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Skin and Soft Tissue Infections among HIV-Infected Persons in the Late HAART Era

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Abstract

Skin and soft tissue infections (SSTIs) occur at higher rates among HIV-infected persons, but current trends and risk factors are largely undefined. We evaluated SSTIs among a prospective cohort of HIV-infected persons during the late HAART era (2006-2010). Of the 1918 HIV-infected persons evaluated, 379 (20%) developed an SSTI during a median of 3.7 years of follow-up; of these, 118 (31%) developed at least one recurrent SSTI. The incidence rate of SSTIs was 101 (95% CI 93-109) cases per 1000 PYs, and rates did not significantly change during the study period. Compared to not receiving HAART and having an HIV RNA level ≥1000 copies/ml, patients receiving HAART with an HIV RNA level <1000 copies/ml had a reduced risk of an SSTI (HR 0.64, 95% CI 0.48-0.86, $p < 0.01$). In summary, initial and recurrent SSTIs are common among HIV-infected persons. HIV control is associated with a lower risk of SSTIs.

Keywords

HIV; Skin and soft tissue infection; SSTI; MRSA; epidemiology; risk factors

Introduction

HIV-infected persons are at higher risk for several infections, including skin and soft tissue infections (SSTIs) [1, 2]. Increasing rates of SSTIs, especially due to methicillin-resistant *Staphylococcus aureus* (MRSA), among HIV-infected persons have been noted in the past decade, although rates may now be falling similar to trends in the general population [1-4]. Most studies have focused on MRSA infections, but these data may underestimate the

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incidence of SSTIs since cultures may not be obtained (e.g., cases of cellulitis) or may have negative results.

The reason(s) for the increased risk for SSTIs among HIV-infected persons is unknown. Some studies have suggested immunosuppression [3-6], but infections often occur in the setting of robust CD4 counts, and rates have remained high despite the availability of highly active antiretroviral therapy (HAART) [2, 4]. Other studies have implicated antibiotic use [2, 7, 9-11], hospital contact and concurrent medical conditions [3, 6-11], and behaviors (e.g., illicit drug use and high-risk sexual practices) with MRSA SSTIs [1-3, 5-10, 12]. Most studies to date have been limited by cross-sectional study designs or short study periods. To expand the current understanding of SSTIs among HIV-infected persons, we utilized the large, prospective US Military HIV Natural History Study (NHS) to evaluate the incidence of and factors associated with SSTIs among HIV-infected persons in the late HAART era.

Methods

Study Design

We examined data collected from HIV-infected participants in the U.S. Military NHS, an ongoing, multicenter, prospective study of military beneficiaries with HIV infection. All active duty U.S. military personnel are confirmed HIV-negative prior to enlistment and undergo routine HIV screening every one to five years. HIV infection is largely acquired sexually, as intravenous drug use is uncommon given the military's mandatory drug testing policy. Participants are evaluated by an HIV specialist every six months and data are prospectively collected on medical conditions, medications (including antibiotic use), and HIV-specific data.

For this study, an SSTI included cellulitis, cutaneous or perirectal abscess, bacterial folliculitis, hidradenitis, or a methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-susceptible *S. aureus* (MSSA) infection of the skin or soft tissues. Standardized collection of SSTI data, including codes for MRSA infections, in the NHS began in 2006. Therefore, we included in this analysis SSTIs occurring from 2006-2010.

HIV-specific data were recorded every six months, including CD4 counts, HIV RNA levels, and HAART use defined by guidelines [13]. An AIDS-defining condition was defined by the 1993 CDC criteria, except for solely a CD4 count <200 cells/mm³ [14]. Diagnoses of syphilis, diabetes, and skin conditions (psoriasis, seborrheic dermatitis, or atopic dermatitis) were based on standardized codes in the NHS. Hospitalization was defined as a 24 hour admission to an inpatient hospital ward and collected at each six month visit using admission records and discharge summaries.

Statistical Methods

The number of SSTIs, person-years (PYs) of risk, and rates of SSTIs (per 1000 person-years of follow-up) were calculated overall and for each year of the study period (2006-2010). Each participant contributed PY at risk from his/her date of HIV diagnosis, January 1, 2006, or one-year prior to his/her enrollment date (whichever was later) to the last clinic visit or December 31, 2010 (whichever was earlier). Participants could be included in multiple years and could contribute more than one SSTI. Each SSTI event recorded must have been separated by 30 days to be counted as a unique event. SSTI rates for each calendar year were computed as the total SSTIs occurring during the year divided by PYs of follow-up during the year. SSTI rates for the entire study period used total SSTI events and total PYs of follow-up. Comparisons of rates by year were assessed using Poisson regression (with offset for PYs) with a compound symmetry covariance structure to account for participants contributing to multiple years. Year was modeled both as a categorical variable (3 degrees of

freedom) and as a continuous variable with the coefficient testing if there was a significant linear change in rates over the study period. Analyses were performed separately for all SSTIs and for MRSA events.

Descriptive summaries of selected factors were computed at the beginning of the observation period for participants who developed and who did not develop an SSTI during follow-up. Cox regression was utilized to assess risk factors for SSTIs; for the primary analysis, only the first SSTI was examined per participant. Fixed covariates considered in models were age (at start of follow-up), gender, and ethnicity (Caucasians, African Americans, and others). Time-updated covariates included 1) historical factors which had occurred at any time prior to the SSTI event, including an AIDS-defining condition [14], sexually transmitted infections (STIs) such as syphilis, and diabetes and 2) recent factors occurring within one year of the SSTI, which included current active duty status, hospitalizations, use of antibiotics, dermatologic conditions, CD4 count, HIV RNA level, and HAART use. To reduce the possibility of factors related to the treatment of the SSTI predicting the SSTI event, factors such as hospitalization, antibiotic use, or dermatologic condition could not be within 14 days before the SSTI. Both univariate and multivariate analyses were conducted.

Cox-regression models were also performed to evaluate factors for the development of a recurrent SSTI. From these models, we examined factors that occurred at or before the first SSTI (as a fixed-effect covariate) that were associated with a second SSTI. SAS (version 9.2, Cary, NC) was used for analysis; PROC GENMOD was used for Poisson regression modeling and PROC PHREG for Cox regression modeling.

Results

A total of 379 (20%) of 1918 HIV-infected persons developed an SSTI during a median follow-up of 3.7 years (IQR 1.9-4.2). Characteristics at the start of observation for all participants and for those developing versus not developing an SSTI during follow-up are shown in Table 1. Mean age at start of follow-up period was 38.2 years, 93% were male, 41% were Caucasian, and 43% were African American. The mean calendar year of HIV infection was 1999, and the average duration of HIV infection was eight years. The mean CD4 count was 563 (SD 281) cells/mm³, 55% were on HAART, and 11% had a prior AIDS-defining event. Factors at entry were similar between groups, except HIV-infected patients who developed an SSTI were slightly younger, more likely to be male, and serving on active duty, and less likely to be African American on receiving HAART.

Among HIV-infected persons with an SSTI, characteristics at the time of the first SSTI event included a mean age of 38.3 (SD 9.5) years, 97% were male, and ethnicity was Caucasian among 47%, African American in 39%, and other in 14%. Fifty-one percent were active duty military members, 51% had received antibiotics in the past year, 15% were hospitalized in the past year, 8% had diabetes, and 6% had a dermatologic condition in the past year. Regarding HIV-specific data, 13% had a history of an AIDS-defining condition, the mean current CD4 count was 549 (SD 264) cells/mm³, HIV RNA level was 2.5 (SD 1.3) log₁₀ copies/ml, and 69% were receiving HAART (data not shown).

Five hundred and ninety-five SSTIs occurred among the 379 participants during 5898 PYs of follow-up. Thirty percent of those with an initial SSTI developed a recurrent infection, which occurred at a median of 7 months later. The types of SSTIs were bacterial folliculitis (n=196), abscess (n=181), cellulitis (n=178), and hidradenitis (n=1); some data were missing. Regarding the body site of the SSTI, the perigenital area was the most common site

(n=140), followed by the lower extremities (n=131), head/neck (n=98), upper extremity (n=70), trunk (n=57) or greater than one locations (n=14); some locations were not recorded.

The overall rate of SSTIs in our study population was 101 (95% CI 93-109) cases per 1000 PYs during the entire study period (2006-2010) (Table 2). The SSTI rate did not significantly differ among the study years ($p=0.24$, 3 degrees of freedom), and the estimated relative rates between consecutive years did not differ from one (RR 1.0 per year, 95% CI 0.9-1.1). The SSTI rate was highest in 2008 (111 cases per 1000 PYs) and lowest in 2010 (82 cases per 1000 PYs), suggesting that the rate of SSTIs may be decreasing but that further data are needed (Figure 1). MRSA was isolated in 100 SSTIs for an incidence rate of 17 (95% CI 14-21) cases per 1000 PYs. MRSA was four times more common than MSSA, with MSSA being diagnosed in 25 cases (rate of 4 cases per 1000 PYs). The rate of MRSA SSTIs increased and then decreased over the study period, with the lowest rate in 2010 (13 cases/1000 PY, Figure 1). There were no significant changes in the rate of MSSA over the study period.

In univariate analyses, risk factors for the development of the initial SSTI included younger age, male gender, active duty status, a history of syphilis, a dermatologic condition in the past year, antibiotic use in the past year, and hospitalization within the past year (all p -values <0.05) (Table 3). There was no significant association with ethnicity, diabetes, or other STIs (any STI, chlamydia, or gonorrhea). Regarding HIV-specific data, lower CD4 count, higher HIV RNA level, and not receiving HAART were also risk factors for SSTIs.

In the multivariate model, younger age (HR 0.78 per 10 years, 95% CI 0.67-0.91, $p<0.01$), hospitalization in past year (HR 1.57, 95% CI 1.14-2.16, $p<0.01$), and antibiotic use in the past year (HR 1.82, 95% CI 1.45-2.28, $p<0.01$) were risk factors for development of an initial SSTI. African Americans compared to Caucasians (HR 0.71, 95% CI 0.56-0.91, $p<0.01$) and females (HR 0.39, 95% CI 0.20-0.76, $p<0.01$) had lower risks of an SSTI. A higher HIV RNA level (HR 1.11 per 1 log₁₀, 95% CI 1.00-1.24, $p=0.06$) and syphilis (HR 1.27, 95% CI 0.98-1.64, $p=0.07$) had marginal associations. There was no significant association between most recent CD4 count or prior AIDs event with the risk of an SSTI.

Since the HIV RNA level and use of HAART are interrelated, we explored a multivariate model using a combination variable consisting of both HIV RNA level and HAART use. Compared to not receiving HAART and having an HIV RNA level ≥ 1000 copies/ml, an HIV-infected person receiving HAART with an HIV RNA level <1000 copies/ml had a 36% reduction in the risk of an SSTI (HR 0.64, 95% CI 0.48-0.86, $p<0.01$). Being on HAART with an HIV RNA level ≥ 1000 copies/ml had a marginally decreased risk of SSTIs compared to not receiving HAART with a HIV RNA level ≥ 1000 copies/ml (HR 0.64, 95% CI 0.42-1.10, $p=0.05$) (Table 4).

Antibiotic use was evaluated by specific type in separate multivariate models. Fluoroquinolone use (HR 1.84, 95% CI 1.37-2.46, $p<0.01$), macrolide use (HR 1.70, 95% CI 1.29-2.23, $p<0.01$), β -lactam use (HR 1.62, 95% CI 1.24-2.11, $p<0.01$), and tetracycline use (HR 2.05, 95% CI 1.36-3.08, $p<0.01$) within the past year significantly increased the risk for initial SSTIs, but there was no significant relationship with trimethoprim-sulfamethoxazole use (HR 1.3, 95% CI 0.85-2.02, $p=0.22$).

Since the majority of the study population was male and this group had a higher rate of SSTIs, a multivariate model with the same factors examining only men was performed and showed similar findings. Additionally, we examined risk factors for the development of recurrent SSTI among the 370 men who developed an initial SSTI. Risk factors present at or proximally before the first SSTI that predicted a recurrent event included marginal associations with the presence of a dermatologic condition (HR 1.99, 95% CI 0.95-4.16,

p=0.07) and higher HIV RNA level (HR 1.18 per 1 log₁₀, 95% CI 0.98-1.43, p=0.08). No other factors were significantly associated with recurrence.

Discussion

Our study noted a high incidence of SSTIs among HIV-infected persons with 20% of participants experiencing at least one SSTI during a median follow-up of 3.7 years. Further, among HIV-infected persons who developed an initial SSTI, 30% developed a recurrent infection. These data, and those of other studies [15], suggest the importance of educating HIV patients regarding the risk of SSTIs and recurrent events and emphasize the need for preventive strategies.

The incidence of SSTIs among HIV patients in our study is elevated compared to the general population. One study noted an incidence rate of ambulatory visits for cellulitis/abscess of 32.5 cases/1000 population [16], compared to our rate of 100 cases/1000 PY. We included other types of SSTIs in our study; however, the rate of SSTIs is likely higher among HIV-infected persons. For example, our rate of MRSA SSTIs (17 per 1000 PYs) is substantially higher than seen in studies examining MRSA infections in the general population (0.18-0.26 per 1000 PY) [17]. Regarding trends over time, most studies have focused on MRSA infections which rose rapidly at the beginning of the new century. However, more recent reports suggest that MRSA may now be declining in both the general population and among HIV patients, although studies to date are limited [3, 4]. Our study showed that SSTI and MRSA rates among HIV-infected persons are no longer increasing over time, but rather have stabilized. The reasons for the stabilizing and possible declining trends are unclear, but may be related to increased preventive strategies including better infection control practices; no changes in the virulence or molecular characteristics of recent MRSA isolates have been reported [4, 18].

Risk factors for SSTIs in our study included younger age. This finding is concurrent with a recent study showing that HIV-infected persons <60 years had an incidence of MRSA infections (primarily SSTIs) of 2.85 per 100 PYs compared to a rate among those ≥60 years of 0.81 per 100 PYs (p<0.004) [3]. We also noted that a recent history of hospitalization or antibiotic use increased the risk of SSTIs, and these findings are concurrent with data from studies which examined MRSA SSTIs [2, 3, 6, 7, 9-11].

We also examined the impact of HIV-specific factors on the development of an SSTI. Lower current CD4 counts, higher HIV RNA levels, and the lack of HAART were risk factors for an SSTI in the univariate analyses. HAART use and HIV RNA levels had the strongest relationships – a 42% reduction of SSTIs among those receiving HAART, and a 26% increased risk per log₁₀ increase in the HIV RNA level (both with p<0.01). In the multivariate model, the combination of HAART use with a HIV RNA load <1000 copies/ml was associated with a significantly decreased risk of SSTIs. The protective effect of HAART against MRSA infections has been suggested [3, 5, 6], with one study showing that the receipt of antiretroviral therapy within the past year was associated with a decreased odds of colonization or infection (OR 0.16; 95% CI 0.07-0.4) [6]. The mechanism of this finding is unknown, but may suggest that HAART improves and/or preserves innate immunity and TH17 responses which may prevent SSTIs including *S. aureus* events [19, 20]. Of note, whether the use of HAART directly protects against SSTIs and MRSA infections or whether it is a surrogate for other protective factors (e.g., better health or hygiene behaviors) requires further study.

Our study has some limitations. First, data entry of SSTIs into our database for the year 2010 is still ongoing, so our data are incomplete for this year; however, our primary study

results are infection rates which are calculated per PYs of follow-up. Second, our rates of MRSA SSTIs may be an underestimate of the true incidence of these infections, likely due to the lack of performance of cultures for several of the SSTI cases. Third, our database does not capture data on potential preventive strategies which may have been implemented to reduce SSTIs/MRSA infections, and some data points were not available including some HIV-specific data at the start of the observation period. Finally, we examined a military HIV population which may have unique risk factors for SSTIs compared to other HIV populations; in addition we were unable to analyze factors such as sexual orientation or illicit drug use due to military policies, however, the rate of the latter is very low in our population.

In summary, SSTIs are common among HIV-infected persons, with 20% of the population experiencing at least one SSTI during median period of 3.7 years. Our results suggest that taking HAART and maintaining a HIV RNA level <1000 copies/ml may reduce the risk for SSTIs, suggesting another potential advantage of early HAART initiation.

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This work is original and has not been published elsewhere.

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Figure 1.
Incidence Rates of Overall SSTIs and MRSA SSTIs during the Study Period

Table 1
Study Population Characteristics at Start of Observation by Subsequent Skin and Soft Tissue Infection (SSTI)

Factor	Total SSTI				P-value
	No.	Mean $\pm$ SD or %	No.	Mean $\pm$ SD or %	
Demographics					
Age (years)	1918	38.2 $\pm$ 10.9	379	37.0 $\pm$ 10.0	0.01
Gender (% female)	1918	7.1	379	2.4	<0.01
Ethnicity	1918		379		
Caucasians		41.1		44.6	0.13
African American		43.2		38.3	0.03
Other		15.7		17.2	0.38
Active duty (%)	1918	58.8	379	62.3	0.13
History (ever had previously)					
AIDS-defining event (%)	1918	10.7	379	10.3	0.75
Syphilis (%)	1918	16.6	379	18.5	0.27
Diabetes (%)	1918	6.5	379	6.9	0.73
HIV measures					
Current CD4 Count	1363	563 $\pm$ 281	275	542 $\pm$ 282	0.15
Nadir CD4 Count ¹	1434	290 $\pm$ 178	283	299 $\pm$ 195	0.38
HIV RNA Level (log ₁₀)	1392	2.5 $\pm$ 1.3	280	2.7 $\pm$ 1.4	<0.01
On HAART (%)	1918	54.5	379	47.2	<0.01
Time/duration					
Year HIV seropositive	1873	1999 $\pm$ 7.7	373	1999 $\pm$ 7.3	0.36
Time from HIV seropositivity to start of observation (years)	1873	7.6 $\pm$ 7.0	373	7.1 $\pm$ 6.8	0.09

¹ Nadir CD4 is lowest CD4 prior to start of observation

HAART, highly active antiretroviral therapy; No., number; SD, standard deviation

Table 2

Incidence Rates of Skin and Soft Tissue Infections (SSTIs) by Year

Year	Number in follow-up during period	HIV patients with an SSTI during period	Total SSTI events	Person-years of follow-up	Unadjusted rate (95% CI) of SSTIs ¹
2006-2010 ²	1918	379	595	5898	101 (93-109)
2006	1335	76	96	1090	88 (72-108)
2007	1496	112	142	1357	105 (89-123)
2008	1594	135	160	1442	111 (95-130)
2009	1626	135	152	1462	104 (89-122)
2010 ²	1436	40	45	548	82 (61-110)

¹ Rates per 1000 person-years.² Clinical data for the end of 2010 is incomplete accounting for the lower person-years of follow-up for this year

Table 3

Risk Factors for Skin and Soft Tissue Infections (SSTIs) among HIV-infected Persons

Factor	Univariate Analyses		Multivariate Analysis ^I	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Demographics/Military Factors				
Age (per 10 years)	0.75 (0.67-0.84)	<0.01	0.78 (0.67-0.91)	<0.01
Gender (female)	0.34 (0.18-0.66)	<0.01	0.39 (0.20-0.76)	<0.01
Ethnicity				
AA vs. Caucasian	0.80 (0.64-1.02)	0.07	0.71 (0.56-0.91)	<0.01
Other vs. Caucasian	0.98 (0.71-1.36)	0.90		
Active Duty Status	1.41 (1.13-1.75)	<0.01		
Medical History				
Diabetes	0.84 (0.56-1.25)	0.38		
Skin condition in past year	1.79 (1.11-2.88)	0.02		
Syphilis	1.29 (1.01-1.64)	0.04	1.27 (0.98-1.64)	0.07
Antibiotic use in past year	2.20 (1.77-2.73)	<0.01	1.82 (1.45-2.28)	<0.01
Hospitalization in past year	1.79 (1.32-2.43)	<0.01	1.57 (1.14-2.16)	<0.01
HIV-Related Information				
AIDS-defining condition	0.90 (0.65-1.25)	0.53		
CD4 cell count (per 50 cells/mm ³)	0.98 (0.96-0.99)	0.03		
HIV RNA level (per 1 log ₁₀)	1.26 (1.16-1.37)	<0.01	1.11 (1.00-1.24)	0.06
HAART use	0.58 (0.46-0.73)	<0.01		

AA, African American; HAART, highly active antiretroviral therapy

^I Shows factors with p-value <0.10

Table 4

Multivariate Analysis¹ of HAART Use and HIV RNA Level and the Risk of Skin and Soft Tissue Infections (SSTIs)

Factor	HR (95% CI) ²	p-value
HAART and HIV RNA <1000 copies/ml	0.64 (0.48-0.86)	<0.01
HAART and VL 1000 copies/ml	0.64 (0.42-1.10)	0.05
No HAART and VL <1000 copies/ml	0.83 (0.51-1.37)	0.47

¹ Adjusted for all variables shown in Table 1

² All comparisons to not receiving HAART with a HIV RNA 1000 copies/ml.