supports previous reports that SENVs are transmitted through blood. We also found that SENV infection prevalence varied by race/ethnicity and sexual orientation, even after we considered the subject's duration of injection drug use.

There were marked differences in the prevalence of SENV-A and SENV-C/H among members of the 3 racial/ethnic groups included in this study. Compared with non-Hispanic white IDUs,

black subjects were several times more likely to be infected with SENV-A and SENV-C/H. The prevalence of these strains among Hispanic participants was between those in the other 2 groups. The distribution of SENV-D differed from that for SENV-A or SENV-C/H, in that SENV-D prevalence was lowest among Hispanic subjects rather than the non-Hispanic white subjects. Our findings of higher rates of SENV infection among black IDUs are consistent with a report from Baltimore, where black IDUs were 5 times more likely to be infected with SENV-D and ~4 times more likely to be infected with SENV-H [5].

SENV-D was about 3 times more common in men than women. Furthermore, compared with other men, those who reported having sex with other men had an increased prevalence of SENV-D but not SENV-A or SENV-C/H. Men who reported at least 1 male sex partner in the past 6 months were more likely to be infected with SENV-D. Future studies should examine SENV prevalence among other groups of men who have sex with men, to determine whether these viruses can be transmitted sexually.

Our data, compared with those from the Baltimore study, indicate that SENV prevalence among IDUs also varies geographically. The prevalence of SENV-D was 3-fold higher among Baltimore IDUs (32.7%, compared with 10.3% in the present study), although San Francisco IDUs had, on average, a longer history of injection drug use and a higher prevalence of HCV, another common bloodborne virus.

The prevalence of the SENV strains that were detected by our PCR-based assays ranged >3-fold (SENV A, 45.7%; SENV C/H, 35.6%; and SENV D, 10.3%). Because almost all the subjects in this study were at very high risk for acquiring bloodborne infections, these data suggest that infectivity or clearance of SENV may vary between strains.

In summary, we found a high prevalence of infection with SENV strains among IDUs in San Francisco, as well as evidence that the frequency of these strains may vary demographically and geographically. The explanations for these differences are unknown, but they may result from interactions among behavioral, social, and biological factors [13, 14]. The pathogenicity and, therefore, the full public health importance of these viruses is unknown, but our data further demonstrate the high risk of bloodborne disease among IDUs. Interventions to prevent the further spread of bloodborne infections among IDUs would likely reduce the spread of SENV strains [15–17].

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