Fusion inhibitors are novel antiretroviral agents, administered as subcutaneous injections, approved for use in treatment-experienced HIV-infected patients.

The fusion inhibitor enfuvirtide (formerly T-20) is a novel antiretroviral agent approved for use in HIV-infected persons. As a fusion inhibitor, this 36-amino acid peptide binds to the envelope glycoprotein 41 of HIV-1 and prevents fusion of the virus with the membrane of the host CD4+ lymphocyte. Clinical trials have demonstrated that the addition of enfuvirtide to an “optimized” antiretroviral regimen significantly improves immunological and virological markers of HIV infection, specifically when given to treatment-experienced patients with a low CD4+ cell count.

Because enfuvirtide is a complex molecule, it is available only as a twice-daily subcutaneous injection. While the most common adverse effect of this drug is a local injection site reaction, a statistically significant increase in the occurrence of bacterial pneumonia was reported in the phase 3 registrational trials in participants receiving enfuvirtide. An increased incidence of sepsis in the enfuvirtide treatment arm was noted compared with the control group; however, the exposure-adjusted rates were not statistically significant. HIV-infected persons are known to be at increased risk for colonization and infection with Staphylococcus aureus, specifically methicillin-resistant S aureus (MRSA). S aureus is one of the pathogens most frequently associated with bloodstream infections in the HIV-infected population. In one 10-year prospective study, 32% of S aureus isolates from the blood of HIV-infected participants were methicillin-resistant. Here we present case summaries of 2 HIV-infected patients receiving subcutaneous fusion inhibitor therapy in whom a range of serious S aureus infections developed.

**CASE SUMMARIES**

**Patient 1**

A 46-year-old HIV-positive, homosexual Cuban man presented to the clinic for a routine visit in July 2003. His CD4+ cell count was 25/µL, and his HIV RNA level was 968,000 copies/mL. His medical history was significant for multiple opportunistic infections and virological failure with numerous antiretroviral regimens, but he had no history of MRSA infection. At this time, an enfuvirtide-based regimen including ritonavir-boosted atazanavir and saquinavir, emtricitabine, didanosine, and tenofovir was started. The patient also took dapsone and azithromycin for opportunistic infection prophylaxis.
In September 2003, he was admitted to the ICU and his antiretroviral therapy was interrupted. Blood cultures grew methicillin-sensitive *S. aureus*, and he was treated with nafcillin and clindamycin. Subsequent chest x-ray films showed bilateral pneumonia, and a sputum culture was positive for MRSA. The patient’s antibiotics were switched to vancomycin, cefepime, and rifampin and, after a prolonged hospitalization, he was discharged to a rehabilitation facility to complete a 6-week course of linezolid. At discharge, the patient's previous antiretroviral regimen was restarted without enfuvirtide. While the patient was in the rehabilitation facility, a sacral decubitus ulcer developed that was culture-positive for MRSA. The patient ultimately died of MRSA bacteremia in April 2004.

**Patient 2**

A 51-year-old HIV-positive bisexual white man presented to the clinic for a routine visit in March 2001. His CD4⁺ cell count was 10/µL, and his HIV RNA level was above 750,000 copies/mL. As in Patient 1, his medical history was significant for multiple opportunistic infections and virological failure with numerous antiretroviral regimens but no history of MRSA infection (Table). At this time, he entered an enfuvirtide clinical trial and received enfuvirtide plus lopinavir/ritonavir, amprenavir, delavirdine, abacavir, and didanosine. He also received trimethoprim/sulfamethoxazole and azithromycin for opportunistic infection prophylaxis.

In July 2001, he was hospitalized with MRSA septic olecranon bursitis and cellulitis. From this point forward, the patient had recurrent MRSA furunculosis and carbunculosis on the nape of the neck and shoulders. He was also found to have nasal colonization with MRSA. Because of persistent HIV plasma viremia, the patient was switched to T-1249, an experimental subcutaneous fusion inhibitor similar to enfuvirtide, in April 2003. In February 2005, he was hospitalized with MRSA pneumonia and bacteremia, and T-1249 was discontinued. While the patient was hospitalized, MRI scans of his cervical spine showed enhancement of the left C3-4 epidural space, suggestive of an early infectious process. He was discharged home to complete 4 weeks of vancomycin therapy. In May 2005, he was hospitalized with a MRSA urinary tract infection that evolved into septic shock. In June 2005, the
Serious Infection From Staphylococcus aureus in 2 HIV-Infected Patients Receiving Fusion Inhibitor Therapy

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DISCUSSION

Enfuvirtide has been shown to be an effective agent for the treatment of HIV infection in patients with multidrug-resistant viral strains and in those who have already undergone therapy with multiple antiretroviral agents. In the enfuvirtide pivotal clinical trials, an increased incidence of pneumonia in patients receiving enfuvirtide was observed, but the reported increased risk of sepsis was not statistically significant. Since FDA approval of enfuvirtide, we report the first 2 cases of documented serious S aureus infections related to fusion inhibitor therapy.

In the current literature, there is a single case report of vertebral osteomyelitis and epidural abscess in a patient receiving enfuvirtide. Portilla and colleagues presented the case of a 38-year-old homosexual man with a CD4+ cell count of 44/µL and an HIV RNA level of 1,250,000 copies/mL with osteomyelitis and epidural abscess at the T6-7 vertebrae that was detected 2 months after he began fusion inhibitor therapy (Table). In this case, cultures were negative for S aureus, but the patient was treated with vancomycin and gentamicin, and subsequently linezolid alone, for presumed S aureus infection.

In the 2 cases reported here, cultures did grow methicillin-sensitive S aureus in 1 patient initially, but cultures were eventually positive for MRSA in both.

Nasal colonization with S aureus is estimated to be 30% to 40% in the general population and as high as 50% in persons with HIV/AIDS, who have diabetes mellitus, who are injection drug abusers, and who are undergoing hemodialysis or continuous ambulatory peritoneal dialysis. A recent study found a 6.2-fold increase in MRSA colonization in HIV clinic patients over a 4-year period. Within the HIV-infected population, factors associated with MRSA colonization included men who have sex with men, injection drug use, recent hospitalization, recent antibiotic use, and history of abscesses or cellulitis. Colonization with S aureus has been shown to be a risk factor for systemic infection.

There are conflicting data in the literature regarding the relationship between the CD4+ cell count and MRSA colonization. The 2 patients presented here and the 1 patient previously reported were all severely immunocompromised, with CD4+ cell counts of less than 50/µL and significant HIV plasma viremia.

The relationship between our patients’ use of enfuvirtide and their subsequent S aureus infections is uncertain, but a possible connection may be the route of administration of the drug. Subcutaneous injection can put patients at risk for systemic bacterial infection. This is particularly true for injection drug users who perform skin-popping; subcutaneous injection in this population is associated with high rates of S aureus and MRSA bacteremia. S aureus infections have also been associated with the subcutaneous injection of insulin in diabetic patients. Our patients and the patient from the literature had a range of infections with this pathogen, including septic bursitis, pneumonia, urinary tract infection, osteomyelitis, and epidural abscess, all of which can be consequences of a bloodstream infection.

Deciphering a cause-and-effect relationship between enfuvirtide exposure and S aureus infection in our patients is difficult given the many confounding factors. Because community-acquired MRSA is very common in the HIV-infected population, it is not surprising that our patients experienced significant morbidity from this pathogen. Our patients, however, did not have a history of MRSA infection before starting treatment with enfuvirtide, and several different sites of infection subsequently developed, possibly indicating a period of bacteremia. Our observations suggest that clinicians should be vigilant for this potential complication and should emphasize sterile technique for the injections.

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