

Correspondence

Reinfection versus Relapse in Patients with Lyme Disease: Not Enough Evidence

TO THE EDITOR—In the 15 October 2007 issue of *Clinical Infectious Diseases*, Nadelman and Wormser [1] describe the “surprising” number of patients with “reinfection” following treatment of an initial episode of Lyme disease. The distinction between reinfection and relapse in these patients is based on the presence of a recurrent erythema migrans (EM) rash and successful completion of a standard 2–4-week course of appropriate antibiotics. These parameters are insufficient to distinguish between the 2 clinical possibilities.

Recurrent EM rashes have been noted in cases of persistent Lyme disease [2], and the Lyme spirochete *Borrelia burgdorferi* has been cultured from normal-appearing skin specimens after resolution of the EM rash [3]. Although the presence of a punctum in a recurrent EM rash might suggest a new tick bite, the authors provide no evidence to support this hypothesis. Furthermore, failure of standard therapy for Lyme disease was first documented in 1989 [4], and since that time, numerous studies have confirmed the failure of short-course antibiotic regimens in patients with Lyme disease [5, 6]. Thus, the clinical features touted by the authors fail to distinguish reinfection from relapse.

An intriguing explanation for recurrent EM following short-course antibiotic therapy is based on the premise that patients may be infected with >1 strain of *B. burgdorferi* [7–10]. In studies from the United States and Europe, this type of mixed-strain spirochetal infection has been documented in up to 44% of patients with Lyme disease and mirrors mixed-strain infection in up to 52% of tick vectors and reservoir mammals [7–10]. It is possible

that short-course antibiotic therapy may suppress one strain of *Borrelia* but allow another strain to emerge in the same host, leading to recurrent Lyme disease symptoms. The presence of *Borrelia* strains with different OspC genotypes in the same patient [8] and detection of spirochetal strains with different OspC genotypes in patients with recurrent EM rashes [11] support this hypothesis.

To establish reinfection versus relapse with a different *Borrelia* strain, additional molecular studies of mixed-strain infections are needed to evaluate the effect of short-course antibiotics in Lyme disease. These studies could also determine whether longer courses of antibiotic treatment are more effective in patients with persistent symptoms of tickborne illness [12].

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Reply to Stricker et al.

We emphatically disagree with Stricker et al. [1]. The vast majority of patients with recurrent erythema migrans (EM) have compelling evidence to support the diagnosis of a new infection rather than relapse of a past infection. In one published study of 28 patients with recurrent EM, recurrences were in an entirely different anatomic location in virtually every patient [2]. Furthermore, none of the cases occurred within 12 months after antimicro-

crobial treatment of the original infection—too long a time interval to reasonably anticipate a relapse [2, 3]. In addition, 29 (90.6%) of 32 recurrences occurred during June–August—exactly the months in which reinfection would naturally occur [2, 4]. The *P* value for such seasonality occurring by chance alone is <.001.

Patients with recurrent EM sometimes recall being bitten by a tick at the site of recurrence, and regardless of whether a tick bite is recalled, residual anatomic evidence of the prior bite (the punctum) may be present [5–8]. Puncta are well described in patients with primary EM skin lesions [5–8] and have also been reported following the bites from a variety of other arthropods [9–12]. In one study, either recollection of a tick bite at the EM site or the presence of a punctum in the EM lesion was documented in nearly 70% of a small group of patients with a primary EM [5]. It is extremely unlikely that a punctum would remain present in a putative relapse of EM occurring after months to years. Thus, when present, a punctum in a recurrent EM lesion provides strong clinical evidence of reinfection.

A preliminary report of a molecular analysis of 6 patients with recurrent EM whose cultures were positive for *Borrelia burgdorferi* during both episodes showed that each episode was associated with a different strain of *B. burgdorferi* [13]. These data overwhelmingly argue for reinfection over relapse as the cause of the recurrent EM in these particular cases. Surprisingly, Stricker et al. [1] posit that, in all 6 cases, the original infection was caused by 2 different strains of *B. burgdorferi*, one of which responded to antibiotic therapy and the other of which was resistant. This singular interpretation was made despite the absence of published data demonstrating resistance of *B. burgdorferi* to the antimicrobial agents recommended to treat Lyme disease [14]. Indeed, patients with second and subsequent episodes of EM appear to respond very well to antimicrobial treatment [2] (R. Na-

delman, unpublished observation; P. Krause, personal communication).

It is true that skin samples of EM lesions taken before the start of antimicrobial treatment may show PCR evidence of a second strain of *B. burgdorferi* in 12.5% [15] to 43.1% [16] of cases. However, amplification of a fragment of DNA does not necessarily indicate the existence of a viable organism. Less than 6% of cultures of EM demonstrate mixed infections [16]. However, even if these PCR results indicated true coinfections, it would be extremely improbable in all 6 of the evaluated cases that coinfections were present during the first episode of EM and that, in the second episode, the originally isolated strain of *B. burgdorferi* would fail to grow in culture (we calculate the probability to be <.001 for rates of coinfection of either 12.5% or 43.1%).

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Performance of the Urine Leukocyte Esterase and Nitrite Dipstick Test for the Diagnosis of Acute Prostatitis

TO THE AUTHOR—We read with great in-

terest the report by Koeijers et al. [1] evaluating the urine dipstick test in afebrile male outpatients with urinary tract infection (UTI), and were surprised that the results were the opposite of those usually observed in female patients with uncomplicated cystitis.

We used the same approach in a nested study that included 136 inpatients with community-acquired acute prostatitis and systemic symptoms (fever in 86% of patients, painful prostate noted by digital rectal examination in 68%, a positive blood culture results in 20%) from a retrospective, multicenter study [2]. The bacterial titers in the 136 urine analyses were as follows: $\geq 10^5$ cfu/mL for 56 patients (41%), 10^4 cfu/mL for 15 patients (11%), 10^3 cfu/mL for 8 patients (6%), and $\leq 10^2$ cfu/mL for 57 patients (42%). Of these 57 patients, 24 had received antibiotic treatment before analysis, and 50 had leukocyte counts of $>10^4$ cells/mm³. Eighty-one percent of the isolated bacteria were nitrite-producing Enterobacteriaceae.

The performance findings for the dipstick urinary test are presented table 1, as organized according to the bacteria load cutoff considered for the diagnosis of UTI in male subjects (either 10^3 or 10^4 cfu/mL). The best positive predictive values (94%–98%) were attained when both nitrites and leukocytes were detected, and the highest negative predictive values (65%–73%) were attained when either leukocytes or nitrites alone were detected.

Two cutoff diagnostic bacteria loads (10^3 and 10^4 cfu/mL) were tested, because this value remains controversial in the literature [5, 6]. We noticed minor variations

in the performances of the dipstick urine test between the 2 cutoff values, likely because our patients had high bacteria loads.

We found that the dipstick urinary test had a high positive predictive value and a low negative predictive value for the diagnosis of acute febrile prostatitis, as Koeijers et al. [1] found for nonfebrile male patients with UTI. These performances were exactly the opposite of those usually observed for uncomplicated acute cystitis in women (i.e., high negative and low positive predictive values), for which recommendations usually agree that the test should be used to exclude infection [3, 4]. We agree with the conclusions of Koeijers and colleagues that, for symptomatic male patients, a positive nitrite test result should be considered indicative of a UTI and that a negative nitrite test result should not exclude the diagnosis of UTI, so that a midstream urine sample should be cultured. It is clear from the data from the study by Koeijers et al. [1] and from the data presented here that, for these patients, the sensitivity (55%–58%) and negative predictive value (42%–49%) are too low for the nitrite test result alone to be used to exclude the diagnosis of UTI in male subjects. Thus, unlike the diagnosis of uncomplicated acute cystitis in women, the dipstick test for the rapid detection of leukocytes and nitrites should be used to diagnose acute prostatitis and UTI in nonfebrile male subjects and not to exclude them.

However, Koeijers et al. [1] concluded that treatment should not be started when the nitrite test result is negative, pending the results of the urine culture. We think

that this conclusion has to be balanced. Indeed, most of the male patients with UTI, like those described in our series, are febrile and require urgent antibiotic treatment because of a high risk of urosepsis and because of a poor tolerance of symptoms [3, 7]. In these cases, we would recommend starting antibiotic treatment after collection of the midstream urine sample, even when the dipstick test result comes back negative for nitrites. The urine dipstick test should be routinely performed for the management of UTI in male subjects, with awareness of its high positive and low negative predictive values.

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Table 1. Performance of the urine dipstick detection of nitrites and leukocytes for the diagnosis of acute prostatitis.

Finding	Bacteria load, $\geq 10^3$ cfu/mL				Bacteria load, $\geq 10^4$ cfu/mL			
	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Leukocyte detection	81	71	89	57	83	67	85	64
Nitrite detection	55	94	97	42	58	90	93	49
Leukocyte and nitrite detection	50	97	98	40	52	93	94	46
Leukocyte or nitrite detection	87	69	89	65	89	64	85	73

NOTE. NPV, negative predictive value; PPV, positive predictive value.

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Reply to Etienne et al.

TO THE EDITOR—We read with great interest the letter by Etienne et al. [1], in which they describe the performance of the leukocyte and nitrite dipstick test in a male population presenting with acute prostatitis. It is reassuring that this study confirms the sensitivity and specificity that were obtained in our male population with acute, nonfebrile urinary tract infection (UTI) [2]. In the female outpatient population, the nitrite test also has a specificity of ~95% and a sensitivity of ~55%, resulting in a positive predictive value of 96% and a low negative predictive value [3, 4]. This result suggests that the dipstick test should be used in both female and male populations to diagnose UTI and not to exclude it. However, the positive predictive value of the nitrite dipstick test has varied in different studies with different populations tested. The same results have been reported for the leukocyte esterase activity test, in which there is an wide

range of positive and negative predictive values [5].

The finding of a high positive predictive value when both the nitrite and leukocyte esterase activity tests were performed in a male population with symptoms of acute community-acquired prostatitis is interesting. In our population of male patients with nonfebrile UTI and female patients with an uncomplicated UTI [3], the leukocyte esterase activity did not have additional value in the diagnosis of UTI [3, 4]. It is possible that prostatitis results in a higher degree of pyuria and, thus, in more positive leukocyte esterase activity.

In our article, we recommended that nonfebrile male patients with symptoms indicative of UTI and a positive nitrite dipstick result should start empirical antibiotic therapy, pending the results of urine cultures. However, patients with a negative nitrite dipstick test result should refrain from antibiotic therapy, pending the urine culture data. However, we agree with Etienne et al. [1] that, in male and female patients with complicated UTIs, the negative predictive value of the dipstick test is not enough to warrant withholding antibiotic therapy in the event of a negative dipstick test result. The difference between their population (with symptoms indicative of acute prostatitis, high fever, and, in 20% of patients, a positive blood culture result) and our population (with symptoms of uncomplicated UTI) is immense. Although it has been stated that all UTIs in male patients are considered to be complicated, it is not clear (for either male or female populations) which percentage of uncomplicated UTIs become complicated. Both studies [1, 2] show a clear role for the urine dipstick test in the management of UTI in male patients, although the presentation of symptoms clearly leads to a different approach in the timing of start of antibiotic therapy.

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Buprenorphine Diversion: A Possible Reason for Increased Incidence of Infective Endocarditis among Injection Drug Users? The Singapore Experience

TO THE EDITOR—We read with interest the article by Cooper et al. [1] regarding the increased number of hospitalizations for illicit injection drug use–related infective endocarditis in the United States from 2000 through 2003. Since 2002, we have noted an increasing incidence of *Staphylococcus aureus* bacteremia (including endovascular infection) among persons who inject buprenorphine (Subutex; Schering-Plough) in Singapore. At the National

University Hospital, Singapore, a 900-bed teaching facility, there was an increase in the overall number of identified hospitalizations for substance abuse at our hospital (based on data from the *International Classification of Diseases, Ninth Revision* coding of diagnoses at hospital discharge) (figure 1). This is reasonably explained by buprenorphine diversion from opioid use, because, of the 92 hospitalized patients who were considered to be buprenorphine abusers in our hospital from 2003 through 2005, 65 (71%) had a history of heroin abuse. Other researchers in Singapore have reported that, for >50% of buprenorphine abusers, this was the first drug that they injected [2]. The consequences of these new injection drug users using an agent that was designed for sublingual administration have been serious, particularly in terms of bloodstream infections. In 2005 alone, 14 (18%) of 77 nonduplicated cases of community-onset methicillin-susceptible *Staphylococcus aureus* bacteremia in our institution occurred in patients who injected buprenorphine. These patients were young (mean age \pm SD, 31.9 \pm 4.6 years) and predominantly male (13 of 14 patients). Eleven patients (79%) had infective endocarditis, including 9 (64%)

with septic pulmonary emboli. This was reflective of nationwide trends [3] and resulted in buprenorphine being reclassified as a controlled drug, with strict penalties for its possession and trafficking.

Although, in the United States, buprenorphine is predominantly used in combination with naloxone, which markedly reduces the potential for abuse of buprenorphine, there have been reports of buprenorphine diversion in the United States [4]. In their article, Cooper et al. [1] attributed increasing methamphetamine use and/or frequency of injection drug use to be causes that may have led to the increased incidence of infective endocarditis in the population of injection drug users in the United States. On the basis of our experiences in Singapore and elsewhere [5], we are concerned that buprenorphine diversion might have been another factor contributing to the increased incidence of infective endocarditis in the United States. Although the drug clearly has benefits in reducing opiate dependence, careful attention should be paid to ensure that all the controls are in place so that persons who use the drug continue to benefit, without unintended consequences of a liberal expanded access policy.

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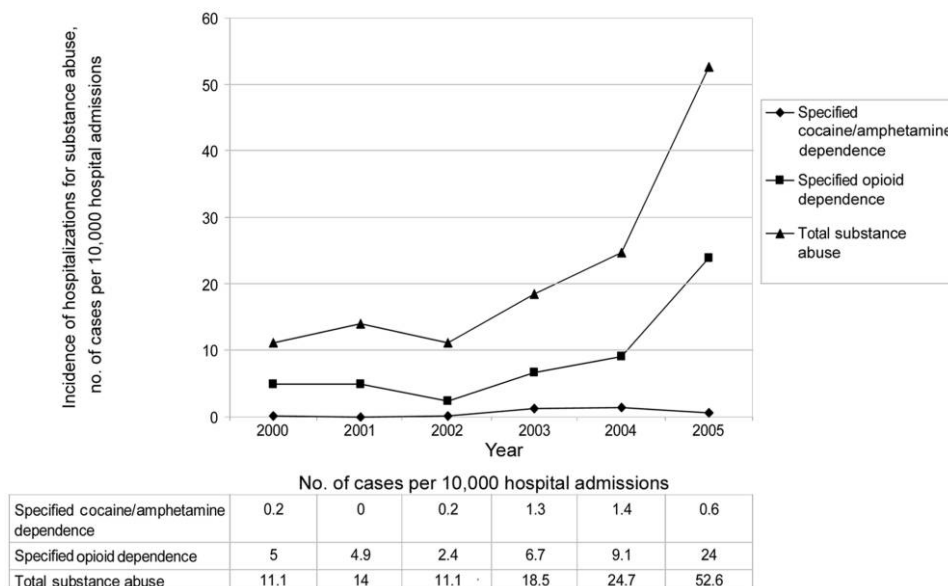


Figure 1. Incidence of hospitalizations for substance abuse at the National University Hospital, Singapore. Source: Data Warehouse, National Healthcare Group, Singapore (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes).

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Reply to Chai et al.

TO THE EDITOR—We read with great interest the article by Chai et al. [1] regarding an increase in the number of hospitalizations for infections (including infective endocarditis [IE]) among injection drug users at Singapore's National University Hospital, Singapore, and its possible links to injected Subutex (Reckitt Benckiser), a formulation of buprenorphine hydrochloride. Chai et al. [1] posit that buprenorphine diversion (specifically, the injection of crushed buprenorphine tablets) may have driven the increases in the number of hospitalizations for IE among injection drug users in the United States between 2000–2001 and 2002–2003 [1, 2]. Buprenorphine is a partial μ -opioid receptor agonist and a κ -opioid receptor antagonist and is approved in many countries as an opiate substitution therapy [3]. At adequate doses, buprenorphine has proven to be an effective treatment for opiate dependence that reduces overdose morbidity and mortality and the incidence of HIV infection among opiate-dependent individuals [3, 4]. Consequently, in 2005, the World Health Organization added buprenorphine to its "Model List of Essential Medications" for substance-dependence treatment [5]. Governments approving access to buprenorphine for the treatment of opiate dependence are, thus, fulfilling the public's right to the highest attainable standard of health, as articulated in the *International Covenant on Economic, Social, and Cultural Rights* [6].

Determinants of single health outcomes can vary across geographic areas. Thus, although buprenorphine diversion may

contribute to an increasing number of cases of injection drug use–related IE in Singapore, there is no evidence to support the hypothesis that it does so in the United States. US surveillance systems have recorded few instances of buprenorphine diversion [3], perhaps because of federal policies governing buprenorphine prescribing. There are 2 sublingual formulations of buprenorphine available: Subutex and Suboxone (Reckitt Benckiser) [3]. Subutex contains only buprenorphine; Suboxone contains buprenorphine and naloxone hydrochloride [7]. Naloxone is an antagonist at the μ -opioid receptor, and Suboxone exploits naloxone's divergent sublingual and parenteral potency profiles [4, 7]. Naloxone's bioavailability is low (8%–10%) when administered sublingually [4, 7]; when injected, however, naloxone's bioavailability is substantially higher, and it induces withdrawal symptoms among individuals dependent on full opioid agonists [4, 7]. For this reason, the US Food and Drug Administration recommends that physicians prescribe Suboxone (not Subutex) after the initial period of buprenorphine therapy [8]. This recommendation was made to reduce the likelihood of injection of buprenorphine among individuals dependent on full opioid agonists [4, 8], and surveillance data suggest that this recommendation largely achieved its purpose [3].

Although non-opiate-dependent individuals may inject Suboxone, US surveillance data suggest that this practice is not widespread (C. Schuster, personal communication) [3], perhaps because naloxone attenuates buprenorphine's opiate agonist effects even among nondependent individuals [7]. Both the rigorous certification process that US physicians undergo to prescribe buprenorphine [4] and the cap on the number of cases each clinic can treat [4] may further reduce the likelihood of inadvertent prescribing to non-opiate-dependent individuals.

Moreover, the Food and Drug Administration approved Subutex and Suboxone as opioid-dependence therapies in late

2002 [8]. Because of slow uptake in 2003 [9], it is unlikely that either contributed substantially to the increase in the number of IE-associated hospitalizations in the United States between 2000–2001 and 2002–2003.

We, therefore, doubt that buprenorphine contributed to the increase in the number of IE-associated hospitalizations of injection drug users in the United States. Ensuring the continued availability of buprenorphine in the United States, while monitoring its possible adverse consequences, is a key step in an ongoing effort to ensure that federal, state, and local governments respect, protect, and fulfill drug users' right to health.

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Recurrent Infection with Epidemic *Clostridium difficile* in a Peripartum Woman Whose Infant Was Asymptomatically Colonized with the Same Strain

TO THE EDITOR—Recent outbreaks of *Clostridium difficile*-associated disease (CDAD) have been attributed to the emergence of an epidemic strain, termed North American PFGE type 1, which produces binary toxin and has a genetic deletion associated with increased toxin production [1]. There have also been recent reports of severe CDAD in low-risk populations, including peripartum women [2]. In 2 cases, peripartum women possibly transmitted *C. difficile* to their children [2]. We report a case of recurrent CDAD due to the epidemic strain in a peripartum woman whose baby was an asymptomatic carrier of the same strain.

A 19-year-old previously healthy woman delivered a baby and was discharged from the hospital 2 days later. She had received azithromycin 6 months earlier but had received no other antibiotics. Diarrhea developed 10 days after delivery, and CDAD was diagnosed on the basis of a positive toxin enzyme immunoassay re-

sult. The patient's symptoms resolved with oral metronidazole, but she subsequently developed 3 recurrences that were treated with oral vancomycin for 10 days, vancomycin taper for 6 weeks, and oral nitazoxanide for 10 days, respectively. Her baby remained healthy with no diarrhea.

To investigate whether the baby could be a potential source for re-exposure of the mother, we cultured stool samples obtained from the mother at the time of her third relapse and obtained concurrently from the baby. *C. difficile* isolates were tested for in vitro cytotoxin production and were analyzed for binary toxin gene *cdtB* and partial deletions of the *tcdC* gene, as described elsewhere [3]. Molecular typing was performed using PCR ribotyping [4]. To assess whether the epidemic strain might be circulating on the newborn unit, we performed cultures and typing of stool samples obtained from healthy babies on the neonatal unit and from environmental sites.

Both the mother and the baby carried the epidemic *C. difficile* strain (figure 1). The baby's stool sample contained $6 \log_{10}$ colony-forming units of *C. difficile* per g of stool. The mother was instructed to perform careful hand washing after changing diapers and to use 10% bleach for surface disinfection. No further recurrences occurred. On the healthy-baby unit, 10 (50%) of 20 stool samples obtained from newborns and 4 (17%) of 24 environmental cultures were positive for *C. difficile*, but none of the isolates were of the epidemic strain.

In summary, we report a case of recurrent CDAD attributable to an epidemic strain in a peripartum woman whose baby carried the same strain asymptotically. It is not known whether the mother acquired the strain and transmitted it to her baby or vice versa, and the original source of the epidemic strain is unclear. Nevertheless, it is plausible that the baby contributed to the mother's recurrences by providing a source of repeated exposure to *C. difficile* during activities such as diaper changing. McFarland et al. [5] pre-

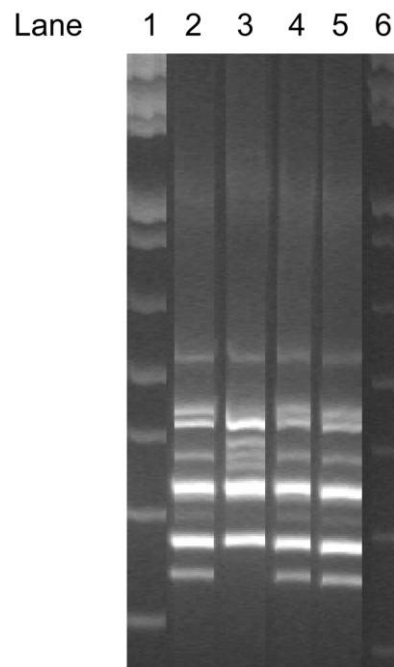


Figure 1. PCR ribotyping results demonstrating carriage of identical epidemic *Clostridium difficile* isolates in stool samples of a peripartum woman with recurrent *C. difficile* infection and her asymptomatic baby. The epidemic control strain and the isolates obtained from the mother and the baby had PCR amplification results positive for binary toxin gene *cdtB* and partial deletions of the *tcdC* gene, whereas the nonepidemic control strain did not. Lanes 1 and 6, 1 kb plus ladder; lane 2, epidemic control strain (restriction enzyme analysis type B16, courtesy of Dale Gerding); lane 3, nonepidemic control strain (restriction enzyme analysis type J29 or 30); lane 4, isolate from the mother; lane 5, isolate from the baby.

viously reported 5 cases of recurrent CDAD in peripartum women; in 2 cases, the babies carried the same strain as their mothers. CDAD should be considered to be a possible cause of diarrhea in peripartum women, even in the absence of recent antibiotic therapy. Asymptomatically colonized babies have the potential to serve as reservoirs for transmission of North American PFGE type 1 strains.

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Initial Hospitalization and Adherence to Highly Active Antiretroviral Therapy

TO THE EDITOR—We read with great interest the article by Mariana Lazo et al. [1] regarding factors influencing adherence to HAART. We would like to add to the ongoing adherence debate by describing our own experience, which examines the importance of 1 additional factor, hospital-

ization [2, 3] at the time of starting HAART.

We reviewed data and compared virological success after 12 months of therapy among all HAART-naïve patients with no resistance to antiretroviral agents who started HAART while hospitalized with that among patients who started HAART at our outpatient clinic from January 2004 through January 2006. Adherence was assessed through medical outcomes study questionnaires administered to all patients at 6 and 12 months after initiation of therapy and through pharmacy refill data. Twenty-one patients were hospitalized (group 1), and there were 76 outpatients (group 2). Group 1 was composed of 15 men and 6 women; 15 white persons, 5 African black persons, and 1 Indian person; 10 heterosexual persons, 9 men who have sex with men, and 3 injection drug users; the median age was 41.4 years (range, 28–55 years). All 21 patients had AIDS. The mean CD4 cell count at initiation of HAART was 75 cells/ μ L (range, 10–298 cells/ μ L), and the mean HIV RNA level was 283,960 copies/mL (range, 3984 to >500,000 copies/mL). All patients received either zidovudine plus lamivudine or tenofovir plus emtricitabine. Fifteen patients were given a protease inhibitor-based regimen (lopinavir plus ritonavir or fosamprenavir), and 6 were given a non-nucleoside reverse-transcriptase inhibitor-based regimen (2 received nevirapine,

and 4 received efavirenz). After discharge from the hospital (mean duration of hospitalization, 24 days), the patients were observed as outpatients.

Group 2 was composed of 40 men and 36 women; 55 white persons and 21 African black persons; and 45 heterosexual persons, 16 men who have sex with men, and 15 previous injection drug users; the median age was 39 years (range, 20–63 years). None of the patients in group 2 had ever experienced serious complications, tumors, or opportunistic infections requiring hospitalization. HAART was started because of low CD4 cell count. The mean CD4 cell count was 220 cells/ μ L (range, 185–299 cells/ μ L), and the mean HIV RNA level was 60,615 copies/mL (521–458,109 copies/mL). Thirty-eight patients initiated a nonnucleoside reverse-transcriptase inhibitor-based regimen, 28 initiated a protease inhibitor-based regimen, and 10 received a triple nucleoside reverse-transcriptase inhibitor combination.

Results are shown in table 1 and clearly indicate a far better adherence to HAART among initially hospitalized patients that among patients who initiated HAART as outpatients. All initially hospitalized patients achieved undetectable HIV RNA levels 8–36 weeks after initiation of therapy and maintained undetectable levels at 1 year after initiation of therapy. In contrast, only 48 outpatients achieved viral

Table 1. Adherence to HAART among hospitalized patients, compared with outpatients.

Variable	Hospitalized patients	Outpatients
At baseline		
CD4 cell count, cells/ μ L	75	220
HIV RNA level, copies/mL	283,960	60,615
At 6 months		
CD4 cell count, cells/ μ L	212	232
HIV RNA level, copies/mL	<50	4697
At 12 months		
CD4 cell count, cells/ μ L	275	288
HIV RNA level, copies/mL	<50	13,146
No. (%) of patients who were fully adherent to HAART	21 (100)	48 (63)

NOTE. Data are mean values, unless otherwise indicated.

suppression, whereas 28 did not achieve viral suppression at 1 year after initiation of therapy.

Thus, our results suggest that hospitalization at the time of starting HAART is an additional factor favoring adherence. The following 3 underlying variables may have favored adherence to therapy: diagnosis of AIDS and, therefore, fear of death; rapid clinical improvement while receiving treatment; and immediate reassurance by physicians and nurses when patients experienced adverse effects during hospitalization. It remains to be seen whether such positive effects of initial hospitalization can be maintained during long-term follow-up.

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Extensively Drug-Resistant Tuberculosis Is Worse than Multidrug-Resistant Tuberculosis: Different Methodology and Settings, Same Results

TO THE EDITOR—We read with interest the article by Kim et al. [1] about the impact of extensively drug-resistant (XDR) tuberculosis (TB) on treatment outcomes of non-HIV-infected patients affected by multidrug-resistant (MDR) TB. Kim et al. [1] found, with univariate analysis, that patients with XDR TB had a borderline-significant higher probability of treatment failure and death than did patients with MDR TB (table 1). Multivariate analysis confirmed that XDR TB is a poor independent prognostic factor for treatment failure (OR, 4.46; 95% CI, 1.35–14.74). Two studies from our group had previ-

ously reached similar conclusions [2, 3]. Our first study found that patients with XDR TB in Italy and Germany, compared with patients with MDR TB, had a 5-fold increase in the risk of death (relative risk, 5.45; 95% CI, 1.95–15.27; $P < .01$), required longer hospitalization (mean duration \pm SD, 241.2 \pm 177.0 vs. 99.1 \pm 85.9 days; $P < .001$), had longer treatment duration (30.3 \pm 29.4 vs. 15.0 \pm 23.8 months; $P < .05$), and, for the few patients whose sputum and smear converted from positive to negative, a longer time to smear or culture conversion ($P < .01$) [2]. The second study (including additional patients from Estonia and Russia) found that patients with XDR TB had a relative risk of 1.58 to die or have treatment failure, compared with patients with MDR TB resistant to all first-line drugs (95% CI, 1.14–2.20; $P < .05$), and a relative risk of 2.61 (95% CI, 1.45–4.69; $P < .001$), compared with patients with MDR TB for whom susceptibility to ≥ 1 first-line drug still existed [3]. Interestingly, the results of the studies from the 2 groups are consistent, although the definitions used were slightly different: Migliori et al. [2] used the World Health Organization definitions of treatment success and failure [4, 5], and Kim et al. [1] applied the definitions proposed by Laserson et al. [6]. Furthermore, Kim et al. [1] (and not Migliori et al. [2])

Table 1. Comparison of outcomes of patients with extensively drug-resistant (XDR) and multidrug-resistant (MDR) tuberculosis (TB).

Outcome	Results of Kim et al. [1]				Results of Migliori et al. [3]			
	No. (%) of patients		Univariate analysis		No. (%) of patients		Univariate analysis	
	XDR TB (n = 43)	MDR TB (n = 168)	RR (95% CI)	P	XDR TB (n = 64)	MDR TB (n = 361)	RR (95% CI)	P
Treatment success								
Overall	23 (53.5)	109 (64.9)			22 (34.4)	165 (45.7)		
Cured	23 (53.5)	84 (50.0)			19 (29.7)	134 (37.1)		
Treatment completed	...	25 (14.9)			3 (4.7)	31 (8.6)		
Treatment failure								
Overall	19 (44.2)	46 (27.4)	1.68 (0.99–2.85)	.057	26 (40.6)	75 (20.8)	2.19 (1.31–3.66)	.002
Relapse	2 (4.7)	4 (2.4)			0	0		
Failure	11 (25.6)	29 (17.3)	1.58 (0.84–2.95)	.16	12 (18.7)	32 (8.9)	2.32 (1.24–4.32)	.008
Death	6 (14.0)	13 (7.7)	1.81 (0.85–3.87)	.143	14 (21.9)	43 (11.9)	2.09 (1.14–3.81)	.017

NOTE. RR, relative risk.

included death with treatment failure. To make a contribution toward the use of standardized definitions and to allow a better comparison of the data from the 2 groups, we recalculated our treatment outcomes from the 4-country study on the basis of the methodology of Kim et al. [1] (table 1). With the univariate analysis, patients with XDR TB had a significantly higher probability of treatment failure than did patients with MDR TB (relative risk, 2.19; 95% CI, 1.31–3.66; $P = .002$). According to our data, patients with XDR TB had a higher probability of death and treatment failure than did patients with MDR TB, even when the 2 outcomes were analyzed separately (table 1). With the multiple regression analysis, the presence of XDR was an independent risk factor for both death (OR, 2.07; 95% CI 1.05–4.05; $P < .034$) and treatment failure (OR, 2.37; 95% CI, 1.14–4.89; $P < .02$).

The different findings related to some of the patient characteristics of the 2 data sets (e.g., radiography findings, number of drugs, and treatment duration) suggest that our patients with MDR TB (especially those from Eastern Europe) have more-severe disease than do those of Kim et al. [1]. Moreover, the consistency of outcomes from both studies suggests that (1) results are robust and (2) XDR TB has a negative clinical and prognostic significance, even in patients with different susceptibility profiles and from different settings (e.g., Korea and Eastern and Western Europe). While we wait for the development of new drugs and rapid diagnostic procedures, there should be a prompt and globally coordinated public health response, to prevent further development of drug resistance.

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