INCIDENCE OF AND FACTORS ASSOCIATED WITH METHICILLIN-RESISTANT \textit{STAPHYLOCOCCUS AUREUS} SKIN AND SOFT-TISSUE INFECTIONS AMONG HIV-INFECTED PERSONS

A Thesis
Presented to the
Faculty of
San Diego State University

In Partial Fulfillment
of the Requirements for the Degree
Master of Science
in
Bioinformatics and Medical Informatics

by
Aladdin H. Shadyab
Spring 2012
SAN DIEGO STATE UNIVERSITY

The Undersigned Faculty Committee Approves the

Thesis of Aladdin H. Shadyab:

Incidence of and Factors Associated with Methicillin-Resistant Staphylococcus aureus Skin and Soft-Tissue Infections among HIV-Infected Persons

Chii-Dean Lin, Chair
Bioinformatics and Medical Informatics Program

Willa Fields
Bioinformatics and Medical Informatics Program

Kung-Jong Lui
Department of Mathematics and Statistics

Nancy Crum-Cianflone
Graduate School of Public Health

4/18/12
Approval Date
DEDICATION

This thesis is dedicated to my family.
ABSTRACT OF THE THESIS

Incidence of and Factors Associated with Methicillin-Resistant
Staphylococcus aureus Skin and Soft-Tissue Infections among
HIV-Infected Persons
by
Aladdin H. Shadyab
Master of Science in Bioinformatics and Medical Informatics
San Diego State University, 2012

Background: Infections caused by methicillin-resistant Staphylococcus aureus (MRSA) are an important cause of morbidity and have become an important public health threat throughout the past decade. Persons infected with human immunodeficiency virus (HIV) have an increased risk for MRSA infections compared to the general population, and a 6-18 fold increase in risk has been reported. Limited studies have examined recent trends in the incidence of MRSA skin and soft-tissue infections (SSTIs) among HIV-infected persons, with one suggesting that the incidence is now declining. Furthermore, factors associated with the development of initial and recurrent MRSA SSTIs have not been fully elucidated among HIV-infected persons. It is currently not known whether specific treatment approaches for the initial MRSA infection reduce the risk for recurrent infection. An understanding of the epidemiology of and the factors associated with MRSA SSTIs is imperative for prevention of MRSA infections. Purpose: The purpose of this study is to examine recent trends in the incidence of MRSA SSTIs and to determine factors associated with the development of initial and recurrent MRSA SSTIs. Methods: We retrospectively evaluated a large cohort of HIV-infected military beneficiaries from 1993-2010 for wound culture-proven MRSA SSTIs. Multiple logistic regression models evaluated factors associated with MRSA SSTIs. Linear mixed-effects models assessed the impact of CD4 cell count and HIV viral load measurements on the development of recurrent infections. Finally, the random forests algorithm determined variables most predictive of initial and recurrent MRSA SSTIs. Results: Of 794 patients, 63 (8%) experienced a total of 108 MRSA SSTIs from 1993-2010 for an incidence of 19.3 infections/1000 person-years. A 2.4-fold increase in the incidence was observed from 2003-2006 (p< 0.01); however, a decreasing trend in the incidence was noted from 2007-2010. Factors associated with initial MRSA SSTIs included a CD4 cell count <500 cells/mm3 and HIV viral load ≥400 copies/mL (OR 5.2; p-value <0.01), CDC stage C (OR 5.4; p-value <0.01), and injection drug use (OR 4.9; p<0.01). Factors associated with recurrent MRSA SSTIs included hospital admission after the initial infection (OR 7.4; p=0.02). Minocycline for treatment of the initial infection was associated with an 80% reduction in the odds for recurrence (OR 0.2; p=0.03). In the linear mixed model, patients who experienced a recurrent infection had on average lower CD4 cell counts than patients who did not experience recurrence (p=0.03). Variables associated with poor immune status were most predictive of initial and recurrent infections in the random forests analysis. Conclusion: HIV-infected persons with poor immune status may be immunologically predisposed to develop MRSA SSTIs. Minocycline for treatment of MRSA SSTIs may
reduce the burden of recurrent disease; prospective, randomized trials are needed to confirm this finding.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT ...........................................................................................................................................................</td>
</tr>
<tr>
<td>LIST OF TABLES .......................................................... ix</td>
</tr>
<tr>
<td>LIST OF FIGURES ..................................................... xi</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS ................................................... xii</td>
</tr>
<tr>
<td>CHAPTER</td>
</tr>
<tr>
<td>1 INTRODUCTION ................................................................. 1</td>
</tr>
<tr>
<td>Statement of the Problem ....................................................... 2</td>
</tr>
<tr>
<td>Purpose of the Study ............................................................. 3</td>
</tr>
<tr>
<td>Goals and Hypotheses ............................................................ 3</td>
</tr>
<tr>
<td>Theoretical Basis .................................................................. 4</td>
</tr>
<tr>
<td>2 LITERATURE REVIEW ....................................................... 5</td>
</tr>
<tr>
<td>Introduction ........................................................................ 5</td>
</tr>
<tr>
<td>Review of Human Immunodeficiency Virus .................................. 5</td>
</tr>
<tr>
<td>Methicillin-Resistant <em>Staphylococcus aureus</em>: Introduction ............... 6</td>
</tr>
<tr>
<td>MRSA Colonization among HIV-Infected Persons ......................... 7</td>
</tr>
<tr>
<td>MRSA Infections among HIV-Infected Persons .................................. 8</td>
</tr>
<tr>
<td>Incidence of MRSA Infections in HIV-Infected Persons .................. 9</td>
</tr>
<tr>
<td>Risk Factors for MRSA Infections .......................................... 10</td>
</tr>
<tr>
<td>Recurrent MRSA Infections ................................................ 14</td>
</tr>
<tr>
<td>Antibiotic Resistance Patterns of MRSA Infections ....................... 15</td>
</tr>
<tr>
<td>Management of MRSA Infections in the HIV-Infected Patient ............ 17</td>
</tr>
<tr>
<td>Prevention of MRSA Infections .............................................. 18</td>
</tr>
<tr>
<td>3 METHODS ........................................................................ 20</td>
</tr>
<tr>
<td>Study Design and Population .................................................. 20</td>
</tr>
<tr>
<td>Data Collection ................................................................... 21</td>
</tr>
<tr>
<td>Variables ........................................................................... 22</td>
</tr>
<tr>
<td>Part I: Factors Associated with the Development of a MRSA Infection</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 1. CDC HIV Staging System .........................................................................................62
Table 2. Medical History Factors Associated with MRSA Infections among HIV-Infected Persons ...........................................................................................................63
Table 3. Behavioral Factors Associated with MRSA Infections among HIV-Infected Persons .........................................................................................................................66
Table 4. Summary of Treatment and Outcomes of MRSA Infections among HIV-Infected Persons ...........................................................................................................67
Table 5. Incidence Rate of MRSA SSTI Events among HIV-Infected Persons by Time Period (1993-2010) .............................................................................................73
Table 6. Clinical Characteristics of Methicillin-Resistant Staphylococcus aureus Skin and Soft-Tissue Infections among HIV Infected Persons ............................................74
Table 7. Clinical Characteristics of the Initial Episode of a Methicillin-Resistant Staphylococcus aureus Skin and Soft-Tissue Infection among HIV Infected Persons ...........................................................................................................75
Table 8. Study Population Characteristics and Univariate Logistic Regression Analysis of Factors Associated with MRSA Skin and Soft-Tissue Infections among HIV-Infected Persons ..........................................................................................................................76
Table 9. Final Multiple Logistic Regression Model of Factors Associated with MRSA Skin and Soft-Tissue Infections among HIV-Infected Persons (n=788) .......................................................................................78
Table 10. Univariate Logistic Regression Analysis of Factors Associated with Recurrent MRSA Skin and Soft-Tissue Infections among HIV-Infected Persons with an Initial MRSA Infection ..........................................................................................................................79
Table 11. Final Multiple Logistic Regression Model of Factors Associated with Recurrent MRSA Skin and Soft-Tissue Infections among HIV-Infected Persons, Including Receipt of Minocycline as Initial Antibiotic (n=59) .......................................................................................83
Table 12. Final Multiple Logistic Regression Model of Factors Associated with Recurrent MRSA Skin and Soft-Tissue Infections among HIV-Infected Persons, Including Receipt of Minocycline at any Time for Treatment (n=59) .......84
Table 13. Factors Associated with Receipt of Minocycline for Initial MRSA SSTI ..........85
Table 14. Final Linear-Mixed Effects Model of the Association between CD4 Cell Count (Cells/mm^3) and Recurrent MRSA Skin and Soft-Tissue Infections (n=54) .................................................................................86
Table 15. Final Linear-Mixed Effects Model of the Association between $\log_{10}$ HIV Viral Load and Recurrent MRSA Skin and Soft-Tissue Infections (n=54) .................86
LIST OF FIGURES

PAGE

Figure 1. Incidence of MRSA SSTIs among HIV infected persons, 1993-2010..................31
ACKNOWLEDGEMENTS

I would like to thank the members of my thesis committee (Dr. Joey Lin, Dr. Willa Fields, Dr. Kung-Jong Lui, and Dr. Nancy Crum-Cianflone) for their guidance with this process. I would like to thank Dr. Lin for serving as my thesis chair and for providing statistical expertise on my thesis. I would like to thank Dr. Crum-Cianflone for allowing me access to this dataset for my thesis and for providing infectious disease expertise on my thesis. I thank Dr. Fields for her input and interest in my topic, and Dr. Lui for his statistical advice. I also thank Kartavya Vyas of the Naval Medical Center San Diego for preparing the dataset for this work.
CHAPTER 1

INTRODUCTION

Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) have become an important public health threat throughout the past decade. Once restricted to the hospital setting, MRSA infections are now observed in the community (community-acquired MRSA [CA-MRSA]) among persons without traditional risk factors for infection. Outbreaks of CA-MRSA infection have been reported in children in daycare facilities, prisoners, athletes, military personnel, and men who have sex with men (MSM) (Campbell et al., 2004; Diep et al., 2008; Fridkin et al., 2005).

Persons infected with human immunodeficiency virus (HIV) have an increased risk for MRSA infection compared to the general population, and a 6-18 fold increase in risk has been reported (Crum-Cianflone, Burgi, & Hale, 2007; Popovich, Weinstein, Aroutcheva, Rice, & Hota, 2010; Senthilkumar, Kumar, & Sheagren, 2001). MRSA can cause a diverse range of infections among HIV-infected persons, including skin and soft-tissue infections (SSTIs) and more severe, life-threatening infections such as bacteremia and necrotizing fasciitis (Nguyen et al., 1999; Olsen, Burns, Chen, Kreiswirth, & Musser, 2008; Onorato et al., 1999; Skiest et al., 2006; Tumbarello et al., 2002). Of growing concern is that HIV-infected persons appear to be at increased risk for recurrent MRSA SSTIs, serving as reservoirs of MRSA in the community; a recurrence rate as high as 71% has been reported (Graber, Jacobson, Perdreau-Remington, Chambers, & Diep, 2008). Additionally, with the emergence of a novel, multidrug resistant strain of MRSA among MSM, an understanding of the epidemiology of and the factors associated with MRSA SSTIs is imperative for prevention of MRSA infections and transmission (Diep et al., 2008).

Risk factors for MRSA SSTIs among HIV-infected persons have been variable across studies and have included immunosuppression as demonstrated by a low CD4 cell count and high HIV viral load, colonization with MRSA, recent hospitalization, and behavioral factors including illicit drug use and participation in high-risk sexual behaviors (e.g., multiple sex partners, public bath use) (Drapeau, Angeletti, Festa, & Petrosillo, 2007; Lee et al., 2005;
Mathews et al., 2005; Szumowski et al., 2009). Factors potentially protective against MRSA SSTIs have included use of highly active antiretroviral therapy (HAART) and prophylaxis with trimethoprim-sulfamethoxazole, or Septra (Hidron, Moanna, & Rimland, 2011; Lee et al., 2005; Mathews et al., 2005).

Limited studies have examined recent trends in the incidence of MRSA infections among HIV-infected persons, with one suggesting that the incidence is now declining (Hidron et al., 2011). Furthermore, studies examining recurrent MRSA SSTIs among HIV-infected persons have been predominantly case reports, and factors associated with recurrent MRSA SSTIs are largely unknown (Anderson, Hawkins, Bolon, & Palella, 2006; Graber et al., 2008; Sztramko et al., 2007; Vyas, Hospenthal, Mende, & Crum-Cianflone, 2011). It has not been established whether proper management including appropriate antibiotic therapy for initial MRSA SSTIs can prevent the development of recurrent infections. Additionally, guidelines for the clinical management of MRSA SSTIs among HIV-infected persons have not been devised. The purpose of this study is to examine recent trends in the incidence of MRSA SSTIs and to determine factors associated with the development of initial and recurrent MRSA SSTIs.

**STATEMENT OF THE PROBLEM**

The incidence of MRSA SSTIs has risen in the past decade among HIV-infected persons (Crum-Cianflone et al., 2007; Hidron et al., 2011). However, recent trends in the incidence of MRSA SSTIs among diverse populations are currently unknown. Furthermore, risk factors for MRSA SSTIs among HIV-infected persons have not been consistent across studies. Some studies have suggested that HIV-infected persons with a low CD4 cell count and a high HIV viral load have an immunologic predisposition to develop MRSA infections (Crum-Cianflone et al., 2007; Hidron et al., 2011; Mathews et al., 2005). Other studies have cited behavioral factors, such as illicit drug use and participation in high-risk sexual behaviors, as important causes of MRSA infections (Hidron et al., 2005; Lee et al., 2005; Mathews et al., 2005). HIV-infected persons are also susceptible to recurrent MRSA infections; however, factors associated with recurrent infections have not been clearly defined. Understanding the factors associated with MRSA infection and recurrence may aid in the development of strategies to prevent MRSA transmission and infection.
PURPOSE OF THE STUDY

The purpose of the current investigation is to examine trends in the incidence of MRSA SSTIs among HIV-infected persons in the past eighteen years, as well as to determine factors associated with MRSA SSTIs. Factors to be examined include demographics (e.g., age, race, gender), history of sexually transmitted infections (e.g., syphilis, herpes simplex virus-2), relevant medical conditions (e.g., hypertension, cancer, diabetes, eczema), injection drug use, and HIV history, including duration of HIV, CD4 cell count, HIV viral load, Centers for Disease Control and Prevention (CDC) HIV stage, and use of highly active antiretroviral therapy. Additionally, SSTIs will be defined, including the type of infection, location of infection, and antibiotic sensitivity patterns of MRSA isolates.

The current study will also examine factors associated with recurrent MRSA SSTIs. In addition to the previously mentioned factors, variables describing the management of the initial infection will be analyzed, including type of antibiotic(s) prescribed, duration of antibiotic therapy, receipt of incision and drainage, and hospital admission for the initial infection. Other variables to be examined include surgery, hospital admission, and antibiotic use after the initial infection.

The results from the current study will contribute to the limited body of evidence on recent trends in the incidence of MRSA SSTIs among HIV-infected persons and will contribute to the current state of knowledge on factors associated with MRSA SSTIs. Additionally, it will provide an understanding of recurrent MRSA SSTIs, which may have important implications for prevention and clinical management.

GOALS AND HYPOTHESES

The incidence of MRSA infections among HIV-infected persons from 1993-2010 will be described. Factors associated with the development of an initial MRSA infection and recurrent infection will also be evaluated. In this study, it is hypothesized that the incidence of MRSA infections has been declining in the past four years. It is also hypothesized that HIV-infected persons with poor immune status (i.e., low CD4 cell count and high HIV viral load) are predisposed to develop MRSA infections. Finally, it is hypothesized that proper management of the initial MRSA infection as demonstrated by receipt of empiric
antimicrobials concordant with the MRSA isolate sensitivity pattern and incision and drainage will prevent the development of recurrent infections.

**Theoretical Basis**

To date, only one study has evaluated recent trends in the incidence of MRSA infections among HIV-infected persons, and suggested that the incidence has been declining since 2007 (Hidron et al., 2011). However, further research is needed to confirm this finding in diverse populations and also evaluate potential reasons for the decrease in incidence. It has been hypothesized that HIV-infected persons are immunologically predisposed to develop MRSA infections, yet findings have not been consistent across studies. Research from the current study may provide additional evidence that poor immune status is a significant predictor of MRSA infections, which may indicate that improved HIV control is essential in the clinical management of MRSA in HIV-infected persons. Furthermore, limited research has been conducted on recurrent infections among HIV-infected persons; moreover, studies on this topic have been largely case reports, and thus could not evaluate factors predictive of recurrent infections. It is of great interest to determine whether proper management of the initial MRSA infection can help prevent the development of subsequent infections, as this may contribute to MRSA prevention and may guide clinical management of MRSA infections.
CHAPTER 2

LITERATURE REVIEW

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important bacterial pathogen causing a wide range of infections including skin and soft-tissue infections, bacteremia, endocarditis, sepsis, and meningitis. The incidence of MRSA infections has increased in the past decade in both the community and hospital settings (Hidron et al., 2011; Klein, Smith, & Laxminarayan, 2009; Popovich et al., 2010).

HIV-infected persons have an increased risk for MRSA colonization and subsequent infection, and are susceptible to recurrent MRSA infections (Crum-Cianflone et al., 2007; Crum-Cianflone, Weekes, & Bavaro, 2009; Szumowski et al., 2009). This review will discuss the epidemiology, clinical manifestations, risk factors, and management of MRSA infections among HIV-infected persons.

REVIEW OF HUMAN IMMUNODEFICIENCY VIRUS

HIV is a retrovirus that results in the destruction of CD4 cells and consequently impairs cell-mediated and humoral immunity (i.e., antibody production) in the human host. CD4 cells, also known as helper T cells, are central to the immune response and as such are essential in antibody production, cytotoxic T cell activation, and macrophage activity. The depletion of CD4 cells in an HIV-infected patient may result in disease progression to acquired immunodeficiency syndrome (AIDS).

CD4 cell count measurements are important in the clinical management of HIV-infected persons. The Centers for Disease Control and Prevention have devised a clinical staging system for HIV infection that classifies HIV-infected persons based on their clinical conditions and nadir CD4 cell count (i.e., lowest CD4 cell count). In a healthy adult, normal CD4 cell count values vary from 600-1200 cells/mm³ of blood. Table 1 (see Appendix for all tables) shows the CDC HIV staging system (Centers for Disease Control and Prevention [CDC], 1993).
Since the advent of HAART in 1996, HIV-infected persons have experienced a decrease in opportunistic infections and an increase in their life expectancies. HAART is antiretroviral treatment taken by HIV-infected persons to suppress HIV viral replication and slow the progression of HIV disease, resulting in a rise in CD4 cell count. HAART involves three or more antiretroviral drugs taken in combination, which are usually two nucleoside reverse transcriptase inhibitors taken with either a non-nucleoside reverse transcriptase inhibitor, protease inhibitor, integrase inhibitor, or a CCR5 agonist (Department of Health and Human Services [DHHS], 2011). However, it is important to note that HAART does not eradicate HIV. Current guidelines recommend that antiretroviral therapy should be initiated in all patients with an AIDS-defining illness or with a CD4 count <350 cells/mm³, and is advised in patients with CD4 cell counts 350-500 cells/mm³ (DHHS, 2011).

**Methicillin-Resistant *Staphylococcus aureus*: Introduction**

*Staphylococcus aureus* is a Gram-positive bacterium that is frequently part of the normal skin flora. The primary reservoir of *S. aureus* is the nares, but it may also be found at the axillae, vagina, pharynx, rectum, and damaged skin surfaces (Lowy, 1998). Of note, more than 30% of healthy adults are colonized with *S. aureus* at any given time (Kluytmans, Belkum, & Verbrugh, 1997). Colonization involves the presence and multiplication of a microorganism without tissue invasion or damage.

Methicillin-resistant strains of *S. aureus* are resistant to beta-lactam antibiotics (e.g., methicillin, amoxicillin, oxacillin, nafcillin) and most cephalosporins (e.g., cephalexin, cefaclor, cefixime). Colonization with MRSA precedes and increases the risk for infection (Kluytmans et al., 1997). Infections caused by MRSA are associated with considerable morbidity and mortality, and range from SSTIs to more severe, life-threatening infections such as bacteremia and necrotizing fasciitis (Huang & Platt, 2003; Miller et al., 2005; Moran et al., 2006).

MRSA has emerged as the most common cause of SSTIs among patients presenting to United States emergency departments (Moran et al., 2006). MRSA infections are also a considerable burden in the outpatient setting; from 1999-2006, the percentage of MRSA infections increased over 90% in outpatients admitted to U.S. hospitals (Klein et al., 2009).
has been reported that ~19,000 hospitalized U.S. patients succumb annually to MRSA infections (Boucher & Corey, 2008).

MRSA was originally identified as a nosocomial pathogen (health care-associated MRSA [HA-MRSA]) among persons with traditional risk factors for infection, such as recent hospitalization or surgery, residence in a long-term care facility, dialysis, or catheter use (Lowy, 1998). However, in the past decade, MRSA has emerged in the community among persons without the predisposing factors for infection (community-acquired MRSA [CA-MRSA]). Outbreaks of CA-MRSA infection have been reported in children in daycare facilities, prisoners, athletes, military personnel, and men who have sex with men (MSM) (Campbell et al., 2004; Diep et al., 2008; Fridkin et al., 2005).

**MRSA Colonization among HIV-Infected Persons**

Compared to the general population, HIV-infected persons are at an increased risk for MRSA colonization and subsequent infection (Kluytmans et al., 1997). In the era of HAART, prevalence estimates of MRSA colonization among HIV-infected persons have ranged from 0-17%, generally higher than the 1.5% MRSA carriage rate reported in the general population (Antoniou et al., 2009; Cenizal, Hardy, Anderson, Katz, & Skiest, 2008; Gorwitz et al., 2008; McDonald, Lauderdale, Lo, Tsai, & Hung, 2003; Shet et al., 2009; Sissolak, Geusau, Heinze, & Witte, 2002; Szumowski et al., 2009; Villacian, Barkham, Earnest, & Paton, 2004). Although nares carriage is most commonly reported among HIV-infected persons, some studies have shown that MRSA may also colonize other body sites such as the axillae and perigenital region (Antoniou et al., 2009; Cenizal et al., 2008; Crum-Cianflone et al., 2011; Szumowski et al., 2009). One prospective cohort study reported a 3% MRSA nares carriage rate and a 2% perianal carriage rate among HIV-infected MSM (Szumowski et al., 2009). In another study, a rectal carriage rate of 0.4% was observed in a cohort of MSM, many of whom were HIV-infected (Antoniou et al., 2009). A recent study observed colonization at multiple body sites among HIV-infected persons, including 3% at the nares, 1% the throat, 0.2% the axillae, 0.5% the groin, and 0.5% the perirectal area (Crum-Cianflone et al., 2011).

Risk factors for MRSA colonization in HIV-infected persons vary by study population and have included low CD4 count, recent exposure to antibiotics, illicit drug use
(e.g., methamphetamines), recent hospitalization, prior MRSA colonization or infection, and chronic skin disease (Cenizal et al., 2008; McDonald et al., 2003; Ramsetty, Stuart, Blake, Parsons, & Salgado, 2010; Szumowski et al., 2009; Villacian et al., 2004). Factors protective against MRSA colonization have included receipt of trimethoprim-sulfamethoxazole and receipt of HAART (Cenizal et al., 2008; McDonald et al., 2003; Melles et al., 2008).

High-risk sexual behaviors have also been shown to increase the risk for MRSA colonization, with some studies implicating anal intercourse, history of sexually transmitted infections, MSM, and sex with >1 partner as potential risk factors for colonization (Antoniou et al., 2009; Crum-Cianflone et al., 2011; Diep et al., 2008; Szumowski et al., 2009). The mechanism of transmission may involve perigenital colonization with subsequent transfer during sexual activities including anal sex. MRSA colonizing the perigenital regions may also be transmitted during sexual activities involving intimate skin-to-skin contact or skin-abrading sexual practices. Notably, a recent study reported that a recent history of syphilis results in a nine-fold increased odds for MRSA colonization at one or more body sites and that public bath use is also associated with MRSA colonization (Crum-Cianflone et al., 2011). Further studies are needed to determine whether high-risk sexual behaviors are also associated with the increasing rate of buttock, genital, and perigenital infections in the HIV-infected population (Crum-Cianflone et al., 2007; Diep et al., 2008; Szumowski et al., 2009).

**MRSA Infections Among HIV-Infected Persons**

MRSA can cause a wide range of infections in HIV-infected persons including bacteremia, pneumonia, necrotizing fasciitis, and endocarditis, as well as SSTIs (Nguyen et al., 1999; Olsen et al., 2008; Onorato et al., 1999; Skiest et al., 2006; Tumbarello et al., 2002).

In the HAART era, MRSA SSTIs are more commonly reported among HIV-infected persons than invasive infections such as bacteremia and endocarditis. One retrospective cohort study among HIV-infected outpatients observed that over 83% of MRSA infections presented as SSTIs, followed by blood (10%), respiratory (6%), and other infections (1%); most of these infections were community-associated (Mathews et al., 2005). In another study among HIV-infected outpatients, 90% of CA-MRSA infections involved the skin and soft-tissue sites (Crum-Cianflone et al., 2007). Even among inpatients, MRSA SSTIs account for
a significant proportion of MRSA infections. A study conducted among HIV-infected inpatients and outpatients in Atlanta reported 226 MRSA infections among 168 patients, the majority (80%) of which were SSTIs (Hidron et al., 2011).

Among HIV-infected persons, SSTIs are most commonly abscesses, cellulitis, carbuncles, furunculosis, or folliculitis; cases of necrotizing fasciitis have also been reported (Crum-Cianflone et al., 2007; Diep et al., 2008; Lee et al., 2005; Miller et al., 2005; Olsen et al., 2008; Srinivasan et al., 2009; Sztramko et al., 2007; Szumowski, Cohen, Kanaya, & Mayer, 2007; Szumowski et al., 2009; Trinh, Short, & Mermel, 2009). The most common location of SSTIs among HIV-infected persons include the upper and lower extremities, trunk, axillae, face, and neck; MRSA SSTIs have also been increasingly described in the perigenital area (Crum-Cianflone et al., 2007; Crum-Cianflone et al., 2009; Diep et al., 2008; Hidron et al., 2011; Lee et al., 2005; Sztramko et al., 2007; Szumowski et al., 2009). In the general population, infection with MRSA SSTIs at these regions has also been documented; one study reported three cases of MRSA infection in the perigenital area (Cook, Furuya, Larson, Vasquez, & Lowy, 2007). Furthermore, a study among patients presenting to U.S. emergency departments found that 29% of SSTIs were located in the lower extremities, followed by the torso in 17%, perineum in 14%, and head/neck in 13% (Moran et al., 2006).

**Incidence of MRSA Infections in HIV-Infected Persons**

The incidence of MRSA SSTIs in HIV-infected persons has increased in the past decade in both the community and hospital settings. The rise in the incidence was likely due to the rise in a USA 300 strain of CA-MRSA (Diep et al., 2008; King et al., 2006). A report by Diep and colleagues (2008) was of interest as it highlighted the rise of a multidrug resistant (MDR) USA-300 CA-MRSA strain among MSM with resistance to multiple classes of antibiotics including fluoroquinolones, but most infections were not MDR and in fact were sensitive to more classes of antibiotics compared to hospital-acquired infections (King et al., 2006). A recent population-based study in Chicago, Illinois reported that from 2000-2003 to 2004-2007, there was a significant increase in the incidence of CA-MRSA SSTIs among HIV-infected persons, from 411 to 1474 cases per 100,000 patients (Popovich et al., 2010). Notably, compared to HIV-negative persons, the overall incidence was >6 times higher for
HIV-infected persons (996 per 100,000 HIV-infected persons vs 157 per 100,000 HIV-negative patients) (Popovich et al., 2010).

A recent prospective study reported that although the incidence of MRSA infections among HIV-infected persons increased from 2002-2007, peaking at 5.10 episodes/patient in 2007, it has since declined (Hidron et al., 2011). However, potential reasons for the decrease in incidence have not been determined. Similarly, a study among the general population reported that from 1999-2006, rates of MRSA infections increased >90%, largely due to the increase in CA-MRSA SSTIs among outpatients (Klein et al., 2009).

As mentioned, since the advent of HAART, the incidence of invasive MRSA infections in HIV-infected persons has declined; however, HIV-infected persons are still at an increased risk for severe MRSA infections compared to the general population. A retrospective study among hospitalized patients found an \( S. \text{ aureus} \) bacteremia incidence of 13.2/1000 patients among HIV-infected men and an incidence of 0.8/1000 patients among HIV-uninfected men, representing a 16- fold increase in the risk for bacteremia in HIV-infected persons (Senthilkumar et al., 2001). Despite this increased risk, rates of bacteremia have declined in the HIV-infected population in the HAART era, and one study reported a decrease in MRSA bacteremia from 1.3/100 person years to 0.4/100 person years in the periods 1991-1996 and 1997-2000, respectively (Tumbarello et al., 2002). A similar trend has been noted in the general population; a population-based study reported that from 2005-2008, there was a 28% and 17% decrease in hospital-onset and health care-associated community onset invasive MRSA infections, respectively, with larger decreases observed in patients with bloodstream infections (Kallen et al., 2010).

**Risk Factors for MRSA Infections**

Demographic characteristics, such as age, ethnicity, and gender, have been associated with MRSA infections in some studies. In a study among hospitalized HIV-infected patients, it was shown that young age may increase the risk for MRSA SSTIs (Popovich et al., 2010). However, it has also been shown that older age may also be associated with an increased risk, and thus findings have been conflicting (Szumowski et al., 2007).

Regarding race/ethnicity, a retrospective cohort study reported that HIV-infected patients with MRSA infections (the majority of which were SSTIs) were more likely to be
male and white (Mathews et al., 2005). In contrast, a retrospective study among HIV-infected outpatients reported that African-American race was significantly associated with MRSA bacteremia, noting an almost five-fold increase in risk in this population (Burkey et al., 2008). Similarly, two studies among the general population found that the annual incidence of MRSA infection was significantly higher among African-Americans than whites (Fridkin et al., 2005; Klevens et al., 2007). Reasons for the increase in risk among African-Americans may be related to socioeconomic, behavioral, or genetic factors; further studies are needed.

Findings from studies examining medical history and behavioral factors associated with MRSA infections among HIV-infected persons are presented in Tables 2 and 3. Poor immune status as indicated by a low CD4 cell count and a high HIV viral load have been significant predictors of MRSA infection in several investigations. A low CD4 cell count renders an HIV-infected patient susceptible to infection with numerous pathogens, including MRSA. One retrospective study noted that having a CD4 cell count <50 cells/µL was associated with a two-fold increased risk for CA-MRSA infection (Mathews et al., 2005). A dose-response effect was observed with HIV viral load; patients with a log10 HIV viral load ≥5.0 demonstrated the greatest risk for infection (Mathews et al., 2005). Furthermore, a recent study reported a decreased incidence of MRSA infection as the CD4 cell count increased (Hidron et al., 2011; 4.17/100 patients for CD4 count ≤50; 1.39/100 patients for CD4 cell count between 51 and 200; and 0.81 episodes for CD4 counts >200). Low CD4 count and high HIV viral load have also been associated with recurrent MRSA infections; one study found that having an HIV-1 RNA level of <1000 copies/mL was associated with a lower rate of MRSA SSTI recurrence (Crum-Cianflone et al., 2009). Despite these associations, HIV-infected persons with improved immune status (i.e., high CD4 cell count and low HIV viral load) continue to experience initial and recurrent MRSA SSTIs, suggesting that other factors besides immune status are important in the development of MRSA SSTIs.

Receipt of HAART, which can result in improved immune reconstitution for HIV-infected patients, has been shown to protect against MRSA infection in some studies. The decrease in HIV viral load and subsequent rise in CD4 cell count due to HAART may provide protection against infection with foreign pathogens such as MRSA. For example, one retrospective study observed an 84% reduction in the odds for MRSA colonization or
infection after controlling for confounding factors such as CD4 cell count, HIV viral load, prior antibiotic exposure, and recent hospitalizations (Ramsetty et al., 2010). A recent study reported a lower incidence of MRSA infections among HIV-infected patients receiving HAART at the time of MRSA infection versus patients not receiving HAART (Hidron et al., 2011; 1.81 episodes/100 patients versus 5.0/100 patients), representing a three-fold increase in risk for non-HAART users. However, most studies have failed to report an association between MRSA infection and receipt of HAART, suggesting that improved immune status may not completely protect against MRSA SSTIs.

Recent use of antibiotics has been a significant predictor of MRSA infection in many studies. In a case-control study among HIV-infected MSM, patients with CA-MRSA SSTIs were more likely than controls to have had recent exposure to ciprofloxacin than controls (Lee et al., 2005). Recent use of beta-lactam antibiotics and recent use of clindamycin have also been associated with an increased risk for MRSA SSTIs among HIV-infected persons (Crum-Cianflone et al., 2007; Diep et al., 2008). Other studies among HIV-infected persons have noted similar findings (Ramsetty et al., 2010; Szumowski et al., 2009). Furthermore, a study among patients from U.S. emergency departments also found that use of an antibiotic in the past month resulted in a two-fold increased risk for MRSA infection (Moran et al., 2006).

Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) has demonstrated a protective effect against MRSA infections in some studies. One case-control study noted that the odds of developing a MRSA SSTI were 70% lower in HIV-infected patients with recent exposure to TMP-SMX than those without recent exposure (Lee et al., 2005). Another study found that TMP-SMX prophylaxis for ≥120 days resulted in a 70% decreased risk for CA-MRSA infections (Mathews et al., 2005). TMP-SMX has also been shown to decrease the risk for MRSA colonization (Cenizal et al., 2008). The protective effect of TMP-SMX may be partially explained by the universally low rate of resistance of MRSA isolates to this antibiotic (Crum-Cianflone et al., 2007; Diep et al., 2008; Lee et al., 2005; Mathews et al., 2005; Skiest et al., 2006).

Prior MRSA colonization or infection has been reported to increase the risk for MRSA infection in several investigations. In a prospective study conducted among 795 MSM, of which one-third were HIV-infected, MRSA colonization at the nares, perianal
region, or wound swabs at baseline was strongly associated with an increased odds for the development of SSTIs; furthermore, recurrent SSTIs were more common among patients with perianal or nares colonization (Szumowski et al., 2009). In another prospective study among 107 HIV-infected MSM, 10 episodes of MRSA SSTIs were observed, all of which occurred in subjects who were colonized with the same strain of MRSA at baseline (Shet et al., 2009). Other studies have also found recent infection with MRSA to be a significant predictor of MRSA infection (Diep et al., 2008; Popovich et al., 2010). Studies among the general population have found similar findings. A study conducted among patients who visit U.S. emergency departments reported that the odds of MRSA infection were three times higher among patients with a history of MRSA infection than in patients without a history of infection (Moran et al., 2006).

Participation in high-risk sexual behaviors may increase the risk for MRSA infection. MRSA may be transmitted during sexual activities involving intimate skin-to-skin contact or skin-abrading sexual practices. Furthermore, MRSA colonizing the gastrointestinal tract may facilitate transmission of MRSA during sexual activities such as anal intercourse. One study found that HIV-infected MSM with MRSA SSTIs were more likely to have a recent history of a sexually transmitted infection (STI) and have visited a group sex party (Lee et al., 2005). In addition, among sexually active respondents, having ≥2 sex partners and meeting a sex partner in a sex club or bathhouse were associated with an increased odds for MRSA SSTIs; of note, condom use resulted in an 80% reduction in the odds for infection (Lee et al., 2005). The use of the internet to find sex partners, participation in anal intercourse, sex with > 10 partners, and participation in anonymous sex have also been associated with MRSA SSTIs (Szumowski et al., 2009). Similar findings have been noted in other studies (Crum-Cianflone et al., 2007; Diep et al., 2008), and high-risk sexual behaviors have also been linked to MRSA colonization (Antoniou et al., 2009; Crum-Cianflone et al., 2011). Among the general population, sexual transmission of MRSA has also been documented; a prospective, community-based study reported three households in which sexual partners developed MRSA colonization with skin infections in the pelvic region following sexual activity (Cook et al., 2007).

Prior hospitalization, a traditional risk factor for MRSA infection, has been associated with healthcare-associated and community-associated MRSA infections among HIV-infected
persons. MRSA may be transmitted in the hospital setting via contact with infected healthcare workers, infected fomites (e.g., bed linens, towels), or during surgical procedures. One study reported a 14% increase in the risk for healthcare-associated MRSA infection for an increase of five days of hospitalization (Drapeau et al., 2007). Diabetes, chronic skin disease, and catheter use, also established risk factors for MRSA infection (Lowy, 1998; Salgado, Farr, & Calfee, 2003), have not increased the risk for MRSA infections among HIV-infected persons in most studies, perhaps due to the low rate of patients with these conditions in the HAART era (Crum-Cianflone et al., 2007; Szumowski et al., 2009).

Illicit drug use, a risk factor for MRSA infection in the general population (Boucher & Corey, 2008; Lowy, 1998), has been shown to increase the risk of MRSA infection among HIV-infected persons. Two retrospective studies reported that methamphetamine use was associated with MRSA SSTIs among HIV-infected persons; an eight-fold increase in the odds was noted in both studies (Lee et al., 2005; Szumowski et al., 2009). Methamphetamine use may be a marker for participation in high-sexual activities, thus facilitating the spread of MRSA. Injection drug use is also a significant predictor of MRSA infection (Burkey et al., 2008, Mathews et al., 2005), and a recent study reported a higher incidence of MRSA infections among HIV-infected injection drug users (Hidron et al., 2011; 3.69 vs. 1.51 episodes/100 patients per year). Injection with needles may lead to tissue trauma and thus damage the skin and surrounding tissue, thus leading to infection. Use of contaminated needles may also contribute to the increase in risk.

Other factors that may increase the risk for MRSA infection—such as gym use, participation in contact sports, and a history of incarceration—have not been associated with MRSA infection in most studies among HIV-infected persons. A study among patients presenting to United States emergency departments also failed to observe significant associations between incarceration and participation in contact sports (Moran et al., 2006).

**Recurrent MRSA Infections**

HIV-infected persons are at increased risk for recurrent MRSA infections, or re-infection with MRSA following resolution of an initial infection. A recent case report observed 24 recurrent MRSA SSTI events in an HIV-infected male (Vyas et al., 2011). Of note, recurrent SSTIs may be observed at anatomical locations distinct from the initial site of
infection (Anderson et al., 2006; Graber et al., 2008). For example, one study among HIV-infected persons reported that all recurrent events of CA-MRSA SSTIs were at a different site than the original infection, and another found that 73% occurred at a different site (Anderson et al., 2006; Graber et al., 2008).

Regarding the incidence of recurrent infections, one study observed a 71% recurrence rate among HIV-infected outpatients presenting with an initial community-onset MRSA SSTI, with a median time to recurrence of 4.5 months (Graber et al., 2008). A retrospective cohort study among HIV-infected outpatients reported an incidence rate for recurrent MRSA SSTIs of 120 cases per 1000 person-years (PY) with 2-8 recurrent events observed per patient and a median time between recurrent events of 4 months (Crum-Cianflone et al., 2009).

Limited studies have examined risk factors for recurrent MRSA SSTIs among HIV-infected persons. Potential risk factors may include low CD4 cell count, high HIV viral load, lack of incision and drainage at the time of the initial MRSA event, or HAART non-adherence (Crum-Cianflone et al., 2009; Graber et al., 2008; Vyas et al., 2011). Furthermore, colonization with MRSA may also be a risk factor, particularly among patients who are persistently colonized with MRSA (Szumowski et al., 2009).

It is currently not known whether proper management of the initial MRSA infection, including appropriate antibiotic therapy and incision and drainage, may prevent the development of recurrent MRSA infections. For example, patients who experience recurrent MRSA SSTIs may be less likely to receive incision and drainage (Anderson et al., 2006; Crum-Cianflone et al., 2009); however, it is currently not known whether incision and drainage can protect against recurrent infections, and patients who received incision and drainage have been observed to develop recurrent infections (Skiest et al., 2006). Further studies are needed to determine the risk factors for the development of recurrent MRSA infections among HIV-infected persons and the optimal treatment and prevention strategies for recurrent events in this population.

**Antibiotic Resistance Patterns of MRSA Infections**

Antibiotic resistance patterns of MRSA isolates among HIV-infected persons are important in the clinical management of infections in this population. Among MRSA
isolates, resistance to TMP-SMX has been generally low, ranging from 0-9% (Crum-Cianflone et al., 2007; Diep et al., 2008; Lee et al., 2005; Mathews et al., 2005; Skiest et al., 2006). Studies among the general population have also found low rates of TMP-SMX resistance (King et al., 2006; Klein et al., 2009; Moran et al., 2006; Naimi et al., 2003). Resistance of MRSA isolates to tetracycline has ranged from 0-54% among HIV-infected persons, with an average resistance of 25% (Crum-Cianflone et al., 2007; Lee et al., 2005; Mathews et al., 2005; Shadyab & Crum-Cianflone, in press; Skiest et al., 2006; Szumowski et al., 2007). Resistance to tetracycline has been lower in the general population, with two studies noting resistance rates of 8% (Moran et al., 2006; Naimi et al., 2003).

Regarding fluoroquinolones, ciprofloxacin resistance has been high among HIV-infected persons, with an average rate of 70% (Shadyab & Crum-Cianflone, in press). One population-based study noted a 40% resistance rate of MRSA isolates to fluoroquinolones (Moran et al., 2006), and another study found a 21% resistance rate for cases of CA-MRSA and a 84% resistance rate for cases of healthcare-associated MRSA (Naimi et al., 2003).

Resistance to erythromycin has been very high among HIV-infected persons, peaking at 100% in two studies (Anderson et al., 2006; Shet et al., 2009). Among the general population, rates of erythromycin resistance have also been high; one study reported a resistance rate of 87%, and another found that 94% of MRSA isolates were resistant to this antibiotic (King et al., 2006; Moran et al., 2006). Regarding clindamycin, resistance has ranged from 3%-70%, averaging at 36% (Anderson et al., 2006; Lee et al., 2005; Mathews et al., 2005; Shadyab & Crum-Cianflone, in press; Shastry, Rahimian, & Lascher, 2007). Clindamycin resistance in the general population has also showed a wide range; one study reported a resistance rate of 17% among CA-MRSA isolates and a rate of 79% among healthcare-associated MRSA isolates. However, a study among patients from U.S. emergency departments only found a 5% resistance rate, and another reported that among outpatients, clindamycin resistance had significantly decreased from 67% to 30% during the study period (Klein et al., 2009; Moran et al., 2006). It is also important to note that clindamycin may develop inducible resistance; a disk diffusion test (D-test) is necessary to exclude the possibility of inducible resistance. Resistance to vancomycin, gentamicin, and rifampin has been largely absent among HIV-infected persons in the HAART era, and no studies have reported vancomycin resistance among MRSA isolates (Anderson et al., 2006; Diep et al.,
2008; Lee et al., 2005; Mathews et al., 2005; Shet et al., 2009; Skiest et al., 2006). In the general population, similar findings have been reported (King et al., 2006; Klein et al., 2009; Moran et al., 2006).

Management of MRSA Infections in the HIV-Infected Patient

MRSA infections among HIV-infected persons may be associated with significant morbidity and mortality. Therefore, proper management of MRSA infections is essential. To date, guidelines for the clinical management of MRSA infections among HIV-infected persons have not been devised. Table 4 provides a summary of treatment and outcomes of MRSA infections among HIV-infected persons across multiple studies.

Empirical antimicrobial therapy for the management of MRSA infections among HIV-infected persons should be guided by local susceptibility patterns. Furthermore, given the increasing prevalence of multidrug resistant strains of MRSA among this population (Diep et al., 2008), antimicrobial susceptibility testing for these infections is important. Antimicrobials with potential MRSA coverage include TMP-SMX, vancomycin, tetracyclines (e.g., minocycline, doxycycline), clindamycin, gentamicin, linzeolid, and rifampin. Of note, rifampin should be used in combination with another antibiotic, such as TMP-SMX, due to development of resistance when it is used as monotherapy. Novel antibiotics against MRSA include an oxazolidinone (linezolid), a lipopeptide (daptomycin), a streptogramin (quinupristin-dalfopristin), a glycyclycline (tigecycline), and a lipoglycopeptide (telavancin). A fifth generation cephalosporin (ceftaroline) is also now available for the treatment of MRSA SSTIs. These novel antibiotics may prove to be of great use, given the rise of multidrug-resistant strains of MRSA (Diep et al., 2008). Resistance to TMP-SMX, rifampin, gentamicin, vancomycin, and the novel agent linezolid has rarely been noted, even in multidrug-strains (Diep et al., 2008); hence, empirical treatment with these agents may be more effective in resolving a MRSA infection in the HIV-infected patient. Some antibiotics, such as rifampin, may interact with antiretroviral drugs; therefore, providers should exercise caution when prescribing antibiotics to patients on HAART (Shadyab & Crum-Cianflone, in press).

Some studies have found that combination therapies may be more effective in improving clinical status following infection with MRSA. One study reported that among 12
HIV-infected patients with SSTIs, 83% were definitively treated with combination regimens consisting of TMP-SMX/rifampin, TMP-SMX/doxycycline, and rifampin/doxycycline; the majority of these patients also received mupirocin for the nares and chlorhexidine body wash (Sztramko et al., 2007). Of note, 91% did not have recurrence of the MRSA infection. The combination of TMP-SMX and rifampin is noteworthy, as these antimicrobials have shown low resistance to MRSA isolates in studies among HIV-infected persons (Anderson et al., 2006; Graber et al., 2008; Lee et al., 2005; Shastry et al., 2007; Skiest et al., 2006; Trinh et al., 2009); however, it is currently not known whether their combination is more effective than their use alone. Other combinations reported among HIV-infected persons include TMP-SMX/minocycline, TMP-SMX/levofloxacin, levofloxacin/rifampin, and minocycline/rifampin (Crum-Cianflone et al., 2007; Skiest et al., 2006). Vancomycin, which to date has shown no resistance among MRSA isolates, is appropriate in the setting of serious infections and is administered intravenously (Anderson et al., 2006; Crum-Cianflone et al., 2007; Diep et al., 2008; Krucke, Grimes, Grimes, & Dang, 2009; Lee et al., 2005; Mathews et al., 2005; Shastry et al., 2007; Skiest et al., 2006; Szumowski et al., 2007). It is of note that conclusions of the aforementioned studies are limited by the small sample sizes and therefore further studies are needed.

Incision and drainage is increasingly performed to treat abscesses among HIV-infected persons, and it has been suggested that incision and drainage alone is sufficient to treat purulent abscesses (Liu et al., 2011; Szumowski et al., 2007). Furthermore, a combination of incision and drainage and antibiotic therapy may be effective in improving the clinical status of HIV-infected patients with MRSA infections. However, the long-term effect of their combination, including their impact on the development of recurrent infections, has not been established. One study found that the majority of patients with improved clinical status following infection with MRSA had been treated with a combination of incision and drainage and antibiotic therapy (Trinh et al., 2009). However, further studies are needed to confirm this finding.

**Prevention of MRSA Infections**

Currently, no guidelines for the prevention of MRSA infections among HIV-infected persons are available; however, prevention may involve several strategies. The Centers for
Disease Control and Prevention have published strategies on the prevention of MRSA, highlighting the importance of practicing good hygiene (e.g., keeping hands clean, avoiding sharing of personal items such as towels, and covering wounds; CDC, 2010). Furthermore, given the rise in MRSA infections in the buttocks and perigenital regions, and the associations between high-risk sexual behaviors and increased risk for MRSA infections noted in several investigations, prevention messages should advocate safe sexual practices among HIV-infected persons. Proper management of MRSA infections, including incision and drainage with consideration for appropriate antibiotic therapy guided by local susceptibility patterns, should be actively pursued. Furthermore, the recent rise in multidrug resistant strains of MRSA among the HIV-infected population highlights the importance of obtaining clinical cultures for the purposes of susceptibility testing. Third, decolonization of MRSA by mupirocin and chlorhexidine or hexachlorophene wash may eradicate MRSA colonization and prevent subsequent infections, but its effect on recurrence is currently not established. Although it is currently not known if decolonization may prove effective in the long-term, this strategy should continue to be investigated in future studies.
CHAPTER 3

METHODS

STUDY DESIGN AND POPULATION

A retrospective study was performed to determine the incidence of and factors associated with methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections among HIV-infected persons. The study population included all HIV-infected patients seen at the Naval Medical Center San Diego (NMCSD) HIV Clinic, including active duty military personnel, their dependents, and retirees. HIV-infected naval beneficiaries are eligible for care at all three United States Navy HIV clinics, including NMCSD, National Naval Medical Center in Bethesda, Maryland, and Naval Medical Center Portsmouth in Portsmouth, Virginia. HIV-infected military beneficiaries have open and free access to medical care, including HIV medications.

HIV-infected military beneficiaries are routinely tested for HIV approximately every two years, and thus are typically diagnosed early in the course of their infection. Upon diagnosis, military beneficiaries are given two-week orders and are referred to one of the three Navy HIV clinics (National Naval Medical Center, Bethesda, Maryland; Naval Medical Center Portsmouth, Portsmouth, Virginia; or Naval Medical Center San Diego, San Diego, California).

The HIV-infected persons of the current study are an ideal population to study the incidence of and factors associated with MRSA SSTIs, due to the close follow-up and comprehensive medical care afforded by the military to its beneficiaries. The current study includes 794 HIV-infected naval beneficiaries followed for a total of 5466 person-years from 1993-2010 [median (interquartile range [IQR]) 5 (1-12)]. The current study was approved by the Institutional Review Board of San Diego State University as well as the Institutional Review Boards of Naval Medical Center San Diego and Uniformed Services University of the Health Sciences.
DATA COLLECTION

Data were collected among all HIV-infected patients seen at the NMCSD HIV clinic from January 1, 1993 to December 31, 2010. Computerized microbiologic results were reviewed to identify all culture-confirmed cases of MRSA skin and soft-tissue infections. Data were collected from the time of the first clinic visit or HIV diagnosis (whichever was later) to time of MRSA infection or last clinic visit (whichever occurred first). Patients' medical records and the hospital computer database were reviewed to collect data on demographics (e.g., age, gender, race); year of first clinic visit and last clinic visit; year of last HIV seronegative and first HIV seropositive; CD4 cell count, HIV viral load, CDC stage, and HAART use at time of MRSA infection (cases) or most recent for those without MRSA infection (controls); nadir CD4 cell count (i.e., lowest CD4 cell count recorded) and maximum HIV viral load at time of MRSA infection (cases) or at last clinic visit (controls); a history of TMP-SMX use; most recent body mass index (BMI) at time of MRSA infection (cases) or at last clinic visit (controls); as well as history of herpes simplex virus-2 (HSV-2), syphilis, hypertension, diabetes mellitus, eczema, cancer, and injection drug use.

Additional data were collected on MRSA cases including wound culture data; number, type, and body site of infection; hospital admission, including duration of hospital stay, for the MRSA infection; and CD4 cell count and HIV viral load <1 year, <6 months, <3 months, <2 weeks before the MRSA infection and >3 months, >6 months, >1 year after the MRSA infection. Data were also collected on treatment for the MRSA infection, including antibiotics prescribed, use of mupirocin nasal ointment and/or hexachlorophene body washes, and whether incision and drainage was performed.

Data were also collected on recurrent MRSA infections defined as a second wound-culture proven MRSA skin and soft-tissue infection at least 30 days following the initial infection or at a distinct anatomical location at least two weeks following the initial infection. Data were collected from the date of the first MRSA infection to the date of the second infection or last clinic visit (whichever occurred first). In addition to the data previously described, data were also collected on the following variables indicating whether or not they occurred after the initial MRSA infection: history of sexually transmitted infections; surgery; hospital admission; use of HAART; and use of antibiotics, including TMP-SMX, beta-lactams, and fluoroquinolones.
VARIABLES

Two separate analyses were performed. In the first analysis, factors associated with the development of a MRSA infection were evaluated among all patients (n=794). Some patients experienced multiple MRSA infections during the study period; however, only the first MRSA event was analyzed. In the second analysis, factors associated with the development of the first recurrent MRSA infection were evaluated among patients who developed an initial MRSA infection (n=63). The following is a list of variables used in each analysis, with their definitions and categories. "Current" represents the value at the time of the MRSA infection (cases) or the most recent value at last clinic visit (controls). For all dichotomous variables, the reference category is "no," unless otherwise noted.

Part I: Factors Associated with the Development of a MRSA Infection

1. **Age at first clinic visit (years):** Analyzed as a continuous variable. The odds ratio represents an increase in 10 years of age.
2. **Gender:** Categorized as male versus female. Reference category is female.
3. **Race:** Reported in the dataset as Caucasian, African-American, Hispanic, Asian/Pacific Islander, Native-American, or Other. Re-categorized as Caucasian, African-American, or Other/missing for the analysis. Reference category is Caucasian.
4. **Duration of HIV (years):** Represents the duration of HIV at time of MRSA infection or last clinic visit. In order to calculate the duration of HIV, the following approach was used: If the date of last HIV seronegative was known, the duration of HIV was found using three steps: (1) Find the difference in years between the last year of follow-up and the year of HIV seropositive; (2) Find the difference between the year of HIV seronegative and year of HIV seropositive and divide this difference by two; (3) Add the results from the previous two steps. If the date of last HIV seronegative was unknown, the duration of HIV was found using two steps: (1) Find the difference in years between the last year of follow-up and year of HIV seropositive; (2) For the patients whose date of HIV seronegative was known, find the median of the difference in years between the date of HIV seronegative and date of HIV seropositive; (3) Add the results from the previous two steps.
5. **Current CD4 cell count (cells/mm³):** Analyzed as a continuous and categorical variable. As a continuous variable, the odds ratio represents an increase in 100 cell/mm³. Categorized as <350 cells/mm³, 350-499 cells/mm³, or ≥500 cells/mm³ (reference category). Represents CD4 cell count at time of MRSA infection (cases) or last clinic visit (controls).
6. **Current HIV viral load (copies/mL):** Analyzed as a continuous and categorical variable. As a continuous variable, the log₁₀ of the HIV viral load was used to be
consistent with the literature and also because this variable has a skewed distribution. As a categorical variable, was categorized as $\geq 400$ copies/mL versus $<400$ copies/mL (reference category). Represents HIV viral load at time of MRSA infection (cases) or last clinic visit (controls).

7. **Nadir CD4 cell count (cells/mm$^3$):** Analyzed as a continuous and categorical variable. As a continuous variable, the odds ratio represents an increase in 100 cells/mm$^3$. As a categorical variable, was categorized as $<200$ cells/mm$^3$ versus $\geq 200$ cells/mm$^3$ (reference category). Represents the lowest CD4 cell count recorded at time of MRSA infection (cases) or last clinic visit (controls).

8. **Maximum HIV viral load (copies/mL):** Analyzed as the log$_{10}$ of the HIV viral load. Represents the maximum HIV viral load at time of MRSA infection (cases) or last clinic visit (controls).

9. **Current CD4 cell count (cells/mm$^3$) and HIV viral load (copies/mL):** Since CD4 cell count and HIV viral load are highly correlated, they cannot be placed in the same multiple logistic regression model. Therefore, a combined category was created so that both could be accounted for in the model. Categories were defined as: CD4 cell count $<500$ and HIV viral load $\geq 400$, CD4 cell count $<500$ and HIV viral load $<400$, CD4 cell count $\geq 500$ and HIV viral load $\geq 400$, and CD4 cell count $\geq 500$ and HIV viral load $<400$ (reference category).

10. **Current use of highly active antiretroviral therapy (HAART):** Represents use of HAART at time of MRSA infection (cases) or at last clinic visit (controls). Analyzed as yes versus no.

11. **Current Centers for Disease Control and Prevention Stage:** Analyzed as Stage C (AIDS-indicator conditions) versus Stage A (asymptomatic, acute HIV, or persistent generalized lymphadenopathy) or B (symptomatic conditions, not A or C). Reference category is Stage A/B. Represents CDC stage at time of MRSA infection (cases) or last clinic visit (controls).

12. **History of syphilis:** Represents a history of syphilis confirmed by rapid plasma reagin (RPR) from year of first clinic visit to year of MRSA infection (cases) or year of last clinic visit (controls). Analyzed as yes versus no.

13. **History of Herpes-simplex virus 2:** Represents a history of HSV-2 confirmed by serologic testing from year of first clinic visit to year of MRSA infection (cases) or year of last clinic visit (controls). Analyzed as yes versus no.

14. **History of hypertension:** Represents a history of physician-diagnosed hypertension from year of first clinic visit to year of MRSA infection (cases) or year of last clinic visit (controls). Analyzed as yes versus no.

15. **Diabetes Mellitus:** Represents whether or not the patient was diagnosed with diabetes mellitus from year of first clinic visit to year of MRSA infection (cases) or year of last clinic visit (controls). Analyzed as yes versus no.

16. **Eczema:** Analyzed as whether or not the patient was diagnosed with eczema from year of first clinic visit to year of MRSA infection (cases) or year of last clinic visit (controls). Analyzed as yes versus no.
17. **Cancer**: Represents whether the patient was diagnosed with cancer from year of first clinic visit to year of MRSA infection (cases) or year of last clinic visit (controls). Types of cancer (in order of frequency) observed included anal cancer, skin cancer, Kaposi's sarcoma, prostate cancer, malignant lymphoma, and breast cancer.

18. **Injection drug use**: Represents a history of injection drug use from year of first clinic visit to year of MRSA infection (cases) or year of last clinic visit (controls). Analyzed as yes versus no.

19. **Use of trimethoprim-sulfamethoxazole (TMP-SMX, Septra)**: Represents a history of TMP-SMX use from year of first clinic visit to year of MRSA infection (cases) or year of last clinic visit (controls). Analyzed as yes versus no.

20. **Current Body Mass Index (BMI)**: Categorized as underweight or normal (≤18.5-24.9 kg/m²), overweight (25-29.9), or obese (≥30). Reference category is underweight/normal. Represents BMI at time of MRSA infection (cases) or last clinic visit (controls).

### Part II: Factors Associated with the Development of a Recurrent MRSA Infection

1. **Age at initial infection (years)**: Analyzed as a continuous variable. The odds ratio represents an increase in 10 years of age.

2. **Gender**: Analyzed as male versus female. Reference category is female.

3. **Race**: Categorized as Caucasian, African-American, or other/missing. Reference category is Caucasian.

4. **Duration of HIV (years)**: Represents the duration of HIV at initial MRSA infection.

5. **CD4 cell count at initial infection (cells/mm³)**: Analyzed as a continuous and categorical variable. As a continuous variable, the odds ratio represents an increase in 100 cells/mm³. Categorized as <350 cells/mm³, 350-499 cells/mm³, or ≥500 cells/mm³ (reference).

6. **Nadir CD4 cell count (cells/mm³)**: Analyzed as a continuous and categorical variable. As a continuous variable, the odds ratio represents an increase in 100 cells/mm³. Categorized as <200 cells/mm³ versus ≥200 cells/mm³ (reference). Represents lowest CD4 cell count recorded at time of recurrent infection (cases) or last clinic visit (controls).

7. **HIV viral load at initial infection (copies/mL)**: Analyzed as a continuous variable (log₁₀ HIV viral load) and categorical variable, categorized as ≥400 copies/mL versus <400 copies/mL (reference).

8. **Maximum HIV viral load (copies/mL)**: Analyzed as a continuous variable (log₁₀ HIV viral load). Represents highest HIV viral load recorded at time of recurrent infection (cases) or last clinic visit (controls).

9. **Use of highly active antiretroviral therapy after initial infection**: Analyzed as yes versus no. Represents use of HAART from the time after the initial infection to recurrent infection (cases) or last clinic visit (controls).
10. **Centers for Disease Control and Prevention Stage at first infection:** Analyzed as Stage C (AIDS-indicator conditions) versus Stage A (asymptomatic, acute HIV, or persistent generalized lymphadenopathy) or Stage B (symptomatic conditions, not A or C). Reference category is Stage A/B.

11. **History of sexually transmitted infections (STI) after initial infection:** Analyzed as yes versus no. Represents whether or not the patient experienced any of the following STIs after initial infection to recurrent infection (cases) or last clinic visit (controls): syphilis, HSV-2, gonorrhea, Chlamydia, HPV, or NGI. Each STI was also analyzed separately.

12. **History of hypertension:** Analyzed as yes versus no. Represents a history of hypertension from year of first clinic visit to year of recurrent infection (cases) or last clinic visit (controls).

13. **Diabetes Mellitus:** Analyzed as yes versus no. Represents whether or not the patient was diagnosed with diabetes from year of first clinic visit to year of recurrent infection (cases) or last clinic visit (controls).

14. **Eczema:** Analyzed as yes versus no. Represents whether or not the patient was diagnosed with eczema from year of first clinic visit to year of recurrent infection (cases) or last clinic visit (controls).

15. **Cancer:** Analyzed as yes versus no. Represents whether or not the patient was diagnosed with cancer from year of first clinic visit to year of recurrent infection (cases) or last clinic visit (controls).

16. **Injection Drug Use:** Analyzed as yes versus no. Represents whether or not the patient had a history of injection drug use from year of first clinic visit to year of recurrent infection (cases) or last clinic visit (controls).

17. **TMP-SMX use after initial infection:** Analyzed as yes versus no. Excludes use of TMP-SMX to treat first MRSA infection. Represents use of TMP-SMX from the time after the initial MRSA infection to year of recurrent infection (cases) or last clinic visit (controls).

18. **Body Mass Index (BMI) at initial infection:** Analyzed as normal weight/underweight (BMI <18.5-24.9), overweight (BMI 25-29.9), or obese (BMI ≥30). Reference category is underweight/normal.

19. **Surgery after the initial infection:** Represents whether a surgical procedure was performed from the time after the initial MRSA infection to year of recurrent infection (cases) or last clinic visit (controls). Analyzed as yes versus no.

20. **Hospital admission after the initial infection:** Represents whether the patient was admitted to a hospital from the time after the initial MRSA infection to year of recurrent infection (cases) or last clinic visit (controls). Analyzed as yes versus no.

21. **Use of immunosuppressants after the initial infection:** Represents whether the patient used immunosuppressants from the time after the initial MRSA infection to year of recurrent infection (cases) or last clinic visit (controls). Analyzed as yes versus no.
22. **Beta-lactam use after the initial infection**: Analyzed as yes versus no. Excludes use of beta-lactams to treat initial MRSA infection. Represents whether the patient used beta-lactams from the time after the initial MRSA infection to year of recurrent infection (cases) or last clinic visit (controls).

23. **Fluroquinolone use after the initial infection**: Analyzed as yes versus no. Excludes use of fluoroquinolones to treat initial first MRSA infection. Represents whether the patient used fluoroquinolones from the time after the initial MRSA infection to year of recurrent infection (cases) or last clinic visit (controls).

24. **Receipt of incision and drainage for initial MRSA infection**: Analyzed as yes versus no/unknown.

25. **Receipt of mupirocin and hexachlorophene for initial MRSA infection**: Analyzed as yes versus no.

26. **Hospital admission for initial MRSA infection**: Analyzed as yes versus no.

27. **Receipt of TMP-SMX for initial MRSA infection**: Analyzed as yes versus no. Represents whether or not the patient was prescribed TMP-SMX for the initial MRSA infection.

28. **Receipt of minocycline for initial MRSA infection**: Analyzed as yes versus no. Represents whether or not the patient was prescribed minocycline for the initial MRSA infection. Also analyzed as receipt of minocycline as the initial antibiotic, minocycline + incision and drainage, minocycline + mupirocin and hexachlorophene, and minocycline + TMP-SMX and/or rifampin as initial antibiotic.

29. **Receipt of vancomycin for initial MRSA infection**: Analyzed as yes versus no. Represents whether or not the patient was prescribed vancomycin for the initial MRSA infection.

30. **Receipt of combination antibiotics for empiric therapy**: Analyzed as yes versus no. Represents whether or not the patient received a combination treatment regimen for empiric therapy.

31. **Receipt of incision and drainage and combination antibiotics for empiric therapy**: Analyzed as yes versus no.

32. **Duration of antibiotic therapy for initial MRSA infection (days)**: Analyzed as a continuous variable.

33. **Receipt of empiric antibiotic concordant with MRSA isolate sensitivity pattern**: Analyzed as yes versus no.

**Statistical Analysis**

Descriptive statistics evaluating the characteristics of the study population were performed. For continuous variables, medians and interquartile ranges were reported. Frequencies and proportions described categorical variables. Univariate analyses were performed using logistic regression to calculate unadjusted odds ratios (OR), 95%
confidence intervals (CI), and p-values (determined using the Wald chi-square test) for each covariate.

The incidence of MRSA skin and soft-tissue infections was determined for the following time periods, which were determined a priori: 1993-2002, 2003-2004, 2005-2006, 2007-2008, and 2009-2010. No infections were observed before 2003; therefore, 1993-2002 was a separate category. The remaining years were grouped into two-year time periods so that trends in infection rates could be easily observed. All patients were assumed to be at risk for developing MRSA SSTIs during their respective follow-up periods (year of first clinic visit to year of last clinic visit). Since only the year of first clinic visit and last clinic visit were available, patients were assumed to be followed from July 1 of the year of first clinic visit (midpoint of the year) to July 1 of the year of last clinic visit. However, patients whose year of first clinic visit and year of last clinic visit were the same were assumed to be followed from July 1-December 31 of that year. Therefore, a patient seen at the clinic from 1993-2010 contributed 17 person-years to the incidence calculation, and a patient seen at the clinic from 2010-2010 contributed 0.5 person-years. In order to calculate the incidence of recurrent MRSA SSTIs, patients who developed a MRSA SSTI were assumed to be at risk for a recurrent MRSA SSTI from the date of the first MRSA SSTI to the date of last clinic visit. Poisson-rate confidence intervals were reported for the incidence rates. Differences in the incidence rates were calculated using a chi-square test.

In the first analysis, factors associated with the development of an initial MRSA skin and soft-tissue infection were examined, with the dependent variable categorized as whether or not the patient developed a MRSA infection during the study period (1993-2010). Follow-up time was from the year of first clinic visit to the year of development of a MRSA infection or year of last clinic visit, whichever came first. In the second analysis, factors associated with recurrence of a MRSA skin and soft-tissue infection were examined among patients who experienced an initial MRSA infection, with the dependent variable categorized as whether or not the patient developed a second (i.e., recurrent) infection. Follow-up time was from the date of the first MRSA infection to the date of development of a recurrent infection or year of last clinic visit, whichever came first (time period: 2003-2010).

Separate multiple logistic regression models were fit to determine factors associated with the development of an initial MRSA infection and the development of a recurrent
MRSA infection among HIV-infected persons. Before performing the multiple logistic regression analysis, collinearity among independent variables was evaluated by examining tolerance values from a multiple regression model; if the tolerance values were greater than 0.10, then it was assumed that collinearity did not occur. Criteria for inclusion in the full model included a p-value ≤ 0.05 in the univariate analysis and not demonstrating collinearity. Age and years of follow-up were placed in all models to control for potential confounding and varying lengths of follow-up time, respectively. The final models were derived using stepwise backward elimination. A p-value <0.05 was used as criteria for remaining in the final model; additionally, if a variable was a confounding factor for at least one covariate in the model, then it was placed back into the final model. A variable was defined as a confounder if its removal changed the association of another variable with the outcome by at least 10%. Adjusted odds ratios, 95% confidence intervals, and p-values were reported for the models. Goodness of fit of the models was assessed using the Hosmer-Lemeshow test; a p-value>0.10 indicated a good fit.

In order to examine whether CD4 cell counts around the time of a MRSA infection affect the development of a recurrent infection, a longitudinal linear mixed effects model was fit using random intercepts associated with each patient as well as a first-order autoregressive covariance matrix for the random error. All patients with at least one CD4 cell count baseline measurement within the 6 months preceding the initial MRSA SSTI and at least one follow-up measurement within the 6 months following the initial MRSA SSTI were included in the linear-mixed effects model analysis. The full linear-mixed effects model included CD4 cell count as the dependent variable and an intercept term; time, a categorical variable representing whether or not a recurrent infection was experienced, and an interaction with time and recurrence were modeled as the fixed effects:

\[(\text{CD4 Cell Count})_i = \beta_0 + \beta_1(\text{Recurrence of MRSA SSTI})_i + \beta_2(\text{Time})_i + \beta_3(\text{Recurrence of MRSA SSTI})_i \times (\text{Time})_i + \mu_{0i},\]

where \(\beta_0\) represents the intercept, \(\beta_1-\beta_3\) represent the fixed effects, and \(\mu_{0i}\) represents the random error associated with each patient.

A separate linear mixed effects model was fit using log_{10} HIV viral load as the dependent variable and similar methods, but with a heterogeneous first-order autoregressive covariance matrix for the random error. The final linear mixed-effects models were derived...
using the likelihood ratio test for the fixed effects. Least-squares means associated with the
categorical factor recurrence of a MRSA SSTI were computed.

In the analyses, all p-values were two-sided and statistically significant at \( p<0.05 \) and
marginally significant at a p-value \(<0.10\). All statistical analyses were performed using SAS
Version 9.2 (SAS Institute, Cary, NC). The SAS proc mixed procedure was utilized for the
linear-mixed effects model analysis.

THE RANDOM FORESTS ALGORITHM

The random forests algorithm is a novel data mining approach and part of supervised
learning methods, which try to learn the relationship between a dependent variable and a set
of one or more independent variables (Dasgupta, Sun, Konig, Bailey-Wilson, & Malley,
2011). Other supervised learning methods include regression (e.g., multiple regression,
logistic regression), decision trees, and support vector machines. Random forest models have
been used extensively in genetic epidemiology, bioinformatics, and cancer research. For
example, random forest models have been used in gene expression studies to select the most
important genes out of thousands potentially predictive of outcome, such as cancer (Diaz-
Uriarte & Alvarez de Andres, 2006). Random forest models were also recently used in a
study to predict virological response to antiretroviral drug combinations among HIV-infected
patients (Revell et al., 2011).

In the random forests algorithm, \( n \) bootstrap samples of the training data (i.e., data
being used to build the model) are drawn; a bootstrap is a sample drawn with replacement
from the training data with the same sample size as the original data (Liaw & Wiener, 2002).
For each of the \( n \) bootstrap samples, a classification tree is grown. At each node, rather than
choosing the best split among all predictors, \( m \) of the predictors are randomly sampled and
used to choose the best split at each node. New data are classified by aggregating the
predictions of the \( n \) trees (i.e., selecting the class with the most votes for that class among the
\( n \) trees).

The random forests algorithm also provides an estimate of the classification error
rate, which is calculated using the following approach. At each bootstrap iteration, the data
not included in the bootstrap sample, called the "out of bag data," are used as the testing set
to predict the outcome from the tree grown using the bootstrap sample. These out of bag
predictions are then aggregated among all trees, and an estimate of the out of bag error rate is determined (Liaw & Wiener, 2002).

The random forests algorithm offers several advantages. It is highly accurate compared to current algorithms; it runs efficiently on large databases; it can handle thousands of input variables; it provides an unbiased estimate of the error rate; it can be used to detect outliers in the data; it detects variable interactions; and it has an effective method for estimating missing data, particularly when a large proportion of the data are missing (Breiman & Cutler, 2001).

The random forests algorithm also provides a means of variable selection by providing an importance score for each variable that helps determine which variables are most predictive of outcome (Dasgupta et al., 2011). These variables can then be used in other regression-based approaches. In order to calculate the score, the prediction accuracy of the out of bag samples is first calculated. The data of a predictor variable are then replaced with a random permutation of its data, which eliminates any predictive power that the variable may have; the prediction accuracy is then re-calculated using the permuted data. The change in prediction accuracy provides a measure of the predictive power of the variable. If there is a large mean decrease in accuracy for the predictor variable, then that variable is an important predictor for the outcome. Predictor variables can be ranked by importance score, and a threshold cutoff value can be used to select the most important variables (Dasgupta et al., 2011).

In the current study, the random forests algorithm will be used to determine variables most predictive of initial and recurrent MRSA SSTIs by evaluating importance scores for each variable; a cutoff score of 50% will be used. These results will then be compared to those of the logistic regression analysis. The random forests algorithm will be implemented using the statistical software package R version 2.12.2.
CHAPTER 4

RESULTS

INCIDENCE OF MRSA INFECTIONS

Sixty-three patients (8%) developed at least one MRSA SSTI during the study period. Table 5 shows the incidence of MRSA infections among the study population from 1993-2010. Patients experienced a total of 108 skin and soft-tissue infection events during 5466 person-years (PY), representing an incidence of 19.8 infections/1000 PY (95% CI 16.4, 23.7 PY). No SSTI events were noted from 1993-2002. The incidence of SSTI events increased significantly from 2003-2004 to 2005-2006, peaking during the latter time period (16.8 infections/1000 PY versus 40.0 infections/1000 PY; p<0.01). However, the incidence has declined since that time, decreasing to an incidence of 29.4 infections/1000 PY from 2009-2010 (Figure 1).

![Incidence of MRSA SSTIs Among HIV-Infected Persons, 1993-2010](image)

Figure 1. Incidence of MRSA SSTIs among HIV infected persons, 1993-2010. The incidence of MRSA SSTIs increased from 2003-2004 to 2005-2006, reaching a peak during the latter time period. However, the incidence has been steadily declining since 2007, with a lower incidence noted in 2009-2010 versus 2005-2006.
**Clinical Characteristics of MRSA Infections**

Table 6 shows the clinical characteristics of MRSA infections among HIV-infected persons. The most common SSTI was an abscess (44%) followed by cellulitis (24%) and a wound infection (18%). Seventeen (27%) patients presented with more than one type of SSTI, including one with cellulitis and osteomyelitis. SSTIs were most commonly located at the lower extremity (31%), buttocks/scrotum (22%), and head/face (21%). Eight (13%) patients presented with an SSTI at multiple body sites. Regarding the antibiotic susceptibility of MRSA isolates, all isolates (108/108) were susceptible to vancomycin, and the majority to TMP-SMX (105/108; 97%) and tetracyclines (96/108; 89%), including minocycline and tetracycline. Susceptibility to erythromycin (10/108; 9%) was low.

Regarding the initial MRSA infection, the majority presented as an abscess (44%), wound infection (27%), or cellulitis (21%) (Table 7). The most common location of the initial infection was the lower extremity (28%) followed by the buttocks/scrotum (27%). All initial MRSA isolates (63/63) were susceptible to vancomycin, and the majority to TMP-SMX (61/63; 27%) and tetracyclines (57/63; 91%). Sensitivity to fluoroquinolones was noted in 68% (15/22) of isolates tested for these antibiotics, and 80% (8/10) were sensitive to clindamycin among isolates tested.

**Study Population Characteristics**

Table 8 shows the demographic and clinical characteristics of the study population. A total of 794 HIV-infected military beneficiaries with a median follow-up time of five years (interquartile range [IQR] 1-12 years) were analyzed in the present study. The median age was 30 years (IQR 25-37 years), 94% were male, and 46% were Caucasian, 30% African-American, and 24% other/missing.

Participants had HIV for a median of 7 years (IQR 2.5-15.0 years) and a median current CD4 cell count of 569 cells/mm$^3$ (IQR 420-743 cells/mm$^3$). Furthermore, 16% had a CD4 cell count <350 cells/mm$^3$, 24% 350-499 cells/mm$^3$, and 60% ≥ 500 cells/mm$^3$. A median nadir CD4 cell count of 294 cells/mm$^3$ (IQR 187-396 cells/mm$^3$) was noted, and 27% had a nadir CD4 cell count <200 cells/mm$^3$. The median log$_{10}$ HIV viral load was 1.7 copies/mL (IQR 1.7-2.7), and 25% had an HIV viral load ≥ 400 copies/mL. Eighty percent of
patients were currently using HAART, and 11% were currently classified as CDC stage C (i.e., AIDS-indicator conditions).

Regarding history of sexually transmitted infections, 23% had a history of syphilis and 48% HSV-2. Forty-one percent had a history of hypertension, 5% diabetes mellitus, 6% eczema, 10% cancer, 4% injection drug use, and 36% TMP-SMX use. Regarding body mass index, 32% were underweight/normal, 45% overweight, and 23% obese.

**FACTORS ASSOCIATED WITH THE DEVELOPMENT OF AN INITIAL MRSA INFECTION**

There were no significant associations between MRSA infection and demographic characteristics, including age, gender, and race (Table 8).

Regarding HIV history, there were no significant associations between development of a MRSA infection and duration of HIV or current use of HAART. There was a significant association between development of a MRSA infection and current CD4 cell count (p-value <0.01). For every 100 cells/mm³ increase in CD4 cell count, the odds of developing a MRSA infection decreased by 20%. Furthermore, patients with a CD4 cell count <350 cells/mm³ were four times as likely to develop a MRSA infection compared to patients with a CD4 cell count ≥500 cells/mm³ (p-value <0.01). There was also a significant association between nadir CD4 cell count and development of a MRSA infection; for every increase in 100 cells/mm³ in nadir CD4 cell count, the odds of developing a MRSA infection decreased by 29% (p-value <0.01). Additionally, patients who developed a MRSA infection were more likely than patients who did not develop a MRSA infection to have a nadir CD4 cell count <200 cells/mm³ (OR 2.5; p-value <0.01). Significant associations between development of a MRSA infection and current as well as maximum HIV viral load were noted (p-value <0.01). Patients who developed a MRSA infection were more likely to have a higher log₁₀ HIV viral load than patients who did not develop an infection (OR 1.5; p-value <0.01), and were also more likely to have an HIV viral load ≥400 copies/mL (OR 2.7; p-value <0.01). Notably, there was a significant association between development of a MRSA infection and a variable combining HIV viral load and CD4 cell count. The highest odds for developing a MRSA infection were in patients with a current CD4 cell count <500 cells/mm³ and HIV viral load ≥400 copies/mL (OR 6.4; p<0.01). An elevated odds for a MRSA infection were noted in patients who had either a CD4 cell count <500 cells/mm³ or HIV viral load ≥400 copies/mL.
compared to patients with optimal levels of these categories. Finally, patients classified as CDC stage C (AIDS-indicator conditions) were more than three times as likely to develop a MRSA infection compared to patients in CDC stage A or B (p-value <0.01).

Regarding medical history, there were no significant associations between development of a MRSA infection and syphilis, HSV-2, hypertension, diabetes mellitus, eczema, cancer, TMP-SMX use, or BMI. However, a history of injection drug use was significantly associated with an approximate five-fold increase in the odds for MRSA infection (OR 4.7; p-value <0.01).

The full and final multiple logistic regression model of factors associated with the development of an initial MRSA infection is shown in Table 9. The following variables were included in the full model (i.e., variables with a p-value ≤ 0.05 in the univariate analysis): current CD4 cell count and HIV viral load, current CDC stage, and injection drug use. In addition, age and years of follow-up were included to control for potential confounding and varying lengths of follow-up time, respectively. All variables besides age had a p-value <0.05, and therefore no variables were removed from the model. The model was a good fit according to the Hosmer-Lemshow Goodness of Fit test (p-value=0.20>0.10).

In the final multiple logistic regression model, the combined category of current CD4 cell count and HIV viral load was significantly associated with the development of an initial MRSA infection. The odds of developing a MRSA infection were highest in patients with a CD4 cell count <500 cells/mm³ and HIV viral load ≥400 copies/mL (OR 5.2; p-value <0.01). Patients with either a CD4 cell count <500 cells/mm³ (OR 2.7; p-value <0.01) or HIV viral load ≥400 copies/mL (OR 3.2; p-value <0.01) also showed an increased odds for a MRSA infection compared to patients who had CD4 cell counts ≥500 cells/mm³ and HIV viral load <400 copies/mL. Current CDC stage was also significantly associated with MRSA infection in the final model (p-value <0.01); patients categorized as CDC stage C were five times as likely to develop a MRSA infection compared to patients in CDC stage A or B. A history of injection drug use was also associated with an increased odds for MRSA infection (OR 4.9; p-value <0.01).
FACTORS ASSOCIATED WITH THE DEVELOPMENT OF A RECURRENT MRSA INFECTION

Of the patients who experienced an initial MRSA SSTI, 27% (17/63) experienced at least one recurrent infection. Overall, a total of 45 recurrent infections were experienced among patients with an initial infection, representing an incidence of 206 recurrent infections/1000 PY. The median time to the first recurrent event was 4.7 months (range 1-80 months), and patients experienced a median of one recurrent event (range 1-20 events). Regarding the first recurrent event, 65% (11/17) occurred at a distinct anatomical location from the initial infection.

Univariate analyses of factors associated with the development of a recurrent MRSA infection are shown in Table 10; in the analyses, only the first recurrent event is analyzed. Regarding demographics, there was a significant association between age and recurrent MRSA infection (OR 1.8; p-value 0.03). Regarding HIV history, there was a borderline significant association between duration of HIV and recurrence (OR 1.1; p-value 0.09). CD4 cell count at the initial infection was significantly associated with recurrence (OR 0.7; p-value 0.02), as were nadir CD4 cell count (OR 0.5; p-value <0.01), log10 maximum HIV viral load (OR 4.0; p-value 0.02), and CDC stage C at the initial infection (OR 4.2; p-value 0.02). However, HIV viral load at the initial infection or HAART use after the initial infection were not significantly associated with recurrence.

There were no significant associations between recurrence and a history of sexually transmitted infections, diabetes mellitus, eczema, TMP-SMX use after the initial infection, immunosuppressant use after the initial infection, beta-lactam use after the initial infection, fluoroquinolone use after the initial infection, or BMI. A history of hypertension (OR 2.9; p-value 0.08) and hospital admission (OR 3.6; p-value 0.05) after the initial MRSA infection were marginally significant. There was a significant association between cancer and recurrence (OR 5.7; p-value 0.02). Patients with a history of injection drug use (OR 6.0; p-value 0.03) or surgery after the initial infection (OR 3.8; p-value 0.03) also had an increased odds for recurrence.

Regarding management of the initial MRSA infection, receipt of incision and drainage, mupirocin and hexachlorophene, TMP-SMX, combination antibiotics for empiric therapy, combination antibiotics for empiric therapy and incision and drainage, an empiric
antibiotic concordant with the MRSA isolate sensitivity pattern, or duration of antibiotic therapy were not significantly associated with recurrence. There was a marginally significant association between recurrence and receipt of vancomycin for treatment of the initial infection (OR 3.0; p-value 0.09). Receipt of minocycline as the initial antibiotic (OR 0.3; p-value 0.05) and receipt of minocycline at any time for treatment (OR 0.3; p-value 0.05) were marginally associated with a reduced odds for recurrence. Furthermore, hospital admission for the initial MRSA infection was significantly associated with an increased odds for recurrence (OR 5.0; p-value 0.01).

As there were several variables to consider for the full multiple logistic regression model, additional criteria were used for selection. Nadir CD4 cell count and maximum HIV viral load were not placed in the full model as these variables are correlated with CD4 cell count at the initial infection. Although hospital admission for the initial infection was significant in the univariate analysis, hospital admission after the initial infection was instead placed in the full model as it may be closer to the time of recurrence. A history of cancer and surgery were also not placed in the full model as they are highly associated with hospital admission after the initial infection. Finally, separate models were fit using minocycline as the initial antibiotic and minocycline for treatment at any time as the variables of interest.

The first full multiple logistic regression model consisted of age at initial infection, years of follow-up at initial infection, CD4 cell count at initial infection, CDC stage at initial infection, history of injection drug use, hospital admission after the initial infection, and receipt of minocycline as the initial antibiotic. The final model is shown in Table 11. There was a significant association between receipt of minocycline as the initial antibiotic and recurrence. Receipt of minocycline as the initial antibiotic was associated with an approximate 80% reduction in the odds for recurrence (OR 0.2; p-value 0.03). Patients who were hospitalized after the initial infection had a significantly increased odds for recurrence (OR 7.4; p-value 0.02). An increase of 100 cells/mm³ in the CD4 cell count was associated with an approximately 30% reduced odds for recurrence; this finding was marginally significant (p-value 0.06). In a separate model including minocycline for treatment at any time for the initial infection, similar findings were observed (Table 12); of note, minocycline for treatment at any time was marginally significantly associated with an 80% reduction in the odds for recurrence in this model (OR 0.2; p-value =0.05).
In order to further examine the relationship between minocycline and recurrence, patients who received versus did not receive minocycline were evaluated on study characteristics; relevant findings are shown in Table 13. Patients who received minocycline had higher CD4 cell counts within the first 6 months following the initial infection (476 vs 378 cells/mm$^3$); however, this finding was not statistically significant. Further, patients who received minocycline were significantly less likely to have had hospital admission for the initial infection, had longer duration of antibiotic therapy, and were more likely to have received mupirocin and hexachlorophene for the initial infection; these findings were statistically significant.

**The Impact of CD4 Cell Count and HIV Viral Load on Recurrence: A Linear Mixed Models Approach**

Fifty-four patients had $\geq 1$ baseline CD4 cell count measurement within the six months preceding the initial MRSA SSTI and $\geq 1$ CD4 cell count measurement within the six months following the initial MRSA SSTI, hence only these patients were included in the linear mixed effects analysis. The full linear mixed effects model included CD4 cell count as the dependent variable, with time, a categorical factor for recurrence of a MRSA SSTI, and an interaction between time and recurrence modeled as the fixed effects; a random effect associated with the intercept for each patient was also included (data not shown). The interaction of recurrence and time was not significant using the likelihood ratio test; therefore, the interaction term was removed from the full model. Furthermore, the time effect was also not significant using the likelihood ratio test, which was also removed from the final model. In the linear mixed model for log$_{10}$ HIV viral load, the interaction effect and time effect were not significant and removed from the full model.

The final linear mixed effects model for CD4 cell count is presented in Table 14, which includes the fixed effect of recurrence of a MRSA SSTI and a random effect associated with the intercept for each patient. A significant association between CD4 cell count and recurrence of a MRSA SSTI was observed ($p=0.03$). The average overall CD4 cell count in the six month window preceding and following the initial MRSA SSTI was approximately 152 cells/mm$^3$ lower in patients who experienced a recurrent MRSA SSTI than in patients who did not experience a recurrent MRSA SSTI. In a separate linear mixed
effects model, there was no significant association between log_{10} HIV viral load and recurrence (Table 15).

**VARIABLE SELECTION BY THE RANDOM FORESTS ALGORITHM**

Due to the random nature of the random forests algorithm, repeated runs of the algorithm do not yield exactly the same importance score. However, with repeated simulations, the ordering of variable importance was consistent in the current analysis. The following variables were found to be most important for prediction of initial MRSA SSTIs according to the random forests algorithm (i.e., variables which resulted in a mean decrease in accuracy of \( \geq 50\% \)): duration of HIV infection, nadir CD4 cell count, CDC stage, log_{10} maximum HIV viral load, age, history of TMP-SMX use, and log_{10} current HIV viral load. Variables associated with initial MRSA SSTIs in both the random forests analysis and logistic regression analysis included nadir CD4 cell count, CDC stage, log_{10} maximum HIV viral load and log_{10} current HIV viral load.

The following variables were found to be most important for prediction of recurrent MRSA SSTIs: hospital admission for the initial infection, hospital admission after the initial infection, nadir CD4 cell count, age at initial infection, CD4 cell count at initial infection, history of cancer, race, history of diabetes, and history of hypertension. Of these variables, only hospital admission for the initial infection, hospital admission after the initial infection, nadir CD4 cell count, CD4 cell count at the initial infection, history of cancer, and age were significantly associated with recurrence in the univariate logistic regression analysis.
CHAPTER 5

DISCUSSION

The purpose of this study was to determine the incidence of and factors associated
with initial and recurrent MRSA skin and soft-tissue infections among HIV-infected persons.
This is one of the first studies to determine the impact that management of the initial MRSA
infection has on the development of recurrent infections, which may have important
implications for the clinical management of MRSA infections among HIV-infected persons.

INCIDENCE OF MRSA INFECTIONS

During the study period, 8% of patients developed at least one MRSA SSTI, which
lies within the range (3%-11%) of MRSA SSTI rates reported in other studies among HIV-
infected cohorts (Mathews et al., 2005; Ramsetty et al., 2010; Shet et al., 2009). We found
that the overall incidence of MRSA SSTIs from 1993-2010 was 19.8 infections/1000 PY.
From 2003-2006, a 2.4-fold increase in the incidence was noted, peaking at 40
infections/1000 PY during 2005-2006. However, the incidence has declined since 2007 to
29.4 infections/1000 person-years in 2009-2010, representing a 27% decrease. Our results
confirm those of a recent study among HIV-infected outpatients and inpatients, which found
that the incidence of MRSA infections increased after 2003 and then began a decreasing
trend after peaking in 2007 (Hidron et al., 2011). Similarly, a population-based surveillance
study found a 28% decrease in hospital onset and 17% decrease in healthcare-associated
community-onset MRSA infections from 2005-2008 (Kallen et al., 2010).

Reasons for the decrease in incidence of MRSA infections among HIV-infected
persons are not known but may be due to several factors. First, the use of MRSA prevention
control practices in U.S. healthcare facilities may partially explain the decrease in incidence
(Aldeyab et al., 2008). Furthermore, temporal variations in MRSA incidence may follow
temporal variations in other factors, such as antibiotic use. For example, a prior hospital-
based study showed that changes in MRSA incidence throughout time were correlated with
changes in antibiotic usage; in particular, use of fluoroquinolones, third-generation
cephalosporins, or amoxicillin was associated with increasing trends of MRSA incidence (Aldeyab et al., 2008). Secondly, some studies have suggested that participation in high-risk sexual behaviors — such as public bath use, anal intercourse, and sex with multiple partners — may facilitate the transmission of MRSA (Crum-Cianflone et al., 2011; Diep et al., 2008; Lee et al., 2005; Szumowski et al., 2009). Whether a reduction in high risk-behaviors as a result of prevention efforts is contributing to the decreasing incidence of MRSA infections needs to be further investigated. Thirdly, increased use of HAART resulting in improved immune status among HIV-infected persons may also play an important role. Given that HIV-infected persons with low CD4 cell counts in our study and in others were more likely to develop MRSA infections (Mathews et al., 2005; Ramsetty et al., 2010), increased use of HAART throughout time among HIV-infected patients is a possible explanation.

Despite the decreased incidence of MRSA infections in our study, HIV-infected persons are still at heightened risk for MRSA infections compared to HIV-negative persons (Popovich et al., 2010). A community-based study found an incidence of MRSA SSTIs of 9.96 per 1000 HIV-infected patients and 1.57 per 1000 HIV-negative patients, representing a 6-fold increase in incidence among HIV-infected patients (Popovich et al., 2010). A study conducted at the same medical facility as the current study found an incidence of 2.3 MRSA infections/1000 PY among the general population served (Crum et al., 2006). Compared to the most recent incidence that we observed in our study (29.4 infections/1000 PY in 2009-2010), this represents a 13-fold increase in risk among HIV-infected persons. The increased risk for MRSA infections among HIV-infected persons compared to HIV-negative patients may be due to immunodeficiency, increased hospitalizations and healthcare exposures, participation in high-risk sexual behaviors, or underlying medical conditions.

**Clinical Characteristics of MRSA Infections**

In our study, patients with SSTIs most commonly had an abscess (44%) followed by cellulitis (24%) and wound infections (10%). Furthermore, SSTIs most often occurred at the lower extremity, buttocks/scrotum, and head/face. Previous investigations among HIV-infected cohorts have noted similar findings (Diep et al., 2008; Lee et al., 2005; Sztramko et al., 2007; Szumowski et al., 2007). In the general population, abscesses and cellulitis are the most commonly reported SSTIs and have also been shown to occur at these regions (Crum et
al., 2006; Fridkin et al., 2006). For example, a study conducted among the general population served at the same medical facility as the current study found that SSTIs most commonly occurred at the extremities followed by the buttock/genital region (Crum et al., 2006). The high proportion of patients with SSTIs at the buttocks/scrotum is noteworthy, given that some studies have suggested that MRSA may be transmitted in the setting of sexual contact (Cook et al., 2007; Crum-Cianflone et al., 2011; Lee et al., 2005). Factors contributing to the spread of perigential infections may include participation in anal intercourse with exposure to MRSA colonizing the gastrointestinal tract, skin-abrading practices, or intimate skin-to-skin contact. Due to the retrospective nature of our study, we were not able to evaluate patients on their sexual practices nor carriage of MRSA at the perigential regions. However, the finding that infections occur at the buttocks/scrotum supports future studies evaluating perigential carriage of MRSA and high-risk sexual behaviors as risk factors for the development of MRSA SSTIs at these regions.

Regarding sensitivity of MRSA isolates, the majority were sensitive to TMP-SMX, tetracyclines, and vancomycin. Resistance to TMP-SMX has been low in the majority of studies among HIV-infected persons, averaging at 2% (range 0-9%); additionally, its resistance has been low among studies in the general population (Moran et al., 2006; Shadyab & Crum-Cianflone, in press). This suggests that TMP-SMX may be a viable option for empiric antimicrobial therapy; however, further data are needed on patient outcomes. No isolates were resistant to vancomycin in our study, and to date no study among HIV-infected persons has reported resistance to this antibiotic (Shadyab & Crum-Cianflone, in press). Despite this low resistance, vancomycin is usually administered intravenously to treat complicated SSTIs.

Similar to previous investigations among HIV-infected persons with MRSA SSTIs, we found a high tetracycline antibiotic (including minocycline) sensitivity (Graber et al., 2008; Skiest et al., 2006; Trinh et al., 2009). Two population-based studies also noted high tetracycline antibiotic sensitivities (Moran et al., 2006; Naimi et al., 2003). Notably, we also found that minocycline may be prophylactic in the setting of recurrent disease. Given these findings, it is reasonable to suggest that minocycline is an important part of the armamentarium of antibiotics against MRSA SSTIs and may be a preferable option for empiric therapy in geographic regions where its sensitivity is high. Erythromycin resistance
was high in our study, consistent with previous reports among HIV-infected persons and the general population (Lee et al., 2005; Mathews et al., 2005; Moran et al., 2006; Naimi et al., 2003; Skiest et al., 2006; Szumowski et al., 2007); these data suggest that erythromycin may not be an effective option for empiric therapy. Additionally, clindamycin sensitivity was high in our study; in previous studies among HIV-infected persons, clindamycin resistance has been variable, ranging from 3%-70% (Shadyab & Crum-Cianflone, in press). Therefore, this antibiotic may also not be a viable option for empiric therapy among HIV-infected persons. In the general population, however, clindamycin susceptibility has been generally high (Moran et al., 2006; Naimi et al., 2003). Finally, fluoroquinolone sensitivity in our study was relatively high compared to other studies among HIV-infected cohorts; however, sensitivity to these antibiotics has been variable according to the geographic region under study both among HIV-infected persons and the general population (Shadyab & Crum-Cianflone, in press).

**Factors Associated with the Initial MRSA Infection**

Factors associated with the initial MRSA SSTI in our study included CD4 cell count and HIV viral load, CDC stage, and injection drug use. The positive association between markers of immunodeficiency and MRSA SSTIs is noteworthy. In the multiple logistic regression analysis, patients with CD4 cell counts <500 cells/mm³ and HIV viral load ≥400 copies/mL experienced a five-fold increased odds for MRSA SSTIs compared to patients with CD4 cell counts ≥500 cells/mm³ and HIV viral load <400 copies/mL. Interestingly, the odds of developing a MRSA SSTI were also elevated in patients with either CD4 cell count <500 or HIV viral load ≥400 copies/mL. Studies evaluating the association between CD4 cell count and MRSA infection have provided conflicting results. Most studies have not found significant associations between CD4 cell count and MRSA infection (Diep et al., 2008; Lee et al., 2005; Popovich et al., 2010; Szumowski et al., 2007; Szumowski et al., 2009). However, a previous investigation among HIV-infected outpatients noted a two-fold increase in the risk for MRSA infection among patients with CD4 cell counts <50 cells/mm³ (Mathews et al., 2005). A case-control study among HIV-infected outpatients observed a two-fold increase in the odds for MRSA colonization or infection among patients with nadir CD4 cell count <200 cells/mm³ (Ramsetty et al., 2010). Similarly, we observed an increased
odds for MRSA SSTIs among patients with nadir CD4 cell count <200 cells/mm³ in the univariate analysis. Two other studies noted similar findings (Drapeau et al., 2007; Hidron et al., 2011).

Our results suggest that indicators of advanced HIV disease, including low CD4 cell count, high HIV viral load, and CDC stage C, may be important predictors of MRSA SSTIs among HIV-infected persons and thus improved HIV control may help reduce the risk for infection among this population. Several factors may explain the association between advanced HIV disease and increased risk for MRSA infection. First, a low CD4 cell count has been associated with increased MRSA colonization (Cenizal et al., 2008). It has previously been demonstrated that HIV patients colonized with MRSA have a greater risk for infection than patients who are not colonized, and patients have been shown to be infected with the colonizing strain (Szumowski et al., 2009). Second, HIV-infected persons with low CD4 cell counts may experience higher rates of hospitalizations (Crum-Cianflone et al., 2010) and may acquire MRSA colonization and subsequent infection in the hospital setting. An additional mechanism explaining the association between indicators of advanced HIV disease and MRSA infection may lie in the host immune response to infection. T helper (Th) cells (CD4 cells) have been implicated in the host cell immune response against cutaneous *S. aureus* infections (Krishna & Miller, 2012). Specifically, Th17 cells have demonstrated important functions in neutrophil recruitment and host defense against *S. aureus* infection through the production of cytokines such as interleukin-17. Hence, HIV-infected persons with low CD4 cell counts and who consequently are deficient in Th17 cells have increased susceptibility to *S. aureus* skin infections (Krishna & Miller, 2012).

Despite the positive association between poor immune status and MRSA SSTIs, we did not note a significant association between use of HAART and MRSA infection in the univariate analysis, potentially related to the high number of patients on HAART. Our lack of an association may also be due to the fact that we measured HAART use within a year of the infection or last clinic visit, and therefore did not evaluate more recent (i.e., within 6 months) use of HAART; additionally, we did not examine the percentage of time on HAART during that time period. Most studies have found that HAART use is not associated with a reduced risk for MRSA infection (Diep et al., 2008; Drapeau et al., 2007; Lee et al., 2005; Szumowski et al., 2007; Szumowski et al., 2009). However, a recent prospective study
among HIV-infected outpatients found a lower incidence of MRSA infections among HAART users, noting a 64% reduction in the risk (Hidron et al., 2011). Given the association between poor immune status and MRSA infection in our study, proper HIV control through use of HAART may provide a protective effect against MRSA SSTIs. Prospective investigations are needed to elucidate the protective effect that HAART may provide among HIV-infected patients with MRSA SSTIs.

We found a significant association between injection drug use and development of a MRSA SSTI, further confirming previous investigations among other HIV-infected cohorts (Hidron et al., 2011; Lee et al., 2005; Mathews et al., 2005; Popovich et al., 2010; Ramsetty et al., 2010; Szumowski et al., 2009). In our study, injection drug users were more than five times likely to develop a MRSA SSTI compared to non-users in the final model. A previous study among a large cohort of HIV-infected outpatients found that HIV-infected persons who were MSM, IDU, or both had a five-fold increased risk for MRSA infection (Mathews et al., 2005). Two studies found that the use of methamphetamines, illicit drugs that may potentiate participation in high-risk sexual activities such as unprotected intercourse and multiple sexual partners, also increase the risk for MRSA infection among HIV-infected persons (Lee et al., 2005; Mimiaga et al., 2008; Szumowski et al., 2009).

Infectious diseases are a leading cause of morbidity and hospitalization among injection drug users (Bassetti & Battegay, 2004). Further, *S. aureus* SSTIs (especially abscesses and cellulitis) are an important reason for hospitalizations and emergency department visits among injection drug users (Bassetti & Battegay, 2004). Previously, it has been shown that HIV infection is an important predictor for increased health care utilization, including longer duration of hospital stay, among injection drug users with SSTIs (Hsieh, Rothman, Bartlett, Yang, & Kellen, 2008). Factors potentiating the spread of MRSA SSTIs among injection drug users may include sharing of infected syringes and drug equipment, as well as participation in high-risk sexual behaviors such as sex with multiple partners or unprotected intercourse (Bassetti & Battegay, 2004). Our findings support prevention efforts to reduce the burden of MRSA SSTIs among injection drug users (including those who are HIV-infected), such as drug abuse treatment, skin cleaning before injection to reduce the risk of soft-tissue abscesses, needle-exchange programs to facilitate the use of clean needles, and participation in injection opiate substitution programs (Bassetti & Battegay, 2004).
FACTORS ASSOCIATED WITH RECURRENT MRSA INFECTIONS

We reported a high recurrence rate among our cohort, with 27% experiencing a recurrent infection. Our recurrence rate lies within the range (23%-71%) reported among other HIV-infected cohorts (Graber et al., 2008; Shastry et al., 2007; Skiest et al., 2006; Szumowski et al., 2007). However, our recurrence rate is higher than that previously reported among the general population served at the same medical facility (27% vs 9%) (Crum et al., 2006). Further, patients in our study experienced a recurrent infection at a median time of 4.7 months after the initial infection. A previous study among HIV-infected outpatients found a similar time to recurrence, and another study among HIV-infected MSM noted a lower time to recurrence of 2.6 months with 31% of patients experiencing a recurrent infection within the first six months (Graber et al., 2008; Shastry et al., 2007). Collectively, these findings suggest that HIV-infected persons not only experience high recurrence rates of MRSA infections but also soon after the initial infection, thus highlighting the importance of preventive strategies to reduce recurrence in this population.

Recurrence of MRSA SSTIs is also a significant issue in other diverse populations. For example, a study among incarcerated patients reported that persons with initial MRSA SSTIs had a recurrence rate of 14% with a median time to recurrence of approximately 2 months, most likely due to crowded living conditions and poor hygiene practices (David, Mennella, Mansour, Boyle-Vavra, & Daum, 2008). A study conducted among college football team players noted several recurrent infections throughout the two-year study period among patients who shared infected towels and did not properly care for infected wounds and abrasions (Nguyen, Mascola, & Bancroft, 2005). In a study among patients presenting to emergency departments with MRSA SSTIs requiring surgical debridement, 21% experienced a recurrent infection, despite adequate surgical drainage and antibiotic therapy (Sreeramoju et al., 2011). Still, HIV-infected patients in our study and those in other studies experienced higher rates of recurrence, consistent with the observation that HIV-infected persons have a higher risk for MRSA infection compared to HIV-negative persons (Graber et al., 2008; Shastry et al., 2007; Skiest et al., 2006; Szumowski et al., 2007).

We found that receipt of minocycline may be associated with a reduced risk for recurrent MRSA SSTIs. Patients who received minocycline had an 80% reduction in the odds
for recurrence in the analysis. To our knowledge, this is the first study to demonstrate that receipt of a specific class of an antibiotic may protect against the development of recurrent MRSA infections, which has important implications for clinical management.

Minocycline is a broad-spectrum, bacteriostatic, tetracycline antibiotic. It is taken orally twice daily at doses of 100 mg, but may also be administered intravenously. Prospective, randomized studies evaluating the efficacy of tetracycline antibiotics for the treatment of MRSA SSTIs are currently not available in the general population and HIV-infected persons (Liu et al., 2011). However, minocycline has been shown to have significant in vitro activity against MRSA with high rates of susceptibility noted in both community-acquired and nosocomial strains (Bishburg & Bishburg, 2009). The antistaphylococcal activity of minocycline has also been shown to be greater than that of other tetracycline antibiotics, and it has demonstrated excellent oral bioavailability, tissue penetration, and tolerability (Bishburg & Bishburg, 2009).

Tetracycline resistance in MRSA isolates is primarily due to the presence of the tetK gene, which confers resistance to tetracycline and inducible resistance to doxycycline, without any affect on minocycline sensitivity (Liu et al., 2011). Additionally, it has been shown that in multidrug resistant strains of community-acquired MRSA, doxycycline, but not minocycline, can induce its own resistance (Schwartz et al., 2009). Therefore, in cases where tetracycline resistance is present in a MRSA isolate, treatment with minocycline should still be considered. Specifically testing for minocycline sensitivity may therefore be beneficial and may result in improved patient outcomes (Bishburg & Bishburg, 2009).

Studies comparing the efficacy of tetracycline antibiotics to other classes of antibiotics to which MRSA isolates are susceptible are limited. Additionally, despite high susceptibilities across studies, tetracycline antibiotics seem to not be increasingly prescribed to treat MRSA SSTIs. A retrospective study among the general population of patients presenting at emergency departments and outpatient centers noted a high (95%) tetracycline antibiotic sensitivity among MRSA isolates, but only 32% of SSTI cases were treated with tetracycline antibiotics (Ruhe & Menon, 2007). A prospective, population-based surveillance study also noted a high tetracycline antibiotic sensitivity across diverse geographic regions; however, only 26% of patients received non-beta lactam antibiotic therapy (Fridkin et al., 2005).
Interestingly, in a survey of adult providers in specialties including primary care, dermatology, and infectious diseases, only 3% reported prescribing doxycycline as the empiric antibiotic for MRSA SSTIs; the majority (75%) favored TMP-SMX (Mascitti, Gerber, Zaoutis, Barton, & Lautenbach, 2010). Additionally, the majority (62%) of providers favored prescribing TMP-SMX based on culture results, whereas only 12% favored minocycline. TMP-SMX was also favored as a decolonization measure to reduce recurrent infections. However, despite the wide use of TMP-SMX and the high rate of sensitivity of MRSA isolates to this antibiotic, no data are currently available to suggest that it may reduce the risk for recurrent infections or that it is clinically superior to tetracycline antibiotics, which have also shown high sensitivity. In our study, we found TMP-SMX did not result in a reduction in the odds for development of an initial or a recurrent MRSA SStI, suggesting that it may not be the most optimal antibiotic of choice.

Limited studies have evaluated the impact of specific classes of antibiotics, including tetracyclines, on MRSA SSTIs among HIV-infected persons. A retrospective study among HIV-infected outpatients reported that of all oral antibiotics tested for sensitivity in MRSA isolates, tetracycline antibiotics showed the highest sensitivity; however, TMP-SMX was the most commonly prescribed empiric antibiotic, whereas minocycline was prescribed as the empiric antibiotic in only 12% of cases (Trinh et al., 2009). In another investigation, tetracycline antibiotics, the majority of which were minocycline, were the most common empiric antibiotic, and tetracycline sensitivity was high (Skiest et al., 2006). Additionally, combination antibiotics were also commonly prescribed for empiric therapy, with TMP-SMX present in most combination regimens. However, the effects of tetracycline antibiotics specifically on clinical outcomes were not assessed (Skiest et al., 2006). A case-series analysis among HIV-infected MSM found that the majority of MRSA isolates were sensitive to tetracyclines, but doxycycline was only prescribed in three cases, with the majority of patients receiving TMP-SMX in their combination regimens (Sztramko et al., 2007). To our knowledge, our study is the first to suggest that receipt of a tetracycline antibiotic may result in improved patient outcomes by conveying a potential prophylactic effect on recurrent infections.

Reasons for the clinical superiority of minocycline in the treatment of recurrent MRSA SSTIs are likely multifaceted. First, minocycline has excellent skin and soft-tissue
penetration, is easily administered thus leading to high completion rates, and is well-tolerated. Secondly, an in vitro investigation demonstrated that minocycline has anti-HIV effects (Szeto et al., 2010). In that study, minocycline was shown to have immunomodulatory effects by inhibiting HIV viral replication and reducing CD4+ T cell activation. Interestingly, we found that patients who received minocycline for treatment of the initial MRSA SSTI had higher CD4 cell counts in the six months following the initial infection compared to patients who did not receive minocycline (476 versus 378 cells/mm³), providing support to the notion that minocycline is an immunmodulatory agent; however, this finding did not reach statistical significance, most likely due to missing data for CD4 cell counts. Thirdly, minocycline may have MRSA decolonization effects. For example, in a survey of adult and pediatric infectious disease providers, 55% reported including oral antibiotics in decolonization regimens to treat recurrent furunculosis, with 15% using minocycline as the decolonization agent (West, Plantenga, Strausbaugh, & The Infectious Diseases Society of America Emerging Infections Network, 2007). However, the exact effect of minocycline on the prevention of recurrent events was not reported. Further, it is not known whether minocycline per se results in decolonization of MRSA or whether its combination with other decolonization agents such as mupirocin nasal ointment and hexachlorophene or chlorhexidine wash is more effective. In a randomized, controlled trial, it was reported that treatment with mupirocin, chlorhexidine wash, rifampin, and doxycycline was effective in eradicating MRSA colonization (Simor et al., 2007). Interestingly, we found that patients on minocycline were significantly more likely to have received mupirocin and hexachlorophene, and there was a marginal association of decreased recurrence among patients who received minocycline in addition to these decolonization agents. In conclusion, the exact mechanism by which minocycline may lead to a decreased risk for recurrent infections is likely multifactorial and needs to be further investigated in prospective studies. In the interim, providers in geographic regions where tetracycline sensitivity is high should consider prescribing minocycline as an empiric antibiotic to patients who experience initial and recurrent MRSA SSTIs, and should also consider minocycline treatment if culture results indicate sensitivity to this antibiotic, as this may contribute to improved patient outcomes.

We did not find significant associations between recurrence and receipt of other classes of antibiotics used for management of the initial infection, including TMP-SMX and
vancomycin. Additionally, receipt of TMP-SMX prescribed after the initial infection (i.e., not including for treatment of the infection) was not associated with reduced recurrence, nor was receipt of fluoroquinolone antibiotics. As mentioned, TMP-SMX has been increasingly reported as the most common antibiotic prescribed to treat MRSA SSTIs in the general population and HIV-infected persons, and it has demonstrated high sensitivity in most studies (Mascitti et al., 2010; Skiest et al., 2006; Sztramko et al., 2007; Trinh et al., 2009). Although TMP-SMX may result in clinical resolution, its efficacy in reducing recurrent events is poorly understood. In a survey of adult providers, TMP-SMX was the most commonly prescribed antibiotic to prevent recurrent MRSA SSTIs, perhaps due to its high sensitivity in most regions (Mascitti et al., 2010). However, our results do not suggest that TMP-SMX is preferable compared to other antibiotic choices.

We also did not find significant associations between recurrence and receipt of combination antibiotics for empiric therapy or receipt of empiric antibiotics concordant with the antibiotic sensitivity pattern. Additionally, receipt of incision and drainage procedures or receipt of both incision and drainage and combination antibiotics for empiric therapy were not associated with decreased recurrent infections. Studies conducted among HIV-infected persons and the general population have noted divergent findings with regard to the effect of these factors on recurrence. A study among HIV-infected outpatients found that there were no differences in MRSA re-infection rates among patients treated with concordant versus discordant antibiotics, those treated with combination therapy versus monotherapy, or those who received incision drainage versus those who did not (Skiest et al., 2006). However, another study found that isolate sensitivity to empirical antibiotics was associated with clinical resolution, but its effect on recurrence was not described (Szumowski et al., 2007). A retrospective study among HIV-infected outpatients reported that among patients with CA-MRSA SSTIs, the majority of those with improved clinical status after four weeks of presentation had received a combination of incision and drainage and antibiotic therapy (Trinh et al., 2009). A population-based surveillance study reported that neither incision and drainage or receipt of ineffective empiric antibiotics were associated with follow-up visits to a healthcare provider, subsequent incision and drainage, or subsequent change of the antibiotic regimen (Fridkin et al., 2006). However, another study among the general population of inpatients and outpatients reported that use of an inactive antibiotic for
antimicrobial therapy was associated with treatment failure, defined as worsening of symptoms with performance of an additional incision and drainage procedure, subsequent hospital admission, or re-infection with MRSA during antibiotic therapy (Ruhe, Smith, Bradsher, & Menon, 2007). Due to these conflicting findings, further studies are needed to evaluate the impact of incision and drainage procedures and effective empiric antibiotic therapy on recurrent infections. However, incision and drainage with consideration for antibiotic therapy is advocated in patients with purulent infections (Liu et al., 2011).

Current guidelines for the clinical management of MRSA infections from the Infectious Diseases Society of America (IDSA) have emphasized the importance of nasal decolonization with mupirocin and body decolonization with antiseptic body washes, such as chlorhexidine, as a measure to prevent recurrent MRSA SSTIs; however, prospective trials evaluating this approach are limited (Liu et al., 2011). A combination of oral antibiotics, such as doxycycline and rifampin, combined with mupirocin and chlorhexidine, has been shown to eradicate MRSA carriage, but its effect on recurrence is currently not known (Simor et al., 2007). We did not find a significant association between recurrence and receipt of decolonization medications. However, a randomized, controlled trial among HIV-infected persons found that patients who took repeated courses of treatment with mupirocin had an 80% reduction in the odds for colonization, but there was no effect on infection (Gordon et al., 2010).

The pathogenesis of recurrent MRSA infection likely involves several factors including host colonization, patient behavior, and environmental exposures (Miller & Diep, 2008). In particular, patient behavior and environmental exposures from increased hospitalizations may play an important role in the pathogenesis of recurrent MRSA infection among HIV-infected persons. In our analysis, we found that hospitalization was associated with increased recurrent infections. Hospitalization may facilitate the transmission of MRSA via contaminated surfaces, direct contact with healthcare workers colonized or infected with MRSA, or may be a result of MRSA exposure during surgical procedures. Furthermore, several investigations among HIV-infected persons have found that high-risk sexual behaviors, such as public bath use and multiple sexual partners, are associated with an increased risk for MRSA colonization and infection (Crum-Cianflone et al., 2011; Lee et al., 2005; Szumowski et al., 2009). However, the effect of high-risk behaviors on recurrence has
not been studied. Due to the retrospective nature of our study, we could not assess patients on their sexual behaviors. Further research is needed to evaluate the precise effect of high-risk sexual behaviors on recurrence. In the meantime, providers should consider implementing a multifaceted approach to the management of patients with recurrent MRSA infections, including obtaining wound cultures for purposes of antibiotic susceptibility testing, educating patients on high-risk behaviors that may facilitate MRSA transmission including avoidance of injection drug use, advocating proper hygiene to reduce MRSA transmission, initiating patients on HAART to improve CD4 cell counts, and potentially consider prescribing minocycline if culture results confirm sensitivity to this antibiotic.

**THE IMPACT OF CD4 CELL COUNT ON RECURRENCE**

In the linear mixed models analysis, we found that patients with low CD4 cell counts may be at increased risk for recurrent infections. HIV-infected persons who experienced recurrent infections had on average lower CD4 cell counts in the six month window preceding and following the initial infection than patients who did not experience recurrence. Previously, the precise relationship between CD4 cell count and recurrence had not been fully described. Our linear mixed models analysis is novel and has the important advantage of taking into account multiple CD4 cell count measurements throughout time. The finding that CD4 cell count may increase the risk for recurrent infections suggests that HIV-infected persons may be immunologically predisposed to develop MRSA infections and that improved HIV control may reduce the burden of recurrence among this population. Hence, providers treating HIV-infected patients with a history of recurrent MRSA SSTIs who are not on HAART may consider initiation of HAART as a viable option to reduce the occurrence of recurrent infections in these patients.

**RANDOM FORESTS ALGORITHM**

Results from the random forests analysis indicated that several HIV-related factors, including nadir CD4 cell count, CDC stage, $\log_{10}$ current HIV viral load, and $\log_{10}$ maximum viral load, were important in the prediction of initial MRSA SSTIs. Further, nadir CD4 cell count and CD4 cell count at the initial infection were important in the prediction of recurrent MRSA SSTIs. Given the high level of accuracy of the random forests algorithm, these data lend strength to our findings that poor immune status, as indicated by a low CD4 cell count
and high HIV viral load, may render HIV-infected patients at increased risk for MRSA SSTIs. However, the random forests algorithm did not predict that injection drug use was important in the prediction of initial MRSA SSTIs or that receipt of minocycline was important in the prediction of recurrent MRSA SSTIs, indicating that these two analyses do not always agree. The usefulness of the random forests algorithm in epidemiological research studies remains to be established.

**STUDY LIMITATIONS**

Our study was subject to several limitations. As our study was retrospective, we could not establish a causal relationship between factors of interest and the development of initial and recurrent MRSA SSTIs. We only analyzed HIV-infected military beneficiaries, which is a unique population in that it has a low prevalence of IDU and co-morbidities, male predominance, mandated follow-up, and unique occupational exposures among active duty members; therefore, our results may not be generalizable to other HIV-infected populations. An additional limitation was that we were not able to assess patient behaviors, including sexual activities, due to the retrospective nature of our study. We only analyzed culture-proven MRSA SSTIs and did not include SSTIs suspected to be caused by MRSA (i.e., by a provider), and hence may have underestimated the impact of MRSA infection. Furthermore, data were not collected on HIV-uninfected persons and direct comparisons could not be made. Finally, data regarding the molecular characterization of MRSA isolates were not collected, and we could not determine whether the same or a different strain caused the initial and recurrent infection.

**STUDY STRENGTHS**

Our study had several strengths. We evaluated a large cohort of HIV-infected persons over a long period of time (18 years) to evaluate trends in the incidence of MRSA infections. Furthermore, our study population consisted entirely of military beneficiaries, who are afforded long-term care and close medical follow-up. An additional strength of our study was the comprehensive data collection, including management of the initial infection. Previous investigations had not evaluated the impact of management on the development of recurrent events.
**CONCLUSIONS**

In conclusion, HIV-infected persons are at high risk for initial and recurrent MRSA SSTIs. Although the incidence of MRSA SSTIs has increased in the past decade among HIV-infected persons, our results suggest that the incidence may now be on the decline. Reasons for the decrease in incidence may be a reflection of improved HIV control due to increased use of HAART, improved infection control practices, reduction in high-risk behaviors, or temporal variations in incidence that follow variations in factors such as antibiotic usage.

Poor immune status, as indicated by a low CD4 cell count and high HIV viral load, may increase the risk for development of MRSA SSTIs. Further, low CD4 cell count appears to increase the risk for recurrent infections. Hence, optimized HIV control is advocated in patients. Finally, minocycline be associated with a decreased risk for recurrent disease. Use of minocycline as the empiric antibiotic to treat MRSA SSTIs should be considered in geographic regions where its sensitivity is high and when culture results indicate sensitivity to this antibiotic. Finally, a multifaceted approach to prevent the incidence of MRSA SSTIs among HIV-infected persons is advocated, including patient education on high-risk behaviors (e.g., avoidance of IDU and high-risk sexual behaviors) and personal hygiene measures, treatment with minocycline to prevent recurrent infections, and initiation of HAART.

**FUTURE STUDIES**

Randomized, controlled trials are needed to evaluate the efficacy of minocycline as treatment for MRSA SSTIs and determine its impact on the development of recurrent events. Additionally, the precise mechanism by which minocycline acts to reduce the incidence of recurrent infections among HIV-infected persons and potentially the general population needs to be investigated in future studies. Furthermore, additional investigations evaluating risk factors for recurrent MRSA infections among HIV-infected persons are needed, and the impact of optimized management of the initial infection on development of recurrent events should be evaluated in future studies. Continued epidemiologic investigations evaluating the trends of MRSA infections are also needed among HIV-infected persons and the general population. Finally, the association between high-risk sexual behaviors and recurrent infections has not been established to date and requires further study. These data may provide novel insights that may guide future prevention efforts.
REFERENCES


APPENDIX

TABLES
Table 1. CDC HIV Staging System

<table>
<thead>
<tr>
<th>CD4 cell categories&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Clinical Categories</th>
<th>B&lt;sup&gt;b&lt;/sup&gt; Symptomatic (not A or C)</th>
<th>A&lt;br&gt;Asymptomatic, PGL, or Acute HIV Infection</th>
<th>AIDS Indicator Condition C&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500/mm&lt;sup&gt;3&lt;/sup&gt; (≥ 29%)</td>
<td>A1</td>
<td>B1</td>
<td>C1</td>
<td></td>
</tr>
<tr>
<td>200-499/mm&lt;sup&gt;3&lt;/sup&gt; (14-28%)</td>
<td>A2</td>
<td>B2</td>
<td>C2</td>
<td></td>
</tr>
<tr>
<td>&lt;200/mm&lt;sup&gt;3&lt;/sup&gt; (&lt;14%)</td>
<td>A3</td>
<td>B3</td>
<td>C3</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Examples of B clinical conditions: bacillary angiomatosis, oropharyngeal candidiasis, herpes zoster (shingles), hairy leukoplakia, and peripheral neuropathy

<sup>b</sup>Examples of C clinical conditions: pulmonary or extrapulmonary *Mycobacterium tuberculosis*, esophageal candidiasis, extrapulmonary cryptococcosis, Kaposi’s sarcoma, recurrent pneumonia, toxoplasmosis of the brain, and *Pneumocystis* pneumonia

<sup>c</sup>Patients in categories A3, B3, and C1-C3 are reported as AIDS based on AIDS indicator conditions and/or CD4 count <200/mm<sup>3</sup>

<sup*e>PGL, persistent generalized lymphadenopathy
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Infection Type</th>
<th>Low CD4 Count</th>
<th>High HIV Viral Load</th>
<th>HAART Use</th>
<th>Prior Antibiotic Use</th>
<th>TMP-SMX Use</th>
<th>Prior Hospitalization</th>
<th>Diabetes</th>
<th>History of STI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumbarrello et al. (2002)</td>
<td>S. aureus: Bacteremia</td>
<td>SS, 16.7</td>
<td>SS</td>
<td>SS, 43.0 (β-lactam use in past month)</td>
<td>NS</td>
<td>SS, 10.7 (past year)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2005)</td>
<td>CA-MRSA SSTI (e.g., abscess, cellulitis)</td>
<td>NS</td>
<td>NS</td>
<td>5.9 (ciprofloxacin use in past year)</td>
<td>0.3, 0.2 (past year)</td>
<td>3.7 (past year)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mathews et al. (2005)</td>
<td>SSTI, BSI, respiratory</td>
<td>2.4, 6.2 (log viral load ≥5.00 vs. &lt;2.99)</td>
<td>SS (higher rates in non-HAART users), NS</td>
<td>SS</td>
<td>0.3, 0.3 (≥120 days vs. &lt;120 days)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Crum-Cianflone et al. (2007)</td>
<td>SSTI, otitis, conjunctivitis</td>
<td>0.81, 0.84 (per 100 CD4 cells)</td>
<td>1.13, 4.54 (per log10 viral load)</td>
<td>NS</td>
<td>1.57 (β-lactam use in past year)</td>
<td>NS</td>
<td>NS</td>
<td>2.89, 4.55 (syphilis)</td>
<td></td>
</tr>
<tr>
<td>Szumowski et al. (2007)</td>
<td>SSTI</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drapeau et al. (2007)</td>
<td>BSI, SSTI, respiratory</td>
<td>0.24 (CD4 count ≥200 vs. &lt;200), NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>1.11, 1.14 (per 5-day stay in past year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkey et al. (2008)</td>
<td>Bacteremia</td>
<td>18.56, 21.52 (CD4 ≤50 vs. CD4 &gt;500), 10.09, 6.43 (CD4 51-200 vs. CD4 &gt;500)</td>
<td>3.05 (viral load &gt;400 vs. ≤400)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*(table continues)*
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Infection Type</th>
<th>Low CD4 Count</th>
<th>High HIV Viral Load</th>
<th>HAART Use</th>
<th>Prior Antibiotic Use</th>
<th>TMP-SMX Use</th>
<th>Prior MRSA Colonization or Infection</th>
<th>Prior Hospitalization</th>
<th>Chronic skin condition</th>
<th>Diabetes</th>
<th>History of STI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diep et al. (2008)</td>
<td>SSTI, BSI, joint, sinusitis</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>2.8^{1,<strong>}, 2.1^{2,</strong>} (clindamycin in past year) use; NS^{1} (β-lactam use in past year)</td>
<td>2.2^{1,**} (in past year)</td>
<td>3.2^{1,<strong>}, 2.1^{2,</strong>} (MRSA infection in past year)</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crum-Cianflone et al. (2009)</td>
<td>SSTI</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS^{1}, 0.14^{2} (RNA level&lt; 1000 copies/mL)</td>
<td>NS^{1}</td>
<td></td>
<td>NS^{1}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szumowski et al. (2009)</td>
<td>SSTI</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>2.99^{1} (past 2 months)</td>
<td>NS^{1^{2}}</td>
<td>10.34^{2} (perianal colonization at baseline)^{a}; 4.92^{1} (MRSA colonization or infection in past 6 months)</td>
<td>NS^{1}</td>
<td>NS^{1}</td>
<td>NS^{1}</td>
<td>3.26^{1} (past 6 months)</td>
</tr>
<tr>
<td>Ramsetty et al. (2010)</td>
<td>SSTI, bacteremia, pneumonia, bone/joint</td>
<td>2.03^{1}, 2.52^{2} (nadir CD4&lt;200)</td>
<td>0.22^{1}, 0.16^{2} (past year)</td>
<td>4.31^{1}, 3.41^{2} (past year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Popovich et al. (2010)</td>
<td>SSTI</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(table continues)
Table 2. (continued)

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Infection Type</th>
<th>Low CD4 Count</th>
<th>High HIV Viral Load</th>
<th>HAART Use</th>
<th>Prior Antibiotic Use</th>
<th>TMP-SMX Use</th>
<th>Prior MRSA Colonization or Infection</th>
<th>Prior Hospitalization</th>
<th>Chronic skin condition</th>
<th>Diabetes History</th>
<th>History of STI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hidron et al. (2011)</td>
<td>SSTI, bacteremia, pneumonia, urinary tract infection, endocarditis</td>
<td>SS¹ (higher risk in lower CD4)</td>
<td>SS¹ (HAART protective)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Univariate association ²Multivariate association

All data presented as odds ratios (OR), unless otherwise noted

*Hazard Ratio (HR)

**Relative Risk (RR)

BSI, bloodstream infection; CA-MRSA, community-acquired methicillin-resistant Staphylococcus aureus; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; IDU, illicit drug use; MDR, multidrug resistant; MRSA, methicillin-resistant Staphylococcus aureus; MSM, men who have sex with men; MSSA, methicillin-susceptible Staphylococcus aureus; NS, not statistically significant; SS, statistically significant; SSTI, skin and soft-tissue infection; STI, sexually transmitted infection; TMP-SMX, trimethoprim-sulfamethoxazole
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Illicit drug use</th>
<th>MSM</th>
<th>Public bath use</th>
<th>Condom use</th>
<th>Multiple sex partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. (2005)</td>
<td>6.7&lt;sup&gt;1&lt;/sup&gt;, 8.5&lt;sup&gt;2&lt;/sup&gt; (methamphetamine use in past 3 months)</td>
<td></td>
<td>3.8&lt;sup&gt;1&lt;/sup&gt;, 3.9&lt;sup&gt;2&lt;/sup&gt; (past 3 months)</td>
<td>0.2&lt;sup&gt;1&lt;/sup&gt;, 0.1&lt;sup&gt;2&lt;/sup&gt; (past 3 months)</td>
<td>4.4&lt;sup&gt;1&lt;/sup&gt; (past 3 months)</td>
</tr>
<tr>
<td>Mathews et al. (2005)</td>
<td>5.0&lt;sup&gt;2&lt;/sup&gt; (MSM, IDU or both vs. not MSM or IDU)</td>
<td>5.0&lt;sup&gt;2&lt;/sup&gt; (MSM, IDU or both vs. not MSM or IDU)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drapeau et al. (2007)</td>
<td></td>
<td>NS&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkey et al. (2008)</td>
<td>4.59&lt;sup&gt;1&lt;/sup&gt;, 4.61&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>0.23&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diep et al. (2008)</td>
<td></td>
<td></td>
<td>12.8&lt;sup&gt;1&lt;/sup&gt;,** 13.2&lt;sup&gt;2&lt;/sup&gt;,**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szumowski et al. (2009)</td>
<td>8.28&lt;sup&gt;1&lt;/sup&gt;, 4.98&lt;sup&gt;2&lt;/sup&gt; (methamphetamine use in past 6 months)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>2.02&lt;sup&gt;1&lt;/sup&gt;</td>
<td>NS&lt;sup&gt;1&lt;/sup&gt;</td>
<td>NS&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.76&lt;sup&gt;1&lt;/sup&gt; (past 6 months)</td>
</tr>
<tr>
<td>Ramsetty et al. (2010)</td>
<td>2.53&lt;sup&gt;1&lt;/sup&gt;, NS&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Popovich et al. (2010)</td>
<td>NS&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>NS&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hidron et al. (2011)</td>
<td>SS&lt;sup&gt;1&lt;/sup&gt; (higher rates in IDU)</td>
<td>SS&lt;sup&gt;1&lt;/sup&gt; (higher rates in MSM)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Univariate association  <sup>2</sup>Multivariate association

All data presented as odds ratios (OR), unless otherwise noted

*Hazard Ratio (HR)

**Relative Risk (RR)

MSM, men who have sex with men; IDU, injection drug use
<table>
<thead>
<tr>
<th>Study</th>
<th>Infection Type</th>
<th>Empirical Treatment</th>
<th>Definitive Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senthilkumar et al., 2001.</td>
<td>15 cases of bacteremia</td>
<td>53% received empirical vancomycin. Duration of hospitalization was 19±6 days.</td>
<td>NR</td>
<td>47% cured, 40% mortality rate, and 13% complication rate. Complications include metastatic seeding, pneumonia, endocarditis, septic shock, relapsed osteomyelitis, sternal wound infection, disseminated intravascular coagulation, multiorgan dysfunction syndrome, &amp; acute renal failure.</td>
</tr>
<tr>
<td>Lee et al., 2005.</td>
<td>Abscess (55%), cellulitis (31%), furunculosis (31%), impetigo (10%), folliculitis (7%), carbuncle (3%)</td>
<td>Oral antibiotics in 80%, I&amp;D in 46%, surgical debridement in 11%, lesion drained by patient (6%). Antibiotics include TMP-SMX (29%), cephalaxin (23%), clindamycin (10%), ceftriaxone (10%), and IV vancomycin (6%)</td>
<td>52% of patients treated with antibiotics discordant with susceptibility findings.</td>
<td>NR</td>
</tr>
<tr>
<td>Anderson et al., 2006.</td>
<td>SSTI among 11 HIV-infected patients</td>
<td>82% received I&amp;D; I&amp;D less common for recurrent infection. Vancomycin (18%); clindamycin (64%), cephalaxin (9%), linezolid+ciprofloxacin (9%)</td>
<td>NR</td>
<td>Recurrence common despite resolution (45% recurrence rate). 2 patients with 1 recurrent infection, 2 with 3 recurrent infections, and 1 with 2 recurrent infections. Each recurrence at new location.</td>
</tr>
</tbody>
</table>

*Table continues*
<table>
<thead>
<tr>
<th>Study</th>
<th>Infection Type</th>
<th>Empirical Treatment</th>
<th>Definitive Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skiest et al., 2006.</td>
<td>41 MRSA SSTI with 3 secondary bacteremia</td>
<td>Tetracycline (37%), β-lactam (15%), TMP-SMX (12%), linezolid (7%), clindamycin (5%), TMP-SMX+rifampin (7%), TMP-SMX+minocycline (2%), TMP-SMX+minocycline+rifampin (2%), levofloxacin+TMP-SMX (5%), levofloxacin+rifampin (2%), vanomycin+doxycycline (2%). 49% underwent I&amp;D.</td>
<td>Antibiotic treatment was concordant in 80% of patients and discordant in 20% of patients. Discordance observed in 5 patients initially treated with β-lactam, two with tetracycline, and one with levofloxacin+rifampin.</td>
<td>93% had resolution, and 8% had worsening, of signs and symptoms. 30% of patients with complete resolution had recurrent SSTI at different location. All patients treated only with β-lactams underwent I&amp;D (20% had resolution, 40% unresolved infection, and 40% with initial resolution followed by recurrence). 90% who underwent I&amp;D had resolution, and 22% of these patients had recurrence at another site. 90% of those without I&amp;D had resolution, and 37% of these patients had recurrence at another site.</td>
</tr>
</tbody>
</table>

(table continues)
<table>
<thead>
<tr>
<th>Study</th>
<th>Infection Type</th>
<th>Empirical Treatment</th>
<th>Definitive Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crum-Cianflone et al., 2007.</td>
<td>SSTI (90%), otitis externa (7%), and conjunctivitis (3%)</td>
<td>38% of patients underwent I&amp;D of soft-tissue infection. 17% required hospitalization with a mean duration of five days (range 1-13 days). 34% of cases received initial β-lactam.</td>
<td>66% of cases received initial antibiotic effective against MRSA isolate; these included minocycline (26%), minocycline+rifampin (21%), minocycline+TMP-SMX (16%), TMP-SMX (11%), linezolid (5%), clindamycin (5%), vancomycin (5%), minocycline+fluoroquinolone (5%), and erythromycin (5%).</td>
<td>One patient had resolution with β-lactam antibiotic and no recurrence after one year. 21% experienced recurrent infections (range 1-3). One patient with three SSTI over 9 month period and another with recurrent deep soft tissue infections requiring 28 days of hospitalization and surgical debridement.</td>
</tr>
<tr>
<td>Shastry et al., 2007.</td>
<td>Abscess (84%); nodule (1%); pustule (14%); ulcer (1%)</td>
<td>TMP-SMX (49%), β-lactam (15%), clindamycin (10%), doxycycline (9%), ciprofloxacin (6%), vancomycin (6%), linezolid (5%). 53% received I&amp;D for infection. 13% hospitalized.</td>
<td>Only 65% of isolates sensitive to empiric antibiotic.</td>
<td>31% had at least one recurrence within 6 months, with two or more recurrences in 13% of the cases; 69% of recurrent cases infected in a site different from original site of infection. 47% of cases had different sensitivity profile from original infection.</td>
</tr>
</tbody>
</table>

(table continues)
<table>
<thead>
<tr>
<th>Study</th>
<th>Infection Type</th>
<th>Empirical Treatment</th>
<th>Definitive Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sztramko et al., 2007.</td>
<td>12 cases of SSTI: Abscess (50%);</td>
<td>Cephalexin (42%); cloxacillin (8%); rifampin+doxycycline</td>
<td>TMP-SMX (17%); rifampin+doxycycline (8%); TMP-SMX+doxycycline</td>
<td>1/12 (8%) patient had recurrence within one month of resolution in the same location as original infection</td>
</tr>
<tr>
<td></td>
<td>furuncles (8%); sinusitis (17%);</td>
<td>(8%); TMP-SMX+rifampin (25%); fusidic to nares (8%);</td>
<td>(17%); TMP-SMX+rifampin (50%); mupirocin to nares (75%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cellulitis (17%); folliculitis (8%)</td>
<td>topical fusidic acid (17%) mupirocin to nares (25%);</td>
<td>mupirocin to wound (17%); chlorhexidine wash (42%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>chlorhexidine wash (17%). Patients with abscess also</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>received I&amp;D. Median duration of therapy 10 days (range</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-30).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szumowski et al., 2007.</td>
<td>227 cases of MRSA SSTI</td>
<td>Of 203 MRSA SSTI treated with oral antibiotics, 51%</td>
<td>NR</td>
<td>Use of HAART, CD4 count, or log viral load not associated with clinical resolution on empirical therapy. Isolate sensitivity to empirical antibiotic associated with clinical resolution after controlling for I&amp;D, HIV status, HAART use, log viral load, and CD4 count</td>
</tr>
<tr>
<td></td>
<td></td>
<td>occurred in HIV+ patients; TMP-SMX used in &gt;76% of cases.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>71% of recurrent SSTI treated with TMP-SMX. Longer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>duration of antibiotic treatment for TMP-SMX therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>compared to other antibiotics. 56% of MRSA infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>received I&amp;D.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*(table continues)*
Table 4. (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Infection Type</th>
<th>Empirical Treatment</th>
<th>Definitive Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olsen et al., 2008.</td>
<td>A severe, life-threatening case of necrotizing fasciitis in an HIV-infected Hispanic male</td>
<td>Empirical therapy with vancomycin, piperacillin-tazobactam, and clindamycin</td>
<td>Following susceptibility testing, regimen included vancomycin, imipenem/cilastatin, rifampin, and voriconazole</td>
<td>Right arm amputated and chest wall debrided. Following antimicrobial therapy and surgery, septic shock continued and necrotizing fasciitis spread to chest walls, abdomen, and back. Nine debridement procedures performed. Infection resolved following rehabilitation.</td>
</tr>
<tr>
<td>Sturgiss &amp; Bowden, 2008.</td>
<td>Penile cellulitis in an HIV-infected male</td>
<td>IV ticarcillin/clavulanate</td>
<td>Following susceptibility testing, regimen included vancomycin and ticarcillin/clavulanate. Patient discharged on oral amoxicillin-clavulanate acid and TMP-SMX</td>
<td>Patient developed swollen penis, bilateral inguinal lymphadenopathy, and features of saxophone penis. Patient remained in hospital for nine days on IV therapy with dressings for areas of ulceration. Ulceration took three weeks to resolve with mild scarring.</td>
</tr>
<tr>
<td>Witte, Braulke, &amp; Strommenger, 2008.</td>
<td>Infected cyst in upper abdominal area in an HIV-infected German male</td>
<td>Primary topical treatment consisted of instillation of Leukase beads containing trypsin, framycetin sulphate and lidocaine hydrochloride</td>
<td>Follow susceptibility testing, oral doxycycline (200 mg per day)</td>
<td>Infection healed completely after 14 days</td>
</tr>
</tbody>
</table>
Table 4. (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Infection Type</th>
<th>Empirical Treatment</th>
<th>Definitive Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trinh et al., 2009.</td>
<td>Abscess (86%), cellulitis (5%), wound (5%), furuncle (2%), necrotizing fasciitis (2%)</td>
<td>79% received antibiotics + I&amp;D, 19% antibiotics alone, and 2% antibiotics + amputation. Initial antibiotic included TMP-SMX (33%), clindamycin (26%), minocycline (12%), doxycycline (9%), cephalexin (5%), ampicillin/sulbactam (2%), levofloxacin (2%), linezolid (2%), and IV vancomycin (9%)</td>
<td>NR</td>
<td>70% improved, 16% did not improve, and 14% not evaluated after four weeks. 87% of improved patients treated with both I&amp;D and antibiotics. 43% of patients with no improvement treated with antibiotics alone. Of 3 patients who failed to respond to treatment, 2 cases had nonhealing wounds and 1 developed bacteremia.</td>
</tr>
</tbody>
</table>

SSTI, skin and soft-tissue infection; I&D, incision and drainage; IV, intravenous; TMP-SMX, trimethoprim-sulfamethoxazole; NR, not reported
Table 5. Incidence Rate of MRSA SSTI Events among HIV-Infected Persons by Time Period (1993-2010)

<table>
<thead>
<tr>
<th>Time Period</th>
<th>No. Person Years of Follow-Up</th>
<th>No. MRSA Infections</th>
<th>Incidence Rate (per 1000 PY) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993-2002</td>
<td>2008</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2003-2004</td>
<td>772</td>
<td>13</td>
<td>16.8 (9.9, 27.2)</td>
</tr>
<tr>
<td>2005-2006**</td>
<td>900</td>
<td>36</td>
<td>40.0 (28.9, 54.1)</td>
</tr>
<tr>
<td>2007-2008</td>
<td>970</td>
<td>35</td>
<td>36.0 (26.0, 49.0)</td>
</tr>
<tr>
<td>2009-2010***</td>
<td>816</td>
<td>24</td>
<td>29.4 (19.8, 42.3)</td>
</tr>
<tr>
<td>1993-2010</td>
<td>5466</td>
<td>108</td>
<td>19.8 (16.4, 23.7)</td>
</tr>
</tbody>
</table>

*63 patients experienced a total of 108 MRSA SSTI events
**Incidence increased significantly from 2003-2004 to 2005-2006 (p<0.01)
***Decreasing trend in incidence was noted during time periods 2005-2006 versus 2009-2010, but did not reach statistical significance (p=0.24)
Table 6. Clinical Characteristics of Methicillin-Resistant *Staphylococcus aureus* Skin and Soft-Tissue Infections among HIV Infected Persons

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of SSTI</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>48 (44)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>26 (24)</td>
</tr>
<tr>
<td>Wound</td>
<td>19 (18)</td>
</tr>
<tr>
<td>Furuncle</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Pustule</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Carbuncle</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of SSTI&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Extremity</td>
<td>33 (31)</td>
</tr>
<tr>
<td>Buttocks/Scrotum</td>
<td>24 (22)</td>
</tr>
<tr>
<td>Head/face</td>
<td>23 (21)</td>
</tr>
<tr>
<td>Upper Extremity</td>
<td>19 (18)</td>
</tr>
<tr>
<td>Trunk</td>
<td>16 (15)</td>
</tr>
</tbody>
</table>

Antibiotic susceptibility of MRSA isolates

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>108/108 (100)</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>105/108 (97)</td>
</tr>
<tr>
<td>Tetracyclines&lt;sup&gt;c&lt;/sup&gt;</td>
<td>96/108 (89)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>10/108 (9)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Seventeen patients presented with more than one type of SSTI, including one with cellulitis/osteomyelitis

<sup>b</sup>Eight patients presented with an SSTI at multiple body sites

<sup>c</sup>Includes minocycline and tetracycline

All data represent n=108, except there were missing data for location of SSTI (n=3)

SSTI, skin and soft-tissue infection; TMP-SMX, trimethoprim-sulfamethoxazole
Table 7. Clinical Characteristics of the Initial Episode of a Methicillin-Resistant *Staphylococcus aureus* Skin and Soft-Tissue Infection among HIV Infected Persons

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of SSTI</strong></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>28 (44)</td>
</tr>
<tr>
<td>Wound</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Furuncle</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Carbuncle</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Pustule</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Location of SSTI</strong></td>
<td></td>
</tr>
<tr>
<td>Lower Extremity</td>
<td>17 (28)</td>
</tr>
<tr>
<td>Buttocks/Scrotum</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Head/ Face</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Upper Extremity</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Trunk</td>
<td>7 (12)</td>
</tr>
<tr>
<td><strong>Antibiotic susceptibility of MRSA isolates</strong></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>63/63 (100)</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>61/63 (97)</td>
</tr>
<tr>
<td>Tetracyclines(^c)</td>
<td>57/63 (91)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>8/10 (80)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>15/22 (68)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>8/63 (13)</td>
</tr>
</tbody>
</table>

\(^a\)Eleven patients presented with more than one type of SSTI, including one with cellulitis/osteomyelitis

\(^b\)Two patients presented with an SSTI at multiple body sites, including one at the head/face and lower extremity, and another at the upper extremity and lower extremity

\(^c\)Includes minocycline and tetracycline

All data represent \(n=63\), except there were missing data for location of SSTI \((n=3)\)

SSTI, skin and soft-tissue infection; TMP-SMX, trimethoprim-sulfamethoxazole
Table 8. Study Population Characteristics and Univariate Logistic Regression Analysis of Factors Associated with MRSA Skin and Soft-Tissue Infections among HIV-Infected Persons

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cohort (n=794)</th>
<th>MRSA Infection (n=63)</th>
<th>No MRSA Infection (n=731)</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first clinic visit, years</td>
<td>30 (25-37)</td>
<td>31 (26-37)</td>
<td>30 (24-38)</td>
<td>1.09 (0.83, 1.43)</td>
<td>0.53</td>
</tr>
<tr>
<td>Gender, male</td>
<td>745 (93.8)</td>
<td>62 (98.4)</td>
<td>683 (93.4)</td>
<td>4.36 (0.59, 32.11)</td>
<td>0.15</td>
</tr>
<tr>
<td>Race</td>
<td>238 (30.0)</td>
<td>18 (28.6)</td>
<td>220 (30.1)</td>
<td>0.94 (0.51, 1.74)</td>
<td>0.96</td>
</tr>
<tr>
<td>African-American</td>
<td>193 (24.3)</td>
<td>16 (25.4)</td>
<td>177 (24.2)</td>
<td>1.04 (0.55, 1.97)</td>
<td>0.85</td>
</tr>
<tr>
<td>Other/missing</td>
<td>363 (45.7)</td>
<td>29 (46.0)</td>
<td>334 (45.7)</td>
<td>1.00</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>HIV History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of HIV, years</td>
<td>7.0 (2.5-15.0)</td>
<td>5.0 (2-12)</td>
<td>7.0 (2.5-15.0)</td>
<td>0.98 (0.94, 1.01)</td>
<td>0.18</td>
</tr>
<tr>
<td>Current CD4 cell count, cells/mm³</td>
<td>568.5 (420-743)</td>
<td>428 (262-619)</td>
<td>576 (427-752)</td>
<td>0.80 (0.71, 0.90)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt;350 cells/mm³</td>
<td>126 (16.0)</td>
<td>20 (33.9)</td>
<td>106 (14.5)</td>
<td>4.07 (2.13, 7.78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>350-499</td>
<td>190 (24.1)</td>
<td>18 (30.5)</td>
<td>172 (23.5)</td>
<td>2.26 (1.17, 4.34)</td>
<td>0.01</td>
</tr>
<tr>
<td>≥500</td>
<td>474 (60.0)</td>
<td>21 (35.6)</td>
<td>453 (62.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Nadir CD4 cell count, cells/mm³</td>
<td>294 (187-396)</td>
<td>242 (100-315)</td>
<td>299 (196-402)</td>
<td>0.71 (0.60, 0.85)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>216 (27.2)</td>
<td>29 (46.0)</td>
<td>187 (25.6)</td>
<td>2.48 (1.47, 4.18)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Current log₁₀ HIV viral load, copies/mL</td>
<td>1.7 (1.7-2.7)</td>
<td>2.0 (1.7-4.4)</td>
<td>1.7 (1.7-2.4)</td>
<td>1.54 (1.26, 1.88)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>≥400 copies/mL</td>
<td>200 (25.3)</td>
<td>27 (45.8)</td>
<td>173 (23.7)</td>
<td>2.72 (1.59, 4.67)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Log₁₀ maximum HIV viral load, copies/mL</td>
<td>4.8 (4.3-5.0)</td>
<td>5.0 (4.9-5.3)</td>
<td>4.8 (4.2-5.0)</td>
<td>2.96 (1.86, 4.70)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

(table continues)
# Table 8. (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cohort (n=794)</th>
<th>MRSA Infection (n=63)</th>
<th>No MRSA Infection (n=731)</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current CD4 cell count (cells/mm³) and HIV viral load (copies/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4&lt;500/VL≥400</td>
<td>104 (13.2)</td>
<td>18 (30.5)</td>
<td>86 (11.8)</td>
<td>6.38 (2.96, 13.75)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CD4&lt;500/VL&lt;400</td>
<td>212 (26.8)</td>
<td>20 (33.9)</td>
<td>192 (26.3)</td>
<td>3.18 (1.52, 6.64)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CD4≥500/VL≥400</td>
<td>96 (12.2)</td>
<td>9 (15.3)</td>
<td>87 (11.9)</td>
<td>3.16 (1.29, 7.72)</td>
<td>0.01</td>
</tr>
<tr>
<td>CD4≥500/VL&lt;400</td>
<td>378 (47.9)</td>
<td>12 (20.3)</td>
<td>366 (50.1)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Current HAART use</td>
<td>635 (80.0)</td>
<td>47 (74.6)</td>
<td>588 (80.4)</td>
<td>0.71 (0.39, 1.30)</td>
<td>0.27</td>
</tr>
<tr>
<td>Current CDC stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>88 (11.1)</td>
<td>16 (25.4)</td>
<td>72 (9.9)</td>
<td>3.11 (1.68, 5.76)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>A/B</td>
<td>704 (88.9)</td>
<td>47 (74.6)</td>
<td>657 (90.1)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>180 (22.7)</td>
<td>17 (27.0)</td>
<td>163 (22.3)</td>
<td>1.29 (0.72, 2.31)</td>
<td>0.39</td>
</tr>
<tr>
<td>HSV-2</td>
<td>378 (47.6)</td>
<td>24 (38.1)</td>
<td>354 (48.4)</td>
<td>0.66 (0.39, 1.11)</td>
<td>0.12</td>
</tr>
<tr>
<td>Syphilis or HSV-2</td>
<td>451 (56.8)</td>
<td>35 (55.6)</td>
<td>416 (56.9)</td>
<td>0.95 (0.56, 1.59)</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypertension</td>
<td>322 (40.7)</td>
<td>29 (46.0)</td>
<td>293 (40.2)</td>
<td>1.27 (0.76, 2.13)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>43 (5.4)</td>
<td>4 (6.4)</td>
<td>39 (5.4)</td>
<td>1.20 (0.41, 3.47)</td>
<td>0.74</td>
</tr>
<tr>
<td>Eczema</td>
<td>46 (5.8)</td>
<td>5 (7.9)</td>
<td>41 (5.6)</td>
<td>1.45 (0.56, 3.80)</td>
<td>0.45</td>
</tr>
<tr>
<td>Cancer</td>
<td>82 (10.4)</td>
<td>10 (15.9)</td>
<td>72 (9.9)</td>
<td>1.72 (0.84, 3.53)</td>
<td>0.14</td>
</tr>
<tr>
<td>Injection drug use (IDU)</td>
<td>30 (3.8)</td>
<td>8 (12.7)</td>
<td>22 (3.0)</td>
<td>4.67 (1.99, 10.99)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Any TMP-SMX use</td>
<td>288 (36.3)</td>
<td>19 (30.2)</td>
<td>269 (36.8)</td>
<td>0.74 (0.42, 1.30)</td>
<td>0.29</td>
</tr>
<tr>
<td>Current BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>336 (45.2)</td>
<td>23 (50.0)</td>
<td>313 (44.9)</td>
<td>1.50 (0.72, 3.13)</td>
<td>0.28</td>
</tr>
<tr>
<td>Obese</td>
<td>172 (23.2)</td>
<td>12 (26.1)</td>
<td>160 (23.0)</td>
<td>1.53 (0.66, 3.55)</td>
<td>0.32</td>
</tr>
<tr>
<td>Underweight/Normal</td>
<td>235 (31.6)</td>
<td>11 (23.9)</td>
<td>224 (32.1)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Years of follow-up</td>
<td>5 (1-12)</td>
<td>4 (1-10)</td>
<td>5 (1-12)</td>
<td>0.96 (0.92, 1.01)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

(table continues)
Table 8. (continued)

Note: Dependent variable categorized as developed or did not develop a MRSA skin and soft-tissue infection
BMI, body mass index; CI, confidence interval; HSV-2, herpes simplex virus-2; HAART, highly active antiretroviral therapy; MRSA, methicillin-resistant Staphylococcus aureus; TMP-SMX, trimethoprim-sulfamethoxazole

aCurrent indicates at last follow-up
bOR, per 10 years
2OR, per 100 cells/mm³

Data presented represent numbers (percentages) for categorical variables and medians (interquartile ranges) for continuous variables.
All data presented are n=794, except there were missing data for hypertension (n=2), diabetes mellitus (n=2), eczema (n=2), cancer (n=2), IDU (n=2), nadir CD4 cell count (n=1), current CD4 cell count (n=4), current HIV viral load (n=4), maximum HIV viral load (n=5), current CDC stage (n=2), and current BMI (n=51)

Table 9. Final Multiple Logistic Regression Model of Factors Associated with MRSA Skin and Soft-Tissue Infections among HIV-Infected Persons (n=788)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first clinic visit, years</td>
<td>1.18 (0.88, 1.60)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Currentb CD4 cell count
(cells/mm³) and HIV viral load
(copies/mL)
CD4<500/VL≥400 | 5.19 (2.34, 11.50) | <0.01 |
CD4<500/VL<400 | 2.67 (1.24, 5.76) | 0.01 |
CD4≥500/VL<400 | 3.20 (1.27, 8.09) | 0.01 |
CD4≥500/VL<400 | 1.00 | |

Current CDC stage
C | 5.43 (2.32, 12.73) | <0.01 |
A/B | 1.00 | |

Injection drug use | 4.93 (1.95, 12.48) | <0.01 |

Years of follow-up | 0.92 (0.86, 0.98) | <0.01 |

Note: Dependent variable categorized as developed or did not develop a MRSA skin and soft-tissue infection
bCurrent indicates at last follow-up
CI, confidence interval; MRSA, methicillin-resistant Staphylococcus aureus
Hosmer-Lemeshow Goodness of Fit test results: χ²=11.00, df=8, p-value=0.20>0.10, which indicates model is a good fit
Table 10. Univariate Logistic Regression Analysis of Factors Associated with Recurrent MRSA Skin and Soft-Tissue Infections among HIV-Infected Persons with an Initial MRSA Infection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=63)</th>
<th>Recurrent MRSA Infection (n=17)</th>
<th>No Recurrent MRSA Infection (n=46)</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at initial infection, years</td>
<td>37 (29-44)</td>
<td>42 (35-51)</td>
<td>35.5 (28-42)</td>
<td>1.80 (1.05, 3.06)</td>
<td>0.03</td>
</tr>
<tr>
<td>Gender, male</td>
<td>62 (98.4)</td>
<td>17 (100)</td>
<td>45 (97.8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>18 (28.6)</td>
<td>5 (29.4)</td>
<td>13 (28.3)</td>
<td>0.73 (0.20, 2.64)</td>
<td>0.31</td>
</tr>
<tr>
<td>Other/Missing</td>
<td>16 (25.4)</td>
<td>2 (11.8)</td>
<td>14 (30.4)</td>
<td>0.27 (0.05, 1.44)</td>
<td>0.63</td>
</tr>
<tr>
<td>Caucasian</td>
<td>29 (46.0)</td>
<td>10 (58.8)</td>
<td>19 (41.3)</td>
<td>1.00</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>HIV History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of HIV at first infection, years</td>
<td>5.0 (2-12)</td>
<td>9 (4-12)</td>
<td>4.8 (2-13)</td>
<td>1.08 (0.99, 1.18)</td>
<td>0.09</td>
</tr>
<tr>
<td>CD4 cell count at initial infection, cells/mm³</td>
<td>428 (262-619)</td>
<td>337 (218.5-413)</td>
<td>475 (295-676)</td>
<td>0.69 (0.51, 0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>CD4 cell count at initial infection (categorical)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;350 cells/mm³</td>
<td>20 (33.9)</td>
<td>8 (50.0)</td>
<td>12 (27.9)</td>
<td>6.33 (1.15, 35.01)</td>
<td>0.05</td>
</tr>
<tr>
<td>350-499</td>
<td>18 (30.5)</td>
<td>6 (37.5)</td>
<td>12 (27.9)</td>
<td>4.75 (0.82, 27.50)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥500</td>
<td>21 (35.6)</td>
<td>2 (12.5)</td>
<td>19 (44.2)</td>
<td>1.00</td>
<td>0.08</td>
</tr>
<tr>
<td>Nadir CD4 cell count (continuous), cells/mm³</td>
<td>242 (100-296)</td>
<td>82 (36-194)</td>
<td>264 (151-315)</td>
<td>0.49 (0.29, 0.82)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nadir CD4 cell count (categorical) &lt;200 cells/mm³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HIV viral load at initial infection (categorical) ≥400 copies/mL</td>
<td>27 (45.8)</td>
<td>8 (50.0)</td>
<td>19 (44.2)</td>
<td>1.26 (0.40, 3.99)</td>
<td>0.69</td>
</tr>
<tr>
<td>Log₁₀ HIV viral load at initial infection, copies/mL</td>
<td>2.0 (1.7-4.4)</td>
<td>2.6 (1.7-4.5)</td>
<td>2.0 (1.7-4.3)</td>
<td>1.14 (0.74, 1.76)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

(table continues)
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=63)</th>
<th>Recurrent MRSA Infection (n=17)</th>
<th>No Recurrent MRSA Infection (n=46)</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Log_{10} maximum HIV viral load</strong></td>
<td>5.0 (4.9-5.3)</td>
<td>5.3 (5.0-5.4)</td>
<td>5.0 (4.8-5.0)</td>
<td>3.99 (1.21, 13.14)</td>
<td>0.02</td>
</tr>
<tr>
<td>HAART use after initial infection</td>
<td>53 (84.1)</td>
<td>14 (82.4)</td>
<td>39 (84.8)</td>
<td>0.84 (0.19, 3.69)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>CDC stage at initial infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>16 (25.4)</td>
<td>8 (47.1)</td>
<td>8 (17.4)</td>
<td>4.22 (1.25, 14.30)</td>
<td>0.02</td>
</tr>
<tr>
<td>A/B</td>
<td>47 (74.6)</td>
<td>9 (52.9)</td>
<td>38 (82.6)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 STI after initial infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>32 (50.8)</td>
<td>8 (47.1)</td>
<td>24 (52.2)</td>
<td>0.82 (0.27, 2.48)</td>
<td>0.72</td>
</tr>
<tr>
<td>HSV-2</td>
<td>17 (27.0)</td>
<td>1 (5.9)</td>
<td>16 (34.8)</td>
<td>0.12 (0.01, 0.97)</td>
<td>0.05</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>13 (20.6)</td>
<td>2 (11.8)</td>
<td>11 (23.9)</td>
<td>0.42 (0.08, 2.15)</td>
<td>0.30</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>2 (3.2)</td>
<td>1 (5.9)</td>
<td>1 (2.2)</td>
<td>2.81 (0.17, 47.66)</td>
<td>0.47</td>
</tr>
<tr>
<td>HPV</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>NGI</td>
<td>13 (20.6)</td>
<td>4 (23.5)</td>
<td>9 (19.6)</td>
<td>1.27 (0.33, 4.81)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29 (46.0)</td>
<td>11 (64.7)</td>
<td>18 (39.1)</td>
<td>2.85 (0.90, 9.08)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (6.4)</td>
<td>1 (5.9)</td>
<td>3 (6.5)</td>
<td>0.90 (0.09, 9.25)</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Eczema</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (7.9)</td>
<td>3 (17.7)</td>
<td>2 (4.4)</td>
<td>4.71 (0.71, 31.13)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (15.9)</td>
<td>6 (35.3)</td>
<td>4 (8.7)</td>
<td>5.73 (1.37, 23.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>Injection Drug Use (IDU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (12.7)</td>
<td>5 (29.4)</td>
<td>3 (6.5)</td>
<td>5.97 (1.25, 28.65)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>BMI at first infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>23 (50.0)</td>
<td>4 (33.3)</td>
<td>19 (55.9)</td>
<td>0.56 (0.10, 3.10)</td>
<td>0.51</td>
</tr>
<tr>
<td>Obese</td>
<td>12 (26.1)</td>
<td>5 (41.7)</td>
<td>7 (20.6)</td>
<td>1.91 (0.33, 11.01)</td>
<td>0.47</td>
</tr>
<tr>
<td>Underweight or Normal Weight</td>
<td>11 (23.9)</td>
<td>3 (25.0)</td>
<td>8 (23.5)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Surgery after initial infection</strong></td>
<td>26 (41.3)</td>
<td>11 (64.7)</td>
<td>15 (32.6)</td>
<td>3.79 (1.18, 12.21)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

(table continues)
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=63)</th>
<th>Recurrent MRSA Infection (n=17)</th>
<th>No Recurrent MRSA Infection (n=46)</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission after initial infection</td>
<td>35 (55.6)</td>
<td>13 (76.5)</td>
<td>22 (47.8)</td>
<td>3.55 (1.00, 12.51)</td>
<td>0.05</td>
</tr>
<tr>
<td>Immunosuppressant use after initial infection</td>
<td>16 (25.4)</td>
<td>5 (29.4)</td>
<td>11 (23.9)</td>
<td>1.33 (0.38, 4.60)</td>
<td>0.66</td>
</tr>
<tr>
<td>Beta-lactam use after initial infection</td>
<td>25 (39.7)</td>
<td>7 (41.2)</td>
<td>18 (39.1)</td>
<td>1.09 (0.35, 3.38)</td>
<td>0.88</td>
</tr>
<tr>
<td>Fluoroquinolone use after initial infection</td>
<td>25 (39.7)</td>
<td>8 (47.1)</td>
<td>17 (40.0)</td>
<td>1.52 (0.49, 4.67)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Management of initial MRSA infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receipt of incision and drainage</td>
<td>23 (36.5)</td>
<td>7 (41.2)</td>
<td>16 (34.8)</td>
<td>1.31 (0.42, 4.11)</td>
<td>0.64</td>
</tr>
<tr>
<td>Receipt of mupirocin and hexachlorophene</td>
<td>36 (57.1)</td>
<td>9 (52.9)</td>
<td>27 (58.7)</td>
<td>0.79 (0.26, 2.42)</td>
<td>0.68</td>
</tr>
<tr>
<td>Receipt of TMP-SMX</td>
<td>33 (52.4)</td>
<td>9 (52.9)</td>
<td>24 (52.2)</td>
<td>1.03 (0.34, 3.14)</td>
<td>0.96</td>
</tr>
<tr>
<td>Receipt of minocycline for treatment (at any time)</td>
<td>35 (55.6)</td>
<td>6 (35.3)</td>
<td>29 (63.0)</td>
<td>0.32 (0.10, 1.02)</td>
<td>0.05</td>
</tr>
<tr>
<td>Receipt of minocycline (at any time for tx) + incision and drainage</td>
<td>11 (17.5)</td>
<td>1 (5.9)</td>
<td>10 (21.7)</td>
<td>0.23 (0.03, 1.91)</td>
<td>0.17</td>
</tr>
<tr>
<td>Receipt of minocycline (at any time for tx) + mupirocin and hexachlorophene</td>
<td>26 (41.3)</td>
<td>4 (23.5)</td>
<td>22 (47.8)</td>
<td>0.34 (0.10, 1.19)</td>
<td>0.09</td>
</tr>
<tr>
<td>Receipt of minocycline as initial antibiotic</td>
<td>24 (38.1)</td>
<td>3 (17.7)</td>
<td>21 (45.7)</td>
<td>0.26 (0.06, 1.01)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*(table continues)*
Table 10. (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=63)</th>
<th>Recurrent MRSA Infection (n=17)</th>
<th>No Recurrent MRSA Infection (n=46)</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of minocycline + TMP-SMX and/or rifampin as initial antibiotic</td>
<td>11 (17.5)</td>
<td>1 (5.9)</td>
<td>10 (21.7)</td>
<td>0.23 (0.03, 1.91)</td>
<td>0.17</td>
</tr>
<tr>
<td>Receipt of vancomycin</td>
<td>13 (20.6)</td>
<td>6 (35.3)</td>
<td>7 (15.2)</td>
<td>3.04 (0.85, 10.93)</td>
<td>0.09</td>
</tr>
<tr>
<td>Receipt of combination antibiotics for empiric therapy</td>
<td>28 (44.4)</td>
<td>8 (47.1)</td>
<td>20 (43.5)</td>
<td>1.46 (0.38, 5.67)</td>
<td>0.58</td>
</tr>
<tr>
<td>Receipt of combination antibiotics for empiric therapy + incision and drainage</td>
<td>12 (19.1)</td>
<td>4 (23.5)</td>
<td>8 (17.4)</td>
<td>1.27 (0.33, 4.82)</td>
<td>0.73</td>
</tr>
<tr>
<td>Duration of antibiotic therapy, days</td>
<td>14 (13-27)</td>
<td>20 (14-27)</td>
<td>14 (11-25)</td>
<td>0.99 (0.96, 1.03)</td>
<td>0.70</td>
</tr>
<tr>
<td>Receipt of empiric antibiotic concordant with MRSA isolate sensitivity pattern</td>
<td>46 (73.0)</td>
<td>12 (70.6)</td>
<td>34 (73.9)</td>
<td>0.85 (0.25, 2.91)</td>
<td>0.79</td>
</tr>
<tr>
<td>Hospital admission for initial MRSA infection</td>
<td>15 (23.8)</td>
<td>8 (47.1)</td>
<td>7 (15.2)</td>
<td>4.95 (1.42, 17.23)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Note: Dependent variable categorized as whether or not the patient developed a recurrent MRSA skin and soft-tissue infection.

BMI, body mass index; HAART, highly active antiretroviral therapy; TMP-SMX, trimethoprim-sulfamethoxazole; STI, sexually transmitted infection; SSTI, skin and soft-tissue infection; MRSA, methicillin-resistant *Staphylococcus aureus*; NGI, non-specific genital infection; HPV, human papilloma virus; HSV-2, herpes simplex virus-2

1OR, per 10 years
2OR, per 100 cells/mm3

Data presented represent numbers (percentages) for categorical variables and medians (interquartile ranges) for continuous variables.

All data represent n=63, except there were missing data for CD4 cell count at first infection (n=4), HIV viral load at first infection (n=4), and BMI at first infection (n=17)
Table 11. Final Multiple Logistic Regression Model of Factors Associated with Recurrent MRSA Skin and Soft-Tissue Infections among HIV-Infected Persons, Including Receipt of Minocycline as Initial Antibiotic (n=59)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial infection(^1), years</td>
<td>1.64 (0.83, 3.25)</td>
<td>0.16</td>
</tr>
<tr>
<td>CD4 cell count at initial infection(^2), cells/mm(^3)</td>
<td>0.74 (0.53, 1.03)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hospital admission after initial infection</td>
<td>7.43 (1.33, 41.50)</td>
<td>0.02</td>
</tr>
<tr>
<td>Receipt of minocycline as initial antibiotic</td>
<td>0.16 (0.03, 0.84)</td>
<td>0.03</td>
</tr>
<tr>
<td>Years of follow-up at initial infection</td>
<td>1.01 (0.84, 1.22)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

*Note*: Dependent variable categorized as developed or did not develop a recurrent MRSA skin and soft-tissue infection.

CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*

\(^1\)OR, per 10 years

\(^2\)OR, per 100 cells/mm\(^3\)

Hosmer-Lemeshow Goodness of Fit test results: \(\chi^2=5.26\), df=8, p-value=0.73>0.10, which indicates model is a good fit.
Table 12. Final Multiple Logistic Regression Model of Factors Associated with Recurrent MRSA Skin and Soft-Tissue Infections among HIV-Infected Persons, Including Receipt of Minocycline at any Time for Treatment (n=59)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial infection(^1), years</td>
<td>1.65 (0.85, 3.21)</td>
<td>0.14</td>
</tr>
<tr>
<td>CD4 cell count at initial infection(^2), cells/mm(^3)</td>
<td>0.75 (0.53, 1.05)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hospital admission after initial infection</td>
<td>7.57 (1.33, 42.96)</td>
<td>0.02</td>
</tr>
<tr>
<td>Receipt of minocycline at any time for treatment</td>
<td>0.23 (0.05, 1.03)</td>
<td>0.05</td>
</tr>
<tr>
<td>Years of follow-up at initial infection</td>
<td>1.03 (0.86, 1.22)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Note: Dependent variable categorized as developed or did not develop a recurrent MRSA skin and soft-tissue infection

CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*

\(^1\)OR, per 10 years

\(^2\)OR, per 100 cells/mm\(^3\)

Hosmer-Lemeshow Goodness of Fit test results: \(\chi^2=11.39, \text{df}=8, \text{p-value}=0.18>0.10\), which indicates model is a good fit
<table>
<thead>
<tr>
<th>Variable</th>
<th>Receipt of minocycline (n=35)</th>
<th>No minocycline (n=28)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>19 (54.3)</td>
<td>10 (35.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>African-American</td>
<td>5 (14.3)</td>
<td>13 (46.4)</td>
<td></td>
</tr>
<tr>
<td>Other/Missing</td>
<td>11 (31.4)</td>
<td>5 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Average CD4 cell count 6 months after initial infection</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥500 cells/mm³</td>
<td>13 (43.3)</td>
<td>8 (29.6)</td>
<td></td>
</tr>
<tr>
<td>350-499 cells/mm³</td>
<td>11 (36.7)</td>
<td>6 (22.2)</td>
<td></td>
</tr>
<tr>
<td>&lt;350 cells/mm³</td>
<td>6 (20.0)</td>
<td>13 (48.2)</td>
<td></td>
</tr>
<tr>
<td>Average CD4 cell count 6 months after initial infection (continuous), cells/mm³</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>476 (406-610)</td>
<td>378 (250-517)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average log₁₀ HIV viral load 6 months after initial infection</td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0 (1.7-4.7)</td>
<td>1.9 (1.7-4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admission for initial infection</td>
<td>5 (14.3)</td>
<td>10 (35.7)</td>
<td>0.047</td>
</tr>
<tr>
<td>Hospital admission after initial infection</td>
<td>22 (62.9)</td>
<td>13 (46.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Receipt of mupirocin and hexachlorophene for treatment of initial infection</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 (74.3)</td>
<td>10 (35.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of antibiotic therapy, days</td>
<td>20 (14-35)</td>
<td>14 (10-20)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data presented represent numbers (percentages) for categorical variables and medians (interquartile ranges) for continuous variables.

All data represent n=63, except there were missing data for average CD4 cell count 6 months after initial infection (n=6), and average log₁₀ HIV viral load 6 months after initial infection (n=7).

MRSA, methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft-tissue infection.
### Table 14. Final Linear-Mixed Effects Model of the Association between CD4 Cell Count (Cells/mm$^3$) and Recurrent MRSA Skin and Soft-Tissue Infections (n=54)

<table>
<thead>
<tr>
<th></th>
<th>Least Squares Mean (SE)</th>
<th>β parameter (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td></td>
<td>495.62 (35.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrence of MRSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>343.94 (60.09)</td>
<td>-151.68 (69.86)</td>
<td>0.03</td>
</tr>
<tr>
<td>No</td>
<td>495.62 (35.64)</td>
<td>Referent</td>
<td></td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft-tissue infection

### Table 15. Final Linear-Mixed Effects Model of the Association between Log$_{10}$ HIV Viral Load and Recurrent MRSA Skin and Soft-Tissue Infections (n=54)

<table>
<thead>
<tr>
<th></th>
<th>Least Squares Mean (SE)</th>
<th>β parameter (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td></td>
<td>3.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrence of MRSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.25</td>
<td>0.39</td>
<td>0.34</td>
</tr>
<tr>
<td>No</td>
<td>2.86</td>
<td>Referent</td>
<td></td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft-tissue infection