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# Risk Factors for Acute and Early HIV Infection Among Men Who Have Sex With Men (MSM) in San Diego, 2008 to 2014

## A Cohort Study

Martin Hoenigl, MD, Nella Green, MD, Sanjay R. Mehta, MD, and Susan J. Little, MD

**Abstract:** The objectives of this study were to identify risk factors associated with acute and early HIV infection (AEH) among men who have sex with men (MSM) undergoing community HIV testing and to compare demographics in those diagnosed with AEH with those diagnosed at chronic stage of HIV infection.

In this retrospective cohort study, we analyzed risk factors associated with AEH among 8925 unique MSM (including 200 with AEH [2.2%] and 219 [2.5%] with newly diagnosed chronic HIV infection) undergoing community-based, confidential AEH screening in San Diego, California.

The combination of condomless receptive anal intercourse (CRAI) plus  $\geq 5$  male partners, CRAI with an HIV-positive male, CRAI with a person who injects drugs, and prior syphilis diagnosis were significant predictors of AEH in the multivariable Cox regression model. Individuals reporting  $\geq 1$  of these 4 risk factors had a hazard ratio of 4.6 for AEH. MSM diagnosed with AEH differed in race ( $P=0.005$ ; more reported white race [ $P=0.001$ ], less black race [ $P=0.030$ ], trend toward less Native American race [ $P=0.061$ ]), when compared to those diagnosed with chronic HIV infection, while there was no difference observed regarding age.

We established a multivariate model for the predicting risk of AEH infection in a cohort of MSM undergoing community HIV screening,

which could be potentially used to discern those in need of further HIV nucleic acid amplification testing for community screening programs that do not test routinely for AEH. In addition, we found that race differed between those diagnosed with AEH and those diagnosed at chronic stage of HIV infection underlining the need for interventions that reduce stigma and promote the uptake of HIV testing for black MSM.

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**Abbreviations:** Ab = antibody, AEH = acute and early HIV infection, CRAI = condomless receptive anal intercourse, HR = hazard ratio, MSM = men who have sex with men, NAT = nucleic acid amplification testing.

## INTRODUCTION

Acute and early human immunodeficiency virus (HIV) infection (AEH) is associated with rapid immune destruction and significantly greater infectivity than during chronic infection, mainly due to transient levels of extremely high HIV-ribonucleic acid.<sup>1,2</sup> The detection of AEH is therefore critical to both prevention and treatment strategies.<sup>3-5</sup> Main deterrents of widespread use of AEH screening algorithms appear to be the elevated costs, which limit AEH testing in some settings to perceived high-risk populations, such as men who have sex with men (MSM).<sup>6</sup> MSM bear the greatest burden of HIV infection in California and the United States.<sup>7-9</sup> But while MSM represent a significant risk group, the risk of HIV infection within this population is not uniform. Studies have shown that MSM presenting to community HIV-screening programs may represent a subsegment of the MSM population at higher risk for the acquisition of HIV infection.<sup>10-12</sup>

The objectives of this study were to identify risk factors associated with AEH among MSM-undergoing community HIV testing and to compare demographics in those diagnosed with AEH with those diagnosed at chronic stage of HIV infection.

## MATERIAL AND METHODS

In this retrospective observational cohort study, we analyzed risk behavior reported for the previous 12 months in individuals who enrolled in the voluntary "Early Test" HIV-screening program between April 2008 and July 2014. The "Early Test" is a community-based, confidential AEH screening program in San Diego, California that provides point-of-care rapid HIV serologic testing followed by reflex HIV nucleic acid amplification testing (NAT) in all antibody (Ab)-negative persons.<sup>13,14</sup> Males and female-to-male transsexual persons who reported sexual contact with one or more male partners during the previous 12 months were included in the analysis.

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AEH was characterized using previously published criteria for serologic and virologic test results.<sup>15</sup> In repeat testers, data reported at the most recent Early Test encounter were used. Eligible participants for the analysis of risk factors associated with AEH included MSM diagnosed with AEH (acute: HIV NAT+/Ab− and early: HIV Ab+/detuned HIV Ab c/w infection <70 days<sup>16,17</sup>) and those who were HIV uninfected.

In addition, we compared demographics and risk factors in those with AEH to those with newly diagnosed chronic HIV infection (ie, HIV Ab+/detuned not consistent with infection <70 days) to identify factors associated with delayed HIV diagnosis.

For statistical analysis SPSS 21 (SPSS Inc., Chicago, IL) was used. Analyses were performed using Chi-Squared and Mann–Whitney *U* tests. Univariate and multivariate Cox proportional hazards regression analysis was conducted for risk factors (such as sexually transmitted infections) and risk behavior variables associated with high AEH prevalence rates (above 4%) in the current and/or previous studies (selected on the basis of epidemiological evidence<sup>12,18–21</sup>). For the Cox regression model, AEH diagnosis was used as outcome, time of follow-up (beginning of study period to last eligible test) as time, and hazard ratios (HR) including 95% confidence intervals were displayed. In the first step, univariate analyses were performed, and variables with  $P < 0.20$  were included in the multivariable model. Variables in the final model were selected with a forward stepwise procedure.

The University of California, San Diego Human Research Protections Program approved the study protocol, consent and all study-related procedures. All study participants provided voluntary, written informed consent before any study procedures were undertaken.

## RESULTS

A large population ( $n = 14,612$  unique clients) underwent HIV screening using the “Early Test” between April 2008 and July 2014, including 8935 (61%) individual MSM (with 17,333 voluntary HIV tests). Overall, 419 of 8935 MSM (4.69%) were newly diagnosed with HIV infection; 219 (2.45%) with chronic HIV infection and 200 (2.24%) with AEH (125/200 [63%] at their first “Early Test”, 75/200 [37%] at a repeat visit).

### Predictors of Acute and Early HIV Infection

Table 1 provides the prevalence of risk behaviors reported for the 12 months prior to the most recent test and demographics for the study population, as well as AEH prevalence per risk behavior. Individuals with AEH were significantly younger (median 30 years interquartile range [IQR 25–40] vs 33 years [IQR 27–43],  $P = 0.001$ ) and reported significantly more male sex partners (median 10 [IQR 5–20] vs 5 [IQR 3–10],  $P < 0.001$ ) than those with negative test results. Condomless receptive anal intercourse (CRAI) was associated with a significantly higher rate of being diagnosed with AEH (3.7% vs 2.2%,  $P < 0.001$ ), as was reporting 5 or more male sexual partners in the prior 12 months (3.1% vs 2.2%,  $P < 0.001$ ). When the number of male sexual partners was combined with CRAI, a dose response relationship between risk and proportion of AEH diagnoses was observed (CRAI and 3 male partners was 4.2%, CRAI and 5 male partners 4.7%, and CRAI and 10 partners was 5.5%, all  $P < 0.001$ ).

Univariate and multivariate Cox regression models of risk factor and behaviors were performed (variables included in the model are listed in Table 2). The combination of CRAI and 5 or

more male partners was the strongest predictor of AEH, followed by CRAI with an HIV-positive male, reported syphilis diagnosis within last 12 months, and CRAI with a person who injects drugs. Individuals reporting at least 1 of the 4 risk behaviors of the multivariable Cox regression model ( $n = 2971$  with 139 AEH) had an HR of 4.612 (95% confidence interval 3.382–6.289;  $P < 0.001$ ) for AEH. AEH prevalence rates increased in those that reported higher numbers of risk behaviors of the final model, as shown in Table 2.

### AEH Diagnoses Versus Chronic HIV Diagnoses

MSM diagnosed with AEH differed in race ( $P = 0.005$ ; more reported white race [ $P = 0.001$ ], less black race [ $P = 0.030$ ], and trend toward less Native American race [ $P = 0.061$ ]), when compared to those diagnosed with chronic HIV infection, while there was no difference observed regarding age. Those with AEH also reported more male partners ( $P < 0.001$ ) and CRAI ( $P = 0.023$ ) than those with newly diagnosed chronic HIV infection. No differences were found for drug use (with the exception of gamma hydroxybutyrate) and sexually transmitted infections (chlamydia, syphilis, and gonorrhea) (Table 1). Overall, 12/22 (55%) black MSM with chronic HIV diagnoses reported at least 1 of the 4 risk behaviors of the multivariable Cox regression model, which was similar to MSM reporting white race (54/99 [55%]).

## DISCUSSION

We conducted a study on risk factors for incident HIV infection and generated a profile for AEH risk among MSM that undergo community-based HIV screening. These data showed a HR of 4.6 for AEH in individuals reporting at least 1 of the 4 risk behaviors of the final model. We also found that a higher proportion of white MSM were diagnosed with AEH, while a higher proportion of black MSM were diagnosed with chronic HIV infection.

By using multivariate modeling, we have created a set of risk factors associated with diagnosis of AEH in MSM undergoing HIV screening (Table 2). Although most previous HIV-risk models have focused on newly diagnosed chronic infection,<sup>10,22–24</sup> this represents one of the biggest studies to date to focus on incident HIV infection.<sup>1,18,25</sup> Although each of the 4 risk behaviors of our final model has been described previously to be associated with HIV infection individually (combination CRAI and 5 or more male partners,<sup>18,26,27</sup> CRAI with an HIV-positive male,<sup>23,28–30</sup> CRAI with a person who injects drugs,<sup>28,31,32</sup> and self-reported syphilis infection during the last 12 months),<sup>33,34</sup> these risk factors have not been described together in a multivariate model. By focusing only on AEH and investigating all of these factors together, we were able to generate a profile for AEH risk among MSM undergoing field-based screening, with an HR of 4.6 for AEH in individuals reporting at least 1 of the 4 risk behaviors.

In contrast to previous studies,<sup>1,18,25</sup> methamphetamine and other noninjection drug use, injection drug use, and injection drug use with shared needles did not remain significant predictors of AEH in our final model. Other studies have reported that methamphetamine and other stimulant drugs seem to be a driver for sexual-risk behavior, and even dose-response associations between number and frequency of substance use and high-risk sexual behaviors among HIV-negative MSM have been described.<sup>35,36</sup> However, usage rates of for example methamphetamine, nitrites, or gamma hydroxybutyrate differ depending on geographic location.<sup>37–39</sup> In addition, methamphetamine use has

**TABLE 1. Risk Behavior and Demographics Reported for the 12 Months Prior to Diagnosis/Last HIV Test in MSM With Acute/Early HIV as Compared to Those With Negative HIV Test Results and Those With Newly Diagnosed Chronic HIV**

Risk-Factor/Risk Behavior and Demographics	Prevalence of Risk Behavior, Demographic Characteristics Among Individuals With and Without HIV			P Value <sup>†</sup>	P Value <sup>†</sup> When Compared to Acute/Early HIV Infection
	Individuals With Negative HIV Test Result(s) (n = 8516)	Individuals With Acute/Early HIV Infection (n = 200)	Individuals With Newly Diagnosed Chronic HIV Infection (n = 219)		
Number of male partners (median, IQR)	5 (3–10)	10 (5–20)	5 (3–10)	<0.001	<0.001
10 or more male partners	2799/8508 (32.9%)	110 (55.0%)	77 (35.2%)	<0.001	<0.001
Intercourse with females	785/8503 (9.2%)	12 (6.0%)	19/217 (8.8%)	n.s.	n.s.
CIAI with male	5173/8434 (61.3%)	153 (76.5%)	145/216 (67.1%)	<0.001	0.045
CRAI	4205/8438 (49.8%)	163 (81.5%)	156/218 (71.6%)	<0.001	0.023
CRAI and 5 or more male partners	2618/8435 (31.0%)	130 (65.0%)	86/218 (39.4%)	<0.001	<0.001
CRAI and 10 or more male partners	1569/8435 (18.6%)	92 (44.5%)	56/218 (25.7%)	<0.001	<0.001
CRAI with HIV positive	411/8096 (5.1%)	35/170 (20.6%)	35/181 (19.3%)	<0.001	n.s.
CRAI with PWID <sup>‡</sup>	104/8347 (1.2%)	12/191 (6.3%)	10/208 (4.8%)	<0.001	n.s.
CRAI with sex worker	36/8337 (0.4%)	3/192 (1.6%)	2/212 (0.9%)	0.022	n.s.
Worked as sex worker	128/6317 (2.0%)	11/136 (8.1%)	8/135 (5.9%)	<0.001	n.s.
Chlamydia	352 (4.1%)	14 (7%)	13 (5.9%)	0.046	n.s.
Syphilis	152 (1.8%)	15 (7.5%)	9 (4.1%)	<0.001	n.s.
Gonorrhoea	507 (6.0%)	23 (11.5%)	19 (8.7%)	0.001	n.s.
Other STI <sup>§</sup>	168 (2.0%)	9 (4.5%)	8 (3.7%)	0.012	n.s.
Methamphetamine, not injected	564 (6.6%)	37 (18.5%)	41 (18.7%)	<0.001	n.s.
Ecstasy, not injected	863 (10.1%)	36 (18.0%)	36 (16.4%)	<0.001	n.s.
GHB, not injected	420 (4.9%)	29 (14.5%)	16 (7.3%)	<0.001	0.027
Nitrites, inhaled	1128 (13.2%)	32 (16.0%)	36 (16.4%)	n.s.	n.s.
Cocaine, not injected	810 (9.5%)	30 (15.0%)	22 (10.0%)	0.009	n.s.
IDU <sup>‡</sup>	108 (1.3%)	6 (3.0%)	8 (3.7%)	0.047	n.s.
IDU with shared needles <sup>‡</sup>	71/8483 (0.8%)	6 (3.0%)	4 (1.8%)	0.008	n.s.
Demographic data					
Age (years; median, IQR)	33 (27–43)	30 (25–40)	31 (26–41)	<0.001	n.s.
Male	8497 (99.8%)	200 (100%)	218 (99.5%)	n.s.	n.s.
Female–male TSX	19 (0.2%)	–	1 (0.5%)	n.s.	n.s.
Hispanic ethnicity	2264/8283 (27.3%)	64/194 (33.0%)	89/216 (41.2%)	n.s.	n.s.
Race					
White	5422/8005 (67.7%)	–	–	n.s.	0.005
Black	428/8005 (5.3%)	137/194 (70.6%)	114/202 (56.4%)	n.s.	0.001
Asian	577/8005 (7.2%)	10/194 (5.2%)	24/202 (11.9%)	n.s.	0.030
Pacific Islander	185/8005 (2.3%)	11/194 (5.7%)	8/202 (4.0%)	n.s.	n.s.
Native American	47/8005 (0.6%)	4/194 (2.1%)	6/202 (3.0%)	n.s.	n.s.
Other	1346/8005 (16.8%)	0	5/202 (2.5%)	n.s.	n.s.
		32/194 (16.5%)	44/202 (21.8%)	n.s.	n.s.

CIAI = condomless insertive anal intercourse, CRAI = condomless receptive anal intercourse, GHB = gamma hydroxybutyrate, IDU = injection drug use, IQR = interquartile range, MSM = men who have sex with men, n.s. = not significant, PWID = person who injects drugs, STI = sexual transmitted infection, TSX = transsexual.  
<sup>†</sup> Data available from all individuals, otherwise denominator depicted.  
<sup>‡</sup> Calculated using Chi-square or Mann–Whitney U test.  
<sup>§</sup> All MSM fulfilling reporting “IDU with shared needles” were included in the IDU group as well. 41/116 MSM that reported CRAI with a PWID did also report IDU, and 37/41 MSM who reported CRAI with a PWID and IDU did also report shared needles.  
<sup>§</sup> Genital herpes, genital warts, and others.

**TABLE 2. Univariate and Multivariate Cox Regression Model of Risk Factors and Risk Behaviors Associated With Acute/Early HIV Infection (vs Negative Test Result) in MSM**

Risk Factor/Risk Behavior (Within 12 Months Prior to Test)	Univariate Cox Regression Analysis			Multivariable Cox Regression Analysis		
	HR	95% CI	P Value	HR	95% CI	P Value
Number of male partners	1.005	1.003–1.006	<0.001			n.s.
CRAI and 5 or more male partners	3.998	2.99–5.347	<0.001	2.823	2.032–3.923	<0.001
CRAI with HIV positive	3.977	2.742–5.769	<0.001	2.081	1.353–3.202	0.001
CRAI with PWID	4.058	2.262–7.281	<0.001	2.113	1.121–3.984	0.021
CRAI with sexworker	3.799	1.213–11.893	0.022			n.s.
STI Chlamydia infection	1.743	1.012–3.001	0.045			n.s.
STI Syphilis	4.673	2.76–7.911	<0.001	3.131	1.722–5.690	<0.001
STI Gonococcal infection	1.979	1.282–3.056	0.002			n.s.
Methamphetamine, not injected	3.662	2.562–5.235	<0.001			n.s.
Nitrites, inhaled	0.966	0.662–1.41	0.857			n.i.
Ecstasy, not injected	1.996	1.391–2.864	<0.001			n.s.
GHB, not injected	3.668	2.473–5.44	<0.001			n.s.
IDU shared needles	3.534	1.567–7.969	0.002			n.s.

  

Number of Reported Risk Factors/Risk Behaviors of the Multivariable Model		Acute or Early HIV Infection Prevalence Rates % (Absolute Numbers)
0		1.1% (61/5745)*
1		3.9% (101/2558)†
2		7.9% (27/340)
≥3		15.1% (11/73)

CI = confidence interval, CRAI = condomless receptive anal intercourse, GHB = gamma hydroxybutyrate, IDU = injection drug use, MSM = men who have sex with men, n.i. = not included due to  $P > 0.200$  in univariate analysis, n.s. = not significant, PWID = person who injects drugs, STI = sexually transmitted infection.

\* A total of 314 of those 5745 (5.5%, 5 with AEH and 309 without) had missing data for 1 or more of the 4 risk behaviors.

† A total of 236 of those 2558 (9.2%, 29 with AEH and 207 without) reported 1 of the 4 risk behaviors but had missing data for 1 or more of the remaining 3 risk behaviors.



recently been decreasing in many settings while sexual-risk behaviors are steadily increasing.<sup>39,40</sup>

Whereas condomless anal intercourse or CRAI alone have been described as predictors of HIV infection in prior studies,<sup>22–24</sup> we found that CRAI alone was associated only with slightly increased AEH risk, whereas the combination of CRAI and number of male partners may be a more useful predictor of AEH. Results going into the same direction were reported by Ostrow et al<sup>18</sup> who found that the risk of seroconversion increased linearly with the number of CRAI sex partners.

We also found that the proportion of individuals reporting white race was higher among AEH diagnoses as compared to chronic HIV diagnoses, while the opposite was true for those reporting black race. This is further evidence of the marked racial disparities found throughout the care continuum of HIV in the United States.<sup>41</sup> In particular, infrequent HIV testing, undiagnosed infection, and late diagnosis are common among black MSM in the United States.<sup>42</sup> Our results indicate additional measures (eg, promotion of AEH testing) for black MSM are needed in order to increase testing and achieve earlier HIV diagnoses. In contrast to previous studies,<sup>43,44</sup> we did not find differences in age between those diagnosed with AEH and those with chronic HIV.

Our study has several limitations including its single-center and retrospective design. Additionally, we cannot completely rule out that subjects reported risk behaviors more openly with time and repeat testing, which may have impacted results of our multivariable model.

In conclusion, we established a multivariate model for predicting risk of AEH infection in a cohort of MSM undergoing community HIV screening, which could be potentially used to discern those in need of further HIV NAT testing for community screening programs that do not test routinely for AEH. In addition, we found that race differed between those diagnosed with AEH and those diagnosed at chronic stage of HIV infection underlining the need for interventions that reduce stigma and promote the uptake of HIV testing for black MSM.

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