Skin and Soft Tissue Infection in People Living With Human Immunodeficiency Virus in a Large, Urban, Public Healthcare System in Houston, Texas, 2009–2014

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Background. Skin and soft tissue infections (SSTIs) disproportionately impact patients with human immunodeficiency virus (HIV). Recent declines in the incidence of SSTIs have been noted in the non-HIV population. We sought to study the epidemiology and microbiology of SSTIs in a population of 8597 patients followed for HIV primary care in a large, urban county system from January 2009 to December 2014.

Methods. SSTIs were identified from the electronic medical record by use of International Classification of Diseases-9 billing codes. Charts were reviewed to confirm each patient's diagnosis of acute SSTI and abstract culture and susceptibility data. We calculated the yearly SSTI incidences using Poisson regression with clustering by patient.

Results. There were 2202 SSTIs identified. Of 503 (22.8%) cultured SSTIs, 332 (66.0%) recovered *Staphylococcus aureus* as a pathogen, of which 287/332 (86.4%) featured *S. aureus* as the sole isolated organism. Among the *S. aureus* isolates that exhibited antibiotic susceptibilities, 231/331 (69.8%) were methicillin resistant, and the proportion did not change by year. The observed incidence of SSTI was 78.0 per 1000 person-years (95% confidence interval 72.9–83.4) and declined from 96.0 infections per 1000 person-years in 2009 to 56.5 infections per 1000 person-years in 2014 ($P < .001$). Other significant predictors of SSTI incidences in both univariate as well as multivariate analyses included a low CD4 count, high viral load, and not being a Spanish-speaking Hispanic.

Conclusions. SSTIs remain a significant problem in the outpatients living with HIV, although rates of SSTIs appear to have declined by approximately 40% between 2009 and 2014.

Keywords. HIV; skin and soft tissue infection; MRSA; epidemiology.

The emergence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) in the United States in the late 1990s and early 2000s [1], primarily caused by the emergence of a novel USA300 strain of MRSA [2], significantly changed the epidemiology of skin and soft tissue infections (SSTIs) [2]. The incidence of SSTIs in the United States doubled between 1997 and 2005 [3], with even larger increases in certain subpopulations, such as prisoners [4], men who have sex with men (MSM) [5], and African-Americans [6].

In the late 2000s, numerous studies demonstrated the disproportionate impact of CA-MRSA on patients with human immunodeficiency virus (HIV), even for those with normal CD4+ lymphocyte counts [7, 8]. Studies have suggested varying

explanations for the increased CA-MRSA risk in patients with HIV. The epidemiologic factors proposed include sexual practices and sexual networks [9], incarceration [10], drug use [11], poverty, and housing. Key to epidemiologic theories is the idea that HIV and MRSA represent “intersecting epidemics” [7]. The biologic reasons proposed for the high rate of CA-MRSA SSTIs in patients with HIV include innate immune factors [12], as well as traditional markers of immunocompromise, such as CD4+ lymphocyte counts and HIV viral loads [13].

However, recent studies in non-HIV populations suggest a decline in the SSTI incidence [14], and the impact of CA-MRSA in the broader population may be waning, for reasons that currently remain unclear. At least 1 study in patients with HIV insured by a health maintenance organization showed a similar pattern [15]. However, the extent of the decline in SSTI incidences in patients with HIV in public health settings, and whether the epidemiology of SSTIs in this population has changed, remains unknown.

MRSA strains belonging to the USA300 MRSA lineages are traditionally identified by pulsed field gel electrophoresis. However, retrospective studies have frequently used sensitivity

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data, such as clindamycin susceptibility or fluoroquinolone susceptibility [16], as a marker for CA-MRSA. Nonetheless, increased use of clindamycin for SSTI [17] may, over time, lead to increased resistance in population strains. Accordingly, ongoing monitoring for resistance is warranted.

Hispanic ethnicity has been noted in other settings to convey a decreased risk of CA-MRSA in populations with HIV [18]. However, the term “Hispanic,” as used in the United States, describes immigrants from multiple countries in the Americas and the Caribbean and their descendants, as well as the inhabitants of or migrants from Puerto Rico, a territory of the United States. Migration patterns may vary greatly from city to city within the United States [19]. Furthermore, in Texas and the Southwestern United States, the term Hispanic may be applied to people whose families have lived in the United States for many generations [20] and who demonstrate a high degree of acculturation, defined as “the degree to which an individual from 1 culture adopts the behaviors or characteristics of a different ‘host’ culture” [21]. In addition, longitudinal data on trends in the SSTI incidence in Hispanic populations are lacking.

Here, we set out to study the incidence, epidemiology, and microbiology of SSTIs in a population of people living with HIV who were followed at a large, publicly funded health system in Houston, Texas, which is a setting with low rates of intravenous drug use [22]. Furthermore, we specifically sought to determine whether the epidemiology of SSTIs was different in English-speaking Hispanics and Spanish-speaking Hispanics, compared to non-Hispanic populations, with the hypothesis that English-speaking Hispanics would demonstrate an SSTI incidence similar to that of non-Hispanic populations.

METHODS

This study was a retrospective cohort study of patients with HIV who were treated in the Harris Health System—the public health system for Harris County, Texas—from 1 January 2009 to 31 December 2014. Harris County includes Houston, Texas, the fourth-largest municipality in the United States. Included in this health system are 2 affiliated urban teaching hospitals, as well as Thomas Street Health Center, a large outpatient HIV clinic.

Patients with HIV were identified via the electronic medical record (EMR) and were eligible for inclusion in this study if they were over age 18 and completed at least 2 visits to Thomas Street Health Center within a 12-month period during the period of the study.

Patient demographics (date of birth, sex, race/ethnicity), dates of clinic visits, and laboratory results (CD4+ lymphocyte count, HIV viral load) completed from 1 January 2008 to 31 December 2014 were electronically abstracted from the EMR. The patient’s language preference was abstracted from their EMR. SSTIs were identified by appropriate International

Table 1. Diagnosis Codes Used to Identify Potential Skin and Soft Tissue Infections in This Study

ICD-9/CPT Code	Description
035	Erysipelas
373.13	Abscess of eyelid
607.2	Other inflammatory disorders of penis
608.4	Other inflammatory disorders of male genital organs
611.0	Inflammatory disease of breast
616.4	Other abscess of vulva
675.0	Infections of nipple associated with childbirth
675.1	Abscess of breast associated with childbirth
675.2	Nonpurulent mastitis associated with childbirth
680	Carbuncle and furuncle
681	Cellulitis and abscess of finger and toe
682	Other cellulitis and abscess
683	Acute lymphadenitis
684	Impetigo
685.0	Pilonidal cyst with abscess
686	Other local infections of skin and subcutaneous tissue
704.8	Other specified diseases of hair and hair follicles
707	Chronic ulcer of skin
705.83	Hidradenitis
728.0	Infective myositis
771.5	Neonatal infective mastitis
10060	Incision and drainage of abscess: simple or single
10061	Incision and drainage of abscess: complicated or multiple
10080	Incision and drainage of pilonidal cyst: simple
10081	Incision and drainage of pilonidal cyst: complicated
10140	Incision and drainage of hematoma, seroma, or fluid collection
10160	Puncture aspiration of abscess, hematoma, bulla, or cyst

Abbreviation: CPT, Current Procedural Terminology; ICD-9, International Classification of Diseases-9.

Classification of Disease-9 codes in the EMR (Table 1). The diagnosis of acute SSTI was confirmed by an EMR review of clinician notes and prescription data. Postoperative infections and infections of prostheses or medical devices were excluded.

Standard statistics (counts, proportions, averages) were calculated. Incidences and incidence rate ratios (IRRs) were calculated using Poisson regression models with clustering by patient [23]. This is equivalent to the use of a generalized estimating equation approach with log link function, independent correlation structure, and robust variance. CD4+ lymphocyte count, HIV viral load, and age were treated as time-varying variables. CD4+ lymphocyte count and HIV viral load were interpolated using a “carry forward” approach between measured values. Patients were deemed to be out of care and to not contribute follow-up time if over 12 months elapsed between visits, consistent with other work in populations that intermittently access care [24]. Stata 12.0 IC (Statacorp, College Station, TX) was used for all analyses.

The institutional review boards of Baylor College of Medicine and the University of Texas Health McGovern School of

Medicine approved the study. The requirement for informed consent was waived for this retrospective study.

RESULTS

In total, 8597 patients met the criteria for study inclusion and contributed follow-up time to the study. Their demographics are presented in Table 2. Of note, the population was predominantly male (68.2%), with approximately equal proportions being heterosexual and MSM. Over 85% of patients were racial or ethnic minorities. The median age at initiation of follow-up was 42.7 years (range 18–84). The number of unique patients visiting the clinic per year increased from 4426 to 5512 from 2009 to 2014, while the number of patient visits with HIV care providers decreased from 16 107 to 14 528 (Table 3), a 28% decrease in visits per patient per year.

We observed that 1136 of 8597 subjects had at least 1 SSTI in follow-up (13.2%). The observed incidence of SSTI was 78.0 per 1000 person-years (95% confidence interval [CI] 72.9–83.4), with a decline from 96.0 per 1000 person-years in 2009 to 56.5 per 1000 person-years in 2014 ($P < .001$; Figure 2).

Of the 2202 SSTIs identified, 503 (22.8%) were associated with culture data (Figure 1). Of cultured SSTIs, 332 (66.0 %) included *S. aureus* as at least 1 of the pathogens, of which 287 out of the 332 (86.4%) featured *S. aureus* as the sole organism recovered. Of *S. aureus* isolates with susceptibilities, 231/331 (69.8%) were methicillin resistant, and the proportion did not vary by year (Table 4). The observed incidence of MRSA-positive SSTIs was 7.1 per 1000 person-years (95% CI 5.9–8.5), with a decline from 11.0 per 1000 person-years in 2009 to 4.7 per 1000 person-years in 2014 ($P < .01$; Figure 1).

Table 2. Demographics of the Study Population

Factor	Number of Patients (N = 8597)
Gender	
Female	2730 (31.8%)
Male	5867 (68.2%)
Race/ethnicity	
Non-Hispanic White/Asian/other	1197 (13.9%)
Non-Hispanic African American	5229 (60.8%)
English-speaking Hispanic	989 (11.5%)
Spanish-speaking Hispanic	1178 (13.7%)
MSM status	
Yes	2858 (33.2%)
No	5739 (66.8%)
Initial Age	
<25	639 (7.4%)
25–34	1852 (21.5%)
35–44	2480 (28.8%)
45–54	2604 (30.3%)
55–64	877 (10.2%)
65+	145 (1.7%)

Abbreviation: MSM, men who have sex with men.

Clindamycin susceptibilities (including the D test, when indicated) [25] were available for 256 of 332 *S. aureus* isolates (77.1%), and were available for 174 of 231 MRSA isolates (75.3%). A total of 145 out of 256 (56.6%) of all *S. aureus* isolates were susceptible to clindamycin. Among MRSA isolates, 93 out of 174 (54%) exhibited susceptibility to clindamycin. Of the remaining 81 MRSA isolates, 80 showed clindamycin resistance. Fluoroquinolone susceptibilities were available for 70 of these MRSA isolates, with 12/70 (17.1%) susceptible and 23/70 (32.9%) reported as intermediate.

The results of univariate and multivariate Poisson regressions are presented in Table 5. The multivariate model excluded gender and MSM status, as they were not significant in a univariate analysis ($P > .10$). Even in the multivariate model, the incidence of SSTI was significantly lower in 2014, compared to 2009 (adjusted IRR [aIRR] 0.66, 95% CI 0.55–0.80; $P < .001$).

Compared with the reference group of non-Hispanic White/Asian/other patients, African-Americans and English-speaking Hispanics exhibited similar incidences of SSTIs in both unadjusted and adjusted analyses. However, the incidence of SSTI in Spanish-speaking Hispanics was less than half that of the reference population (unadjusted IRR 0.46, 95% CI 0.36–0.60; $P < .001$), a finding that remained significant in the adjusted model (aIRR 0.44, 95% CI 0.34–0.57; $P < .001$). A CD4+ lymphocyte count under 50 cells/mm³ and an HIV viral load over 1000 copies/mL were, as expected, factors that were highly associated with each other; both were independent predictors of an increased SSTI risk in the multivariate model. An increased age was associated with a decreased risk of SSTI, with those aged 65 and older demonstrating a risk that was a fraction of that seen in patients under age 25 (IRR 0.25, 95% CI 0.15–0.43; $P < .001$), a finding which remained significant in the multivariate analysis (aIRR 0.33, 95% CI 0.19–0.55; $P < .001$).

In a further exploratory analysis, we did not see evidence that the decline in the incidence in SSTI was more or less pronounced in specific subgroups—defined by gender, age, race/ethnicity/language status, CD4+ lymphocyte count, or HIV viral load—either statistically, via an interaction analysis (data not shown), or graphically (Figure 3).

Table 3. Number of Unique Patients and Patient Visits and Community Viral Load per Year of the Study

Year	Unique Patients	Total Visits	Proportion of Patient-days With Viral Load Under 1000 Copies/mL
2009	4426	16 107	74.8%
2010	4924	16 129	80.3%
2011	5140	15 587	83.5%
2012	5248	14 931	84.9%
2013	5426	14 357	86.1%
2014	5512	14 528	87.0%

Figure 1. Breakdown of culture availability and results for 2202 SSTIs in this paper. Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; *S. aureus*, *Staphylococcus aureus*; SSTI, skin and soft tissue infection. ^a287 (86.5%) *S. aureus* monomicrobial infections.

DISCUSSION

In this study of a large cohort of patients living with HIV in a publicly funded health system, the incidence of medically attended SSTI markedly declined from 2009 to 2014, even after adjusting for improvements in CD4 counts and HIV viral loads. Nevertheless, the incidence of SSTIs in this population remains markedly elevated compared with HIV-negative populations, despite some suggestions—based on data in other cities—that the MRSA epidemic in persons living with HIV might have waned by the end point of this study [8].

Our findings regarding the association between age and SSTI risk reflect findings in other studies of patients with HIV [15], and may be explained by younger people being at a higher risk for person-to-person transmission, whether through contact

Figure 2. Yearly SSTI (top line) and MRSA incidence (bottom line) with 95% confidence intervals, 2009–2014, total population. Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft tissue infection.

Table 4. Number of Methicillin-resistant and -Susceptible *Staphylococcus aureus* Infections in Each Year of the Study

Year	MRSA	MSSA
2009	40 (76.9%)	12 (23.1%)
2010	55 (66.3%)	28 (33.7%)
2011	37 (66.1%)	19 (33.9%)
2012	36 (73.5%)	13 (26.5%)
2013	33 (76.7%)	10 (23.3%)
2014	30 (62.5%)	18 (37.5%)

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

sports, sexual contact, or incarceration. Similarly, our finding regarding the importance of the HIV viral load in determining the SSTI risk replicates observations from other cohorts [26]. Our observed association between a low CD4+ count and the SSTI risk has been previously described in some [27], but not all [26], studies that have examined this relationship, though adjustment, or lack thereof, for trimethoprim-sulfamethoxazole prophylaxis may explain some of the study-to-study variation [28]. The association between immunologic parameters and SSTI risk may reflect a direct relationship between immunocompromise and SSTI risk, lack of adherence to antibiotic prophylaxis [28], or an association between advanced HIV and dermatologic conditions associated with SSTI risk, such as psoriasis [18].

Spanish-speaking Hispanics demonstrated a lower incidence of SSTIs than other populations in both unadjusted and adjusted analyses, while English-speaking Hispanics showed an incidence of SSTIs comparable to other populations. We believe our study is the first to specifically look at the interaction between language preferences and SSTI risks in patients living with HIV. A potential explanation of this difference could include social network effects. The structure of social networks has been associated with the transmission dynamics of pathogenic strains of *S. aureus* [29]. Some data may suggest that Hispanic immigrants have social networks that differ in structure from the rest of the population [30], with differences found in Chicago between Hispanic immigrants and US-born Hispanics [31]. Cultural differences and the language barrier itself may both serve to limit connections between the social network of those Hispanic immigrants who predominantly speak Spanish and the broader population, reducing opportunities for CA-MRSA to be transmitted in this population.

Our findings may also be explained by Spanish-speaking Hispanics using less health care or outside health care for SSTIs. Although patients in our study had a clinic at which they could access care, a study in another Southern United States city found that geographic and transportation barriers were a significant contributor to decreased healthcare use among Hispanic immigrants [32]. Further, studies within Thomas Street itself have found that transportation is a significant barrier to accessing

Table 5. Predictors of Skin and Soft Tissue Infections in Univariate and Multivariate Poisson Regression Models With Clustering by Patient

Factor	Univariate IRR (95% CI)	Multivariate IRR (95% CI)
Race/ethnicity		
Non-Hispanic White/Asian/Other	Ref	Ref
Non-Hispanic African American	0.92 (.76–1.11)	0.84 (.69–1.01)
English-speaking Hispanic	0.88 (.69–1.12)	0.83 (.65–1.06)
Spanish-speaking Hispanic	0.46 ^a (.36–.60)	0.44 ^a (.34–.57)
CD4+ count (cells/mm³)		
100+	Ref	Ref
50–100	1.56 ^b (1.19–2.04)	1.21 (.92–1.60)
<50	2.28 ^a (1.80–2.90)	1.45 ^b (1.13–1.87)
Viral load (copies/mL)		
<1000	Ref	Ref
1000+	2.17 ^a (1.91–2.46)	1.79 ^a (1.56–2.06)
Male gender		
Men who have sex with men	1.06 (.92–1.22)	...
Year		
2009	Ref	Ref
2010	0.89 (.75–1.06)	0.92 (.78–1.10)
2011	0.90 (.75–1.07)	0.97 (.81–1.15)
2012	0.91 (.76–1.09)	1.00 (.84–1.20)
2013	0.71 ^a (.58–.85)	0.78 ^c (.65–.95)
2014	0.59 ^a (.49–.71)	0.66 ^a (.55–.80)
Age		
<25	Ref	Ref
25–34	0.88 (.64–1.22)	0.99 (.71–1.37)
35–44	0.85 (.61–1.17)	0.98 (.71–1.36)
45–54	0.69 ^c (.50–.95)	0.80 (.58–1.10)
55–64	0.55 ^b (.40–.78)	0.67 ^c (.48–.95)
65+	0.25 ^a (.15–.43)	0.33 ^a (.19–.55)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; Ref, reference category.

^a $P < .001$.^b $P < .01$.^c $P < .05$.

care [33]. Hispanics in general are lower users of emergency services in Harris County [34]. National data suggest that more-acclulturated Hispanics have been described as more likely to use emergency services [21] than less-acclulturated Hispanics. Moreover, studies in multiple settings have found that Hispanic immigrants in the United States frequently obtain antibiotics without a prescription or without seeing a physician [35], either from leftover antibiotics from previous prescriptions, from friends, or from local ethnic stores (*tiendas*). Accordingly, the decreased incidence of SSTIs observed in Hispanics in other studies, and of Spanish-speaking Hispanics in this study, may be artefactual and reflect self-treatment of SSTIs outside of healthcare settings. That said, a study in Houston (conducted, in part, in the same healthcare system as our study) found that the use of unprescribed antibiotics was common in all populations described [36]. The observed nonprescription use within the prior year was 7.7% in Hispanics, 3.8% in African-Americans, and 2.6% in other populations. No specific analysis of English-speaking Hispanics and Spanish-speaking Hispanics was performed.

The reasons for the decline in the SSTI risk in this population over the course of the study are unclear, though these patients are part of a nationwide pattern that has been observed in patients with HIV, as well as in the general population [14]. The reasons for this nationwide trend are themselves unknown. The marked increase in the SSTI incidence seen in the early 2000s may have reflected the emergence of a novel *S. aureus* strain, USA300, in an immunologically naive population, and the subsequent decreases in the SSTI incidence that have been observed may relate to changes in the host-pathogen relationship over time [37]. The role of individual- and population-level immunities in determining the emergence and decline of new *S. aureus* strains in the general population, as well as in specific subpopulations, remains to be elucidated.

The high level of clindamycin resistance in this study is notable. That most of these strains were either fluoroquinolone-intermediate or -resistant suggests that many of the patients in our study may have been developing SSTIs with strains other than USA300, either from other hospital strains or other community strains, although the emergence of clindamycin

Figure 3. Yearly SSTI incidence with 95% confidence intervals, 2009–2014, subpopulations. *A*, Sex. *B*, Race/ethnicity/language. *C*, Age. *D*, CD4+ lymphocyte count. *E*, Human immunodeficiency virus RNA. Abbreviations: MSM, men who have sex with men; SSTI, skin and soft tissue infection.

resistance in USA300 cannot be ruled out. We do not have detailed data on hospitalizations in this study. However, other studies have found hospitalization to be a common event in patients in HIV at risk for SSTIs [26].

Strengths of this study include the large, diverse, urban cohort that was studied, the validation of SSTI diagnoses by EMR reviews, the longitudinal nature of the data itself and the statistical analysis, and the merger of billing data with microbiologic data. Limitations include its retrospective nature in a single health system. We did not capture SSTIs for which

patients did not seek care or sought care at other institutions. The number of visits per patient decreased over the course of the study, suggesting that the number of incidentally detected SSTIs may have decreased as well. We depended on clinician diagnoses and billing for the study and may have missed SSTIs if they were not billed for. However, as the EMR requires a diagnosis for an antibiotic prescription and for procedures, we do believe we captured most of the SSTIs associated with either antibiotic prescriptions or with incisions and drainage. Although the positive predictive value of International

Classification of Disease–based ascertainment methods for SSTIs has been studied [38], the sensitivity remains unknown. However, our methods are consistent with prior studies on the topic [14]. We do not have genotype data for *S. aureus* isolates. We lack data on trimethoprim-sulfamethoxazole (TMP-SMX) adherence and usage, but previous internal audit data have shown that over 95% of patients who qualify for a TMP-SMX prophylaxis at our center are, in fact, prescribed the drug. Our patient population has a high rate of loss to follow-up and intermittent use of care, but this is common in studies of many HIV populations using public health systems [39]. The transgender status of patients was not documented, and there was inconsistent documentation of gender for transgender patients at the time of the study, though the overall number of transgender patients followed at Thomas Street Health Center at the time of the study was low. We were dependent on EMR reporting for data on race, ethnicity, and language status. The use of the EMR for language status, in particular, is problematic, as these data are collected by front-line clinic staff as part of “meaningful use” requirements. Only 1 language can be selected, ignoring the complex spectrum of multilingualism. However, given that the use of the “Language” tab in the EMR was to identify patients in need of Spanish-speaking providers or translational assistance, we believe that patients who preferred Spanish but were bilingual were mostly identified as having an “English” language preference. An earlier study conducted in a different health system showed that 1 of 3 patients recorded as “Spanish-speaking” in the EMR opted to complete an offered survey in English even though a Spanish version was readily available; similarly, a substantial proportion of patients who opted to complete the survey in Spanish were listed in the EMR as “English-speaking” [40]. However, misclassifications would have biased our findings towards the null hypothesis. The degree of acculturation was not assessed in this retrospective study. Our EMR was newly phased-in for inpatient and emergency room settings at the beginning of the study. While we believe our findings are real, we cannot exclude the EMR implementation affecting some of our results. Finally, the data are from an area with a low and stable prevalence of injection drug use in people with HIV, so may not be generalizable to areas with increasing rates.

CONCLUSION

Although SSTI rates in a large, urban cohort of outpatients living with HIV declined by approximately 40% between 2009 and 2014, SSTIs remained a significant problem even at the end of the study period. A CD4+ count under 50 cells/mm³ and an elevated HIV viral load were associated with an increased SSTI risk, while older age and Spanish-speaking Hispanic ethnicity were protective. The majority of *S. aureus* SSTIs throughout the study period were methicillin-resistant, and there were no

signs of methicillin-susceptible *Staphylococcus aureus* replacing MRSA in this population. Although MRSA is a less salient issue in patients with HIV than it was in the past, SSTIs remain a significant problem in patients with HIV, for reasons which merit further study.

Notes

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