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Sexually Transmitted Infections among Patients with Acute HIV in North Carolina

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Sexually transmitted infections (STIs) have a well-established synergistic relationship with HIV infection. Co-infection with HIV and an STI can increase the probability of HIV transmission to an uninfected partner by increasing HIV concentrations in genital lesions, genital secretions, or both.[1,2] STI infection can also increase the likelihood of HIV acquisition by interrupting mucosal barriers, increasing the access to and concentration of HIV receptor cells, and, in women, changing the vaginal microflora to favor HIV infection.[3–6] Among patients with acute HIV (AHI), the 4–6 week interval in the HIV disease course when the virus can be detected in the blood prior to seroconversion, co-infection with an STI may be common.[7] More than 70% of AHI patients had an STI co-infection in a Malawian sexually transmitted disease (STD) clinic in two separate studies.[8,9] However, little is known about the frequency of STI and acute HIV infection co-infection outside of the STD clinic setting.

To further examine this issue, we conducted a secondary data analysis of AHI patients identified from November 1, 2002 through October 31, 2006 by the Screening and Tracing Active Transmission Program (STAT) of the North Carolina Department of Health and Human Services (NC DHHS) and the University of North Carolina at Chapel Hill (UNC). Our goal was to describe the prevalence and predictors of acute HIV and STI co-infection in a systematically collected, statewide sample of AHI patients.

The STAT screening methodology has been previously described.[10,11] In brief, clients presenting for confidential HIV counseling and testing at approximately 135 publicly funded sites in NC are included in a testing algorithm to detect acute HIV infection. Serum samples

submitted for HIV testing are first tested for HIV-1 antibody, and then all antibody negative samples are screened for HIV-1 RNA by pooling.[10] Antibody indeterminate samples are tested for HIV RNA individually. Samples in which HIV-1 RNA is detected and are either EIA negative or EIA positive and Western Blot negative or indeterminate represent acute infections, and are confirmed by follow-up antibody testing. Serum HIV-1 RNA is quantified with an HIV-1 reverse transcriptase polymerase chain reaction assay (Amplicor HIV-1 Monitor Test, version 1.5, Roche Diagnostic). We included 75 clients with AHI identified from November 1, 2002 through October 31, 2006.

The NC DHHS assigns potential AHI cases to a team of disease intervention specialists (DIS) who perform initial interviews, confirmatory testing, and referrals to care within 72 hours of notification.[11] After interview with the patient and medical record review(s), DIS complete standardized case report forms. Patients with AHI who presented for confidential HIV testing signed informed consent forms authorizing the collection of personal information and release of information and blood to the STAT program. This study was approved by the UNC Institutional Review Board.

We defined STI co-infection as the diagnosis of gonorrhea, chlamydia, trichomoniasis, Human Papillomavirus (HPV), genital herpes, bacterial vaginosis (BV), or syphilis during the same month and year of the AHI diagnosis. STI infections were confirmed by medical record review. We considered appropriate symptoms reported during an eight week window period ($\pm$ four weeks of the test date, inclusive) to be acute retroviral syndrome. To determine factors associated with STI co-infection, we computed the prevalence of co-infection, prevalence ratios (PR), and 95% exact confidence intervals. We examined variations in mean $\log_{10}$ (HIV-1 RNA) with one-way analysis of variances.[12] All analyses were performed with SAS Software (version 9.1.2, SAS Institute, Cary, NC).

From November 1, 2002 to October 31, 2006, 79 persons with AHI were detected through the STAT program. Of these, three could not be located and one refused post-test counseling and partner notification services, leaving a sample of 75 patients with AHI for analysis. Seventy-five percent were male and 52% were MSM. The median age was 28 years (range: 16–56). The majority of the population were Black, followed by a quarter White, non-Hispanic. Half of the cases were identified at STD clinics. A majority of persons ($n=45$, 60%) reported at least one acute retroviral symptom at or before the initial testing date, most commonly, fever (37%), night sweats (24%), fatigue (24%), body aches (21%), and nausea (21%).

Nearly one third of patients ($n=23$, 31%) had an STI at or near the time of the AHI diagnosis, consistent with co-infection (Table 1). The most common co-infections were gonorrhea (39%), trichomoniasis (22%), and syphilis (17.4%) although they differed substantially by gender – the majority of male co-infections were gonorrhea (54%) whereas among women the most common co-infection was trichomoniasis (50%, Fisher's exact test, $p<0.01$).

We identified an interrelationship between gender, race, risk category, and STI co-infection. The prevalence of co-infections was lower in MSM (18%, PR=0.34, 95% CI 0.15, 0.76) and heterosexual men (35%, PR=0.67, 95% CI 0.31, 1.45) than women (53%, Table 2). Non-Whites were 3.9 times as likely to report a co-infection as Whites (95% CI 1.00, 15.10). Among MSM, all seven STI co-infections occurred in non-Whites ($p=0.03$); this finding was consistent for heterosexual men as all six co-infections were in non-Whites, although only one White heterosexual man was in the study population. Among women, two of the three White women were co-infected and half (eight of 16) of the non-White women reported an STI co-infection.

The prevalence of STI co-infection was roughly equal among AHI patients detected at HIV counseling and testing (CTS) locations and STD testing locations. The overall mean serum

viral load at the time of testing was 5.2 log₁₀ copies/ml, and we found little variation by demographic or risk factors.

The proportion of AHI patients with STI co-infections is surprising as our study was not limited to the STD clinic setting. Although about half of the AHI cases were identified in STD clinics where STI screening is routine, the proportion with co-infections from STD clinics (35%) was roughly the same as those cases identified from HIV counseling and testing sites (36%), where STI screening is less frequent and likely restricted to urine-based nucleic-acid amplification testing (NAAT) for gonorrhea and chlamydia, if it is conducted at all. While the coding of testing site type is variable from county to county and therefore subject to misclassification, our results underscore the importance of STI symptoms as an indicator of AHI risk, even in non-STD clinic settings. Further, high rates of STIs near the time of HIV transmission in NC may suggest the importance of STIs on HIV transmission in the southeastern U.S., a region that has been disproportionately impacted by HIV and STIs.[13–17]

The variation in STI co-infection prevalence of STI co-infection by gender, risk category, and race is compelling. MSM in our study were less likely to have a co-infection (18%) than heterosexual men (35%) or women (53%), and almost all (91%) co-infections occurred in non-Whites. These findings may reflect the epidemiology of the NC HIV epidemic where racial disparities are dramatic – the HIV rate for non-Hispanic blacks is more than eight times greater than for non-Hispanic Whites – and heterosexual transmission is nearly as prominent as MSM transmission.[13,18] Heterosexual transmission of HIV in NC occurs largely among African-Americans; high rates of STIs in this group would facilitate HIV transmission and may be a necessary component of the HIV epidemic for this population.[18] While we have likely underestimated the number of co-infections as not all cases are uniformly screened for STIs, this bias may be most dramatic for MSM as pharyngeal and rectal cultures for gonorrhea are only collected based on a risk assessment at STD clinics.

Our study has several noteworthy limitations. Our sample size is small and does not represent all HIV cases identified in NC. The STAT program routinely tests for HIV RNA in all samples from publicly funded clinics but approximately 60% of NC HIV cases are detected outside of the public testing system. If people who test through the publicly-funded system are systematically different than those who test outside of the publicly-funded system, selection bias may be introduced. In addition, STI screening practices and diagnostic methods vary throughout the state; however, we would expect this to result in an underestimate of STI co-infections. As we have defined them, STI co-infections can represent prevalent infections acquired before HIV infection, co-transmission events, or incident infections acquired after HIV infection. Finally, our modest sample size results in limited power to detect small differences and a decreased ability to control confounding in multivariable models.

The detection of AHI affords a tremendous public health opportunity to interrupt transmission and detect networks at high risk, but recognition requires a unique synergy of clinical suspicion, risk awareness, and appropriate diagnostic tests. Although people with primary infection often present to medical care, the opportunity for diagnosis is frequently missed either by not recognizing acute retroviral syndrome or reliance on antibody testing alone.[19–22] Patients who co-acquire HIV and an STI infection may be missed by standard HIV antibody tests when STI symptoms appear, given the short incubation periods of some bacterial STIs. This is an important limitation of strategies to offer HIV testing services to all STI patients, as acute HIV infection will often be missed in settings where testing is limited to standard third-generation EIAs.

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TABLE 1

Types of STI co-infections among 23 patients diagnosed with acute HIV and another STI in North Carolina, November 1, 2002 through October 31, 2006.

STI Type *	N (%)	Men (n=13)	Women (n=10)
Gonorrhea	9 (39.1)	7 (53.8)	2 (20.0)
Trichomoniasis	5 (21.7)	0 (0)	5 (50.0)
Syphilis	4 (17.4)	4 (30.8)	0 (0)
Herpes	3 (13.0)	2 (15.4)	1 (10.0)
Chlamydia	3 (13.0)	1 (7.7)	2 (20.0)
Bacterial vaginosis	3 (13.0)	0 (0)	3 (30.0)
Genital ulcer disease, unspecified	1 (4.3)	1 (7.7)	0 (0)

* Five (21.7%) of 23 participants with an STI co-infection had more than one concurrent STI diagnosis.

TABLE 2

Frequency and prevalence of STI co-infections by demographic factors among 75 patients with acute HIV in North Carolina

Characteristic	STI co-infection at diagnosis [†]		Prevalence	Prevalence Ratio
	Yes (n=23)	No (n=52)	(95% CI)	(95% CI)
Gender and risk behavior				
Man who has sex with men	7	32	18.0% (7.5, 33.5)	0.34 (0.15, 0.76)
Heterosexual man	6	11	35.3% (14.2, 61.7)	0.67 (0.31, 1.45)
Female	10	9	52.6% (28.9, 75.6)	Referent
Age (years)				
≤ 25	13	20	39.4% (22.9, 57.9)	1.97 (0.74, 5.21)
26–35	4	16	20.0% (5.7, 43.7)	Referent
≥ 36	6	16	27.3% (10.7, 50.3)	1.36 (0.45, 4.14)
Race or ethnic background				
White, non-Hispanic	2	18	10.0% (1.2, 31.7)	Referent
Non-White	21	33	38.9% (25.9, 53.1)	3.89 (1.00, 15.10)
Testing Location				
HIV Counseling and Testing site	6	11	35.3% (14.2, 61.7)	Referent
STI Clinic	13	23	36.1% (20.8, 53.8)	1.01 (0.66, 1.55)
Other type of clinic	4	18	18.2% (5.2, 40.3)	0.52 (0.17, 1.54)
History of injection drug use				
Yes	1	1	50.0% (1.3, 98.7)	1.66 (0.40, 6.93)
No	22	51	30.1% (19.9, 42.0)	Referent
Symptoms at or before testing				
Yes	11	34	24.4% (12.9, 39.5)	0.61 (0.31, 1.20)
No	12	18	40.0% (22.7, 59.4)	Referent

[†]Note: Numbers may not add to 75 due to missing data.