Correspondence

Is Routine Testing Mandatory or Voluntary?

The AIDS Treatment Activists Coalition (ATAC) is a national coalition of AIDS activists, many of whom are living with HIV/AIDS, working together to end the AIDS epidemic by advancing research on HIV/AIDS. ATAC's Access to Health Care for the Incarcerated working group has the goal of increasing access to health care for incarcerated people through strategy coordination, information sharing, training, and advocacy for allied individuals, groups, and communities. The Access to Health Care for the Incarcerated working group opposes the call for routine HIV testing recommended in the recent editorial commentary entitled "HIV Infection Behind Bars" by Boutwell and Rich [1].

We believe that routine HIV testing in prison is virtually synonymous with mandatory testing. Prisoners often receive no pretest counseling or education about HIV infection; frequently, they are unaware of the implications of testing positive for HIV while incarcerated. Consent often means something completely different in prison than it does outside of prison. Many prisoners are unaware that they have consented to HIV testing—or that they actually were tested for HIV, despite the consent form.

We agree wholeheartedly that identification of infected individuals is an important step in addressing HIV infection in any setting. However, prisoners do not have guaranteed access to the standard of care for HIV treatment, so beginning the process of addressing HIV disease behind bars must entail providing access to counseling, education, and the standard of care for HIV treatment, as defined by the Department of Health and Human Services' guidelines [2]. Without guaranteed access to quality care, any testing will only result in continued retaliation, stigmatization, threats, lack of confidentiality, and substandard medical care.

The disproportionately high number of HIV-infected persons in our prisons is more than "a challenge to correctional health systems" and a "public health opportunity" [1]. It is a human rights catastrophe of vast proportions, and it challenges our society as a whole. Our priorities must be ordered by the thousands of prisoners whose lives are on the line.

The commentary by Boutwell and Rich [1] echoes the unfortunate new position on mandatory testing for prisoners currently held by the Centers for Disease Control and Prevention (CDC). Although testing may have led to better treatment in Rhode Island (which, not surprisingly, has the smallest correctional system in the country), this is not the case in most state prison systems. The experience inside most prison systems is that testing does not lead to education, care, and treatment. It leads to discrimination, segregation, and just plain poor care. HIV-infected prisoners are not eligible for many prison jobs and programs, such as work-release programs and halfway house placement. Despite the success of peer education in the community, behind the walls, there are fewer HIV peer education programs than ever before. The reality is that testing positive inside feels like—and, in some cases, is—a death sentence.

We must ask whether it is in anyone's interest for people inside the walls of prison to be treated any differently than people on the outside.

Mandatory HIV testing is a vast departure from commonly held public health standards. Is this a precursor to a broader CDC policy that all people should be tested, regardless of consent? Right now, people outside of prison walls have the right to make informed decisions about whether to be tested for HIV. Prisoners deserve the same rights.

Our first priority must be programming that provides education, counseling, and a continuum of quality care and treatment to inmates while they are imprisoned and after they have been released.

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Reply to Walker et al.

Sir—We laud Mealy et al. [1] for bringing more attention to the complex issue of HIV testing for incarcerated populations in the United States. We share their

stated goals of advancing research to end the AIDS epidemic and increasing access to health care for incarcerated people, including provision of education, counseling, medical care, and linkage to care in the community upon discharge for HIV-infected inmates. Our original article described the high burden of disease in the incarcerated population and recommended ways to address this from a medical and public health perspective [2]. It is true that we did not emphasize the human rights tragedy that exists in our society, in which minority and impoverished populations are disproportionately incarcerated, and the underlying causes of racism, addiction, mental illness, and poverty are not addressed. This is a problem that we all must strive to solve.

A few key misconceptions in the letter from Mealy et al. [1] warrant specific clarification. The most significant misconception is their incorrect equation of routine testing with mandatory testing. Testing can be voluntary ("opt in"), mandatory (no choice—all must get tested), or routine ("opt out"). Each option has its pros and cons. Voluntary testing preserves maximal autonomy but fails to identify many infected individuals and fails to offer testing to noninfected individuals, a procedure that, in itself, can cause individuals to reflect upon their risk behaviors and reduce them (primary prevention). Voluntary testing also may increase stigmatization, because only those who admit to having risk factors get tested. Mandatory testing can identify nearly all infected individuals in the most timely fashion, but it does not provide the individuals with any choice. This is analogous to what happens in most correctional facilities with regard to screening for tuberculosis, another potentially fatal, treatable contagious disease. We do not advocate mandatory HIV testing, because we believe that the same benefits (identification and treatment of most infected individuals, as well as some prevention) can be achieved with a well-designed system of routine testing. Routine testing preserves the ability of the individual to opt out. There are several examples of programs that have been able to achieve testing rates of close to 90% [3], and we have found this to be well accepted by inmates. Routine HIV testing of prisoners was able to identify one-third of all known HIV-infected individuals in the entire state of Rhode Island [4].

Testing for HIV is the first step in linkage to care, whether in the community or in the correctional setting. Linkage to care includes connecting individuals with posttest counseling and education to identify opportunities to decrease personal risk of HIV acquisition or transmission and to understand the importance of accessing medical care to prolong survival.

Incarcerated individuals are among the most stigmatized and disenfranchised. As such, they are often systematically excluded from accessing health services in the community. Because it is imperative to ensure linkage to care after a diagnosis of HIV infection for individuals in the community, so too is it for individuals in the correctional setting. The challenges of doing this in the two settings are unique; however, they are not insurmountable, as evidenced by model programs [5, 6]. In fact, the constitutional standard established by the US Supreme Court in *Estelle v. Gamble* in 1976 offers a unique opportunity and requirement to provide appropriate health care to incarcerated individuals, a protection that does not exist in the community setting. Thus, the encounter with the correctional health system is an incredible opportunity to provide health care to individuals from traditionally underserved and hard-to-reach communities. Some studies have found that 3 of 4 HIV-infected inmates began their first antiretroviral regimen while incarcerated [7]. With the widespread use of effective antiretroviral therapy in the late 1990s, mortality rates for HIV infection plunged in the United States. In the correctional setting, there was a parallel 75% decrease in mortality rates [8]. Correctional health care systems are not perfect at providing care for HIV-infected persons, but clearly, many HIV-infected inmates are getting access to treatment.

Mealy and colleagues' [1] dismissal of Rhode Island as the "smallest correctional system in the country" is neither accurate (7 states have smaller correctional populations) nor on point. Model programs, such as that in Rhode Island, demonstrate feasibility and effectiveness. Large departments of corrections often comprise numerous smaller facilities; thus, implementation in other venues is more a matter of process and content than scale.

To reject use of a diagnostic test because the health care system is imperfect is to tacitly accept the shortcomings of the broken system and thus to be complicit in systematically excluding individuals subject to that system from accessing vital health information. This is certainly not the intention of any advocate for incarcerated individuals. We all must insist that correctional health care services do a better job of addressing what is known to be a disproportionately high burden of infectious diseases among the populations they are charged to serve [9].

The time is now to address the need for improved HIV testing and linkage to care in the incarcerated population. As routine testing becomes more and more encouraged in the community, this trend should not lag behind in the correctional setting. Indeed, this is an area where correctional health systems should be on the forefront of leadership in this epidemic. As HIV testing in high prevalence areas becomes routine in the community, there is no defensible reason for this service to be denied to those behind bars. The sooner that HIV-infected prisoners are aware of their diagnoses, the more likely they can begin to receive life-saving treatment and, perhaps, at the same time reduce transmission to others. Our challenge is to ensure that timely diagnosis and treatment are offered to as many individuals as possible.

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Does Counseling Increase Sustained Benefit of HAART among Prison Inmates after Release to the Community?

SIR—The lack of sustained effectiveness of HAART after release to the community of HIV-infected inmates treated in prison was well demonstrated by Springer et al. [1] in a recent article. This disappointing result occurred even though all of the patients scheduled for release were referred for transitional case management services to a community-based organization and were provided with a 2-week supply of medications, a medical appointment with an HIV care provider, emergency housing and food, and assistance with other identified unmet needs.

In Italy, 7.5% of the ~56,000 inmates are HIV infected (Ministry of Justice, Dipartimento dell'Amministrazione Penitenziaria, personal communication); it is estimated that approximately one-third of them are receiving treatment with antiretroviral drugs. Our data on the effectiveness of HAART in the prison setting are consistent with those of Springer et al. [1]; however, in some of the 220 Italian prisons, the implementation of directly observed treatment (DOT) has been found to increase the proportion of patients with undetectable HIV RNA levels [2].

We also observed that interruption of HAART after release from the prison is a common event. As suggested by Springer et al. [1] and as emphasized in the editorial commentary by Boutwell and Rich [3], there is a need for implementation of more-effective programs to reduce the probability of discontinuation of and/or reduced compliance with therapy. These programs must prevent use of illegal drugs and alcohol, homelessness, and the relapse of other behavior that may interfere with adherence to antiretroviral drug treatment.

To this end, in January 2001, we started an intensive counseling program that addressed sustained correct use of HAART. During their detention, prison inmates met with the medical staff of drug treatment units who were in charged with observing them after release.

The study was conducted in 4 prisons on Sardinia island; the prisons were located in the towns of Alghero, Macomer, Tempio Pausania, and Sassari. Of ~500 inmates, 16.4% were HIV infected. DOT was implemented in only 1 of the 4 prisons. During the 36-month study period, a total of 153 HIV-infected patients who were receiving HAART were released from prison (59 patients in 2000, 51 in 2001, and 43 in 2002). All of the subjects were injection drug users, and all attended the same drug treatment unit after prison release.

We compared the proportion of patients sustaining HAART among those released in the 12 months before versus the 24 months after the initiation of the counseling program (i.e., the year of 2000 versus the years of 2001–2002). The proportion of patients with an HIV RNA level of <50 copies/mL at the time of release from the prison increased from 20 (33.9%) of 59 subjects in 2000 to 24 (47.1%) of 51 subjects in 2001 ($P > .05$) and to 27 (62.8%) of 43 subjects in 2002 (OR, 3.29; 95% CI, 1.34–8.15; $P < .01$). Compared with the year 2000, when only 7 (12.5%) of 56 patients were found to continue HAART, as measured by frequency of follow-up visits and drug distribution by the community staff after the release from the prison, the proportion increased to 17 (37.8%) of 45 patients in 2001 (OR, 4.25; 95% CI, 1.43–13.01; $P < .01$) and to 20 (52.6%) of 38 patients in 2002 (OR, 7.77; 95% CI, 2.56–24.66; $P < .0001$). Undectectable HIV RNA levels occurred in 5 (71.4%) of 7 patients in 2000, increasing to 14 (82.3%) of 17 patients in 2001 and to 16 (80%) of 20 patients in 2002.

Our data suggest that an intensive counseling program that addresses creation of a relationship between the inmate and the medical team committed to patient clinical follow-up outside the prison

may improve adherence both in prison and in the community after release, at least in countries with a high proportion of injection drug users among HIV-infected inmates.

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Reply to Babudieri et al.

Sir—Development of novel interventions for vulnerable populations of prisoners as they are released to the community is urgently needed. According to data we presented, case management services alone appear to be inadequate [1]. Babudieri et al. [2] describe a novel counseling program that they believe has contributed not only to virological success in subjects in the correctional setting, but also to continued success in subjects after release from prison. They should be commended for recognizing the problem and addressing an obstacle that many view as insurmountable. Notwithstanding the limitations of their small sample size and the use of a preintervention/postintervention analytic approach, there is merit in examining the lessons learned from their experience.

The high rates of viral suppression observed 2 years after implementation of the intervention are impressive. Several questions regarding the effect of the intervention, however, remain. Unlike the situation in the United States and elsewhere, the Sardinian experience suggests that all released prisoners are linked to continued drug treatment programs after release. The lack of a control group leads us to speculate that several additional factors may have contributed to the described success. Correctional and community HIV care providers may have developed enhanced counseling skills, may have increased their diagnosis and treatment of comorbid mental illness among the released prisoners, or may have prescribed simpler, less toxic, and more potent regimens as clinicians and health care systems began to embrace the importance of adherence [3]. It is also possible that sentencing laws or treatment practices changed over the observation period. For instance, a greater number of prisoners released on probation or parole may result in increased rates of abstinence from illicit drug use because of the stringent and often punitive conditions of release. A description of the types of linkages, amount of education provided, and the duration of success after release to the community would further inform us regarding the benefit of their program.

Irrespective of the extenuating circumstances, novel approaches that sustain the benefit of antiretroviral therapy between the correctional and community settings must be developed and tested using rigorous, unassailable, controlled trials. Only such trials will result in policy changes. We recently reported, in a randomized, controlled trial of directly administered antiretroviral therapy, that supervised therapy was superior at reducing viral load and increasing CD4 lymphocyte count, compared with self-administered therapy, among HIV-infected drug users [4]. The details of the intervention have been described elsewhere [5]. These data suggest that provision of structure and social support provide benefit to HIV-infected drug users prescribed antiretroviral therapy—perhaps this might be applicable for released prisoners. Drug treatment programs that provide effective structure and support, such as prescription of methadone or buprenorphine, are absent from most prisons and their respective release programs and should be considered in future interventions [6]. The Sardinian experience appears to integrate drug treatment into the prison and postrelease program—a wise and likely beneficial contribution to success. Direct access to such structured programs, recommended by the World Health Organization [7], would likely result in improved outcomes for HIV-infected prisoners. Unfortunately, no empirical studies have been conducted to date. Interventions for released prisoners must incorporate elements that address social instability, untreated substance abuse disorders, and psychiatric conditions and that provide structure to otherwise disorganized and chaotic lives. It is incumbent on science and society to render beneficial and effective antiretroviral therapy to everyone affected by HIV/AIDS, including released prisoners.

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Sonographic Assessment of Lipodystrophy in HIV-Infected Patients: Some Open Questions

Sir—We have read with interest the article by Asensi et al. [1] because we are conducting a similar study. The sonographic assessment of lipodystrophy in human immunodeficiency virus (HIV)–infected patients who are treated with HAART has been the subject of recent publications [1, 2]. Ultrasonography is a more practical method than CT scanning and dual-energy X-ray absorptiometry; its lack of ionizing radiation, low cost, availability, simplicity, and reproducibility, as well as its acceptability among patients, make it an ideal tool for diagnosis of lipodystrophy and for early identification of subcutaneous fat thickness reduction and visceral fat increase. We have encountered some methodological issues that need to be addressed, if the potential of ultrasonography is to be fully exploited.

A good correlation between the findings of ultrasonography and CT scanning has been demonstrated for the measurement of visceral fat in patients who do not have HIV infection [3]. However, no such data are available for HIV-infected patients and with regard to subcutaneous fat thickness. Given the importance of a correlation between the findings of ultrasonography and CT scanning, which remains the gold standard, ultrasonography measurements should be validated with CT scanning, at least in a preliminary group.

Subcutaneous fat thickness is related to the body mass index (BMI) in HIV-infected patients [4], who tend to have an increased amount of visceral fat when their BMI is >27. Although Asensi et al. [1] claim that there is no correlation between BMI, subcutaneous fat thickness, and perirenal fat diameter, all of their patients had a BMI of <27. We believe that the cutoff values of all measurements, particularly that of perirenal fat diameter, should be readjusted for patients with a BMI of >27, to avoid a possible bias.

Sex-related differences in body fat distribution are still a controversial issue [5, 6]. In our cohort, crural and brachial subcutaneous fat thickness values were higher in women than in men, in both HIV-positive and HIV-negative patients, and we feel that this finding warrants the division of the cohort into 2 subgroups. There is no such distinction made in the article by Asensi et al. [1]. In fact, the low number of female patients in their cohort could represent an additional source of bias. The reproducibility of their results in a female group is a crucial point, particularly with regard to the promising predictive role of perirenal fat diameter [1].

Dismetabolic abnormalities, such as dislipidemia and insulin resistance, have been described in hepatitis C virus–infected patients [7, 8], and these abnormalities are strictly related to the increase of visceral fat. This could be a source of bias in the evaluation of visceral fat and secondarily subcutaneous fat thickness in patients coinfected with HIV and hepatitis C virus with lipodystrophy. Because hepatitis C virus–infected patients are numerous in the series of Asensi et al. [1], this bias in the assessment of perirenal fat diameter cannot be avoided if one fails to include those patients in a specific subgroup.

The ability of ultrasonography to replace—partially or completely—other more cumbersome and expensive methods needs be clearly defined, given what is at stake. The interruption of a life-saving treatment such as HAART or a switch of the regimen to nonnucleoside reverse-transcriptase inhibitors because of impending lipodystrophy, a serious and nonreversible condition, are very important steps to take and require the support of a proven and fully standardized method.

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Reply to Gulizia et al.

Sir—We agree with Gulizia et al. [1] that the value of ultrasonography to assess the visceral fat and subcutaneous fat thickness of HIV-infected patients has to be validated by comparison with other objective methods, such as CT scanning. Using a more subjective tool—the score of the body fat changes directly observed by HIV-infected patients and their physicians during every follow-up visit by use of criteria published elsewhere [2]—we have found a significant correlation between the score of the directly observed facial and abdominal fat changes and the echographic malar (Bichat) subcutaneous fat thickness ($r = 0.280$; $P < .001$) and abdominal subcutaneous fat thickness ($r = 0.180$; $P < .001$). In addition, a significant correlation between the score of the directly observed abdominal fat changes and the visceral fat measured as the perirenal fat diameter (PRFD) was also found ($r = 0.320$; $P < .001$) (unpublished data). However, we observed no significant correlation between the score of the directly observed changes in arm or thigh fat and the subcutaneous fat thickness of the limbs, as assessed by ultrasonography.

As suggested by Gulizia et al., the body mass index has to be considered, especially for overweight patients. To avoid a possible bias in using the PRFD measure, we recommend using a new adjusted PRFD, which represents the ratio PRFD:body mass index. By use of adjusted PRFD and receiver operating characteristic curves, the most discriminant pre-HAART baseline adjusted PRFD for predicting the development of lipodystrophy at the end of the 27-month follow-up period was $\geqslant 0.118$. Measurement of the adjusted PRFD had identical sensitivity but was slightly more specific than measurement of the PRFD (sensitivity, 85.3%; specificity, 77.3%) [3]. The most discriminant adjusted PRFD for predicting the development of lipodystrophy during receipt of HAART was $\geqslant 0.182$, although measurement of the adjusted PRFD had a discriminant power that was identical to that of measurement of the PRFD (sensitivity, 100%; specificity, 75.7%).

We also agree with Gulizia et al. [1] that the small number of women (18 patients [24.3%]) in our series—which was mostly due to the predominance of males among intravenous drug users in Spain [4], many whom are coinfected with hepatitis C virus (29 patients [39.2%])—could represent a bias due to differences in sex, status of hepatitis C virus coinfection, and body fat distribution.

Our group and others have reported that coinfection with hepatitis C virus increases the level of lipodystrophy (mostly lipoatrophy) in HIV-infected patients, perhaps because of liver mitochondrial toxicity, although mitochondrial toxicity also decreases the serum levels of cholesterol and triglycerides, probably because of liver damage due to hepatitis C virus infection [5–10]. Therefore, coinfection with HIV and hepatitis C virus could have consequences for subcutaneous fat thickness and visceral fat changes, and this should be considered as well.

Our study was conducted to evaluate the usefulness of several parameters, mainly echographic measurements to predict lipodystrophy in a nonselected population of HIV-infected individuals that was considered as a whole. The sample size of this pilot study was relatively small, severely limiting the evaluation of different subgroups that could be of interest. Further multicenter studies that include higher numbers of HIV-infected patients who are at baseline and receiving HAART, and that include specific subgroups of females and people coinfected with hepatitis C virus and HIV, are needed to validate the utility of ultrasonography in the assessment of subcutaneous fat thickness and visceral fat in HIV-infected patients, as well as to confirm the value of PRFD and adjusted PRFD measures as predictors of lipodystrophy.

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Classical Diphtheria Caused by *Corynebacterium ulcerans* in Germany: Amino Acid Sequence Differences between Diphtheria Toxins from *Corynebacterium diphtheriae* and *C. ulcerans*

Table 1. Amino acid sequence differences in diphtheria toxin of *Corynebacterium diphtheriae, Corynebacterium ulcerans* X959, *C. ulcerans* A2911, and *C. ulcerans* A6361.

Amino acid position	*C. diphtheriae* (referent)	*C. ulcerans* X959	*C. ulcerans* A2911	*C. ulcerans* A6361
2	Ser	Asn	Asn	Asn
14	Leu	Ile	Leu	Leu
22	Ser	Ser	**Leu**	**Leu**
31	Val	**Asp**	Val	Val
67	Thr	**Ala**	Thr	**Ala**
116	Val	Ile	Ile	Ile
183	Ala	Ala	**Glu**	**Glu**
210	Ala	**Ser**	**Ser**	**Ser**
233	Val	Ala	Ala	Ala
262	Thr	**Ile**	Thr	Thr
277	Gln	Gln	**Arg**	Gln
294	Thr	**Val**	**Val**	**Val**
296	Pro	**Ser**	**Ser**	**Ser**
305	Ala	**Ser**	**Ser**	**Ser**
314	Ile	Val	Val	Val
317	Glu	**Lys**	**Lys**	**Lys**
378	Ile	Leu	Leu	Leu
415	Leu	Val	Val	Val
417	Asp	**Gly**	**Gly**	**Gly**
421	Val	Ala	Ala	Ala
432	Arg	Lys	Lys	Lys
491	Gly	**Asp**	**Asp**	**Asp**
492	Asp	**Ala**	**Ala**	**Ala**
493	Val	**Thr**	**Thr**	**Thr**
500	Ser	Thr	Thr	Thr
518	Arg	Arg	Thr	Arg
527	Asn	**Asp**	**Asp**	**Asp**
529	Ile	**Thr**	**Thr**	**Thr**
530	Ser	**Pro**	**Pro**	**Pro**
531	Ser	Leu	Leu	Leu
532	Asp	**Ser**	**Ser**	**Ser**
535	Gly	**Asp**	**Asp**	**Asp**
556	Phe	Ala	Ala	Ala
558	Ile	Val	Val	Val

NOTE. Bold face indicates a change in the amino acid class from that of the reference strain. Ala, alanine; Arg, arginine; Asn, asparagine; Asp, aspartic acid; Ile, isoleucine; Gln, glutamine; Glu, glutamic acid; Gly, glycine; Leu, leucine; Lys, lysine; Phe, phenylalanine; Pro, proline; Ser, serine; Thr, threonine; Val, valine.

Sir—*Corynebacterium ulcerans* is increasingly recognized as an emerging pathogen in various countries, including the United States [1], the United Kingdom [2], Japan [3], The Netherlands [4], Switzerland [5], and Italy [6]. In some of these countries, *C. ulcerans* is now the leading cause of classical pharyngeal diphtheria [2]. The ability of *C. ulcerans* infection to mimic diphtheria is explained by the fact that *C. ulcerans*—similar to *Corynebacterium diphtheriae* and *Corynebacterium pseudotuberculosis*—carries lysogenic β-corynephages coding for the diphtheria toxin (DT). We previously described 2 *C. ulcerans* isolates that were associated with cases of extrapharyngeal diphtheria (one was isolated from a cutaneous infection and the other caused lethal necrotizing sinusitis); sequencing of the respective *tox* gene of both strains revealed differences in nucleotide and amino acid sequences between *C. diphtheriae* and *C. ulcerans* DTs [7].

Here, we report a case of classical diphtheria caused by *C. ulcerans* in a 53-year-old woman who developed severe pharyngeal swelling and a whitish pseudomembrane. Her family practitioner obtained a swab specimen from the lesion, which grew *C. ulcerans* (API code 0111326), as detected by biochemical methods (API Coryne; bioMérieux) and 16S rRNA gene sequencing. The presence

of DT was tested both by *tox* PCR and an Elek test, as described elsewhere [7]. Because of the severity of the swelling, the patient was referred to an ear, nose, and throat specialist who treated the infection with 2 injections of penicillin (1.2 million units). The patient recovered completely. She had received a complete course of primary immunizations during childhood; however, booster immunizations were never administered.

Because no sequence data are available for the *tox* gene of *C. ulcerans* associated with classical pharyngeal diphtheria, we sequenced the complete *tox* gene of this strain (X959; GenBank accession number AY703827) and compared the amino acid sequence with those of a *C. diphtheriae* strain (GenBank accession number V01536) and 2 *C. ulcerans* strains, A2911 and A6361, that cause extrapharyngeal disease (GenBank accession numbers AY141013 and AY141014, respectively) [7]. The *C. diphtheriae* strain and the 3 *C. ulcerans* strains differed from each other in 26 amino acids (homology, 95.4%), 13 of which belonged to different amino acid classes (table 1). Most differences were located in the B fragment of the DT. In 3 positions (aa14, aa31, and aa262), the DT from *C. ulcerans* X959 was unique, harboring an amino acid that was not present in the other DTs. Interestingly, the DTs from both the *C. diphtheriae* and the *C. ulcerans* X959 strains have a serine in position 22 of the A fragment and an alanine in position 183 of the A fragment, whereas the DTs of the *C. ulcerans* A2911 and A6361 strains have a leucine in position 22 of the A fragment and a glutamine position 183 of the A fragment. Because these are the only differences between the DTs of the *C. diphtheriae* and *C. ulcerans* X959 strains, on the one hand, and the DTs of the 2 extrapharyngeal *C. ulcerans* strains, on the other hand, it might be speculated that these amino acids could be involved in pseudomembrane formation; however, loss of activity in mutated *C. diphtheriae* DT has not yet been linked to aa22 or aa183.

The difference between *C. diphtheriae* and *C. ulcerans tox* genes was further corroborated by *C. ulcerans tox*–specific PCR using primers DT1 with 1467R or 1586R, respectively [7], yielding a positive PCR result only for the 3 *C. ulcerans* strains, and not for the *C. diphtheriae* strain.

To our knowledge, this is the first report of classical diphtheria caused by *C. ulcerans* in Germany since the description of this species in 1995 [8]. Moreover, the sequence data on the isolated strain that caused classical diphtheria in the patient we describe confirm the previous results that we obtained for 2 isolates of *C. ulcerans* that caused extrapharyngeal infections, suggesting that DTs from *C. diphtheriae* and *C. ulcerans* are different, independent from an association with pharyngeal or extrapharyngeal disease. In addition, this first sequenced DT from a *C. ulcerans* isolate associated with classical diphtheria indicates that *C. ulcerans* DT amino acid sequences are less well conserved than their *C. diphtheriae* counterparts [9].

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Influence of GB Virus Type C and HIV Coinfection on γδ T cells

Sir—GB virus type C (GBV-C) coinfection has been associated with decreased mortality and better outcome for human immunodeficiency virus (HIV)–infected persons [1, 2]. However, recent studies suggest that GBV-C coinfection can be secondary to HIV-disease progression, rather than an independent prognostic factor for such progression [3]. Several immunological mechanisms have been proposed that associate GBV-C coinfection with the interference of HIV replication, such as reduction of CCR5 chemokine receptor expression, induction of antiviral chemokines, preservation of Th1 immune-response, and other mechanisms of viral interference [4, 5]. In a recent article by Sathar et al. [6], it has been shown that GBV-C coinfection in HIV-infected persons was associated with increased frequency of γδ T cells. An accompanying

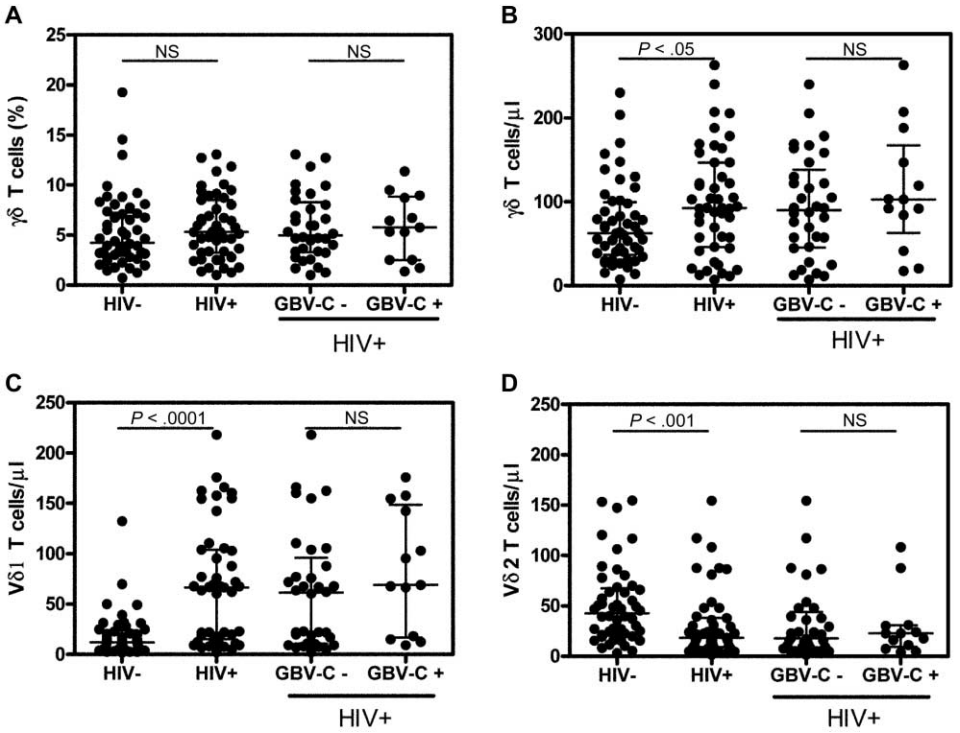

Figure 1. Frequencies and absolute numbers of circulating γδ T cells in 50 healthy control subjects (HIV−) and 47 HIV-infected patients (HIV+), of whom 34 tested negative for GB virus type C (GBV-C) RNA in plasma (GBV-C−) and 13 tested positive (GBV-C+). *A,* Percentage of circulating γδ T cells. *B,* Absolute number of circulating γδ T cells. *C,* Absolute number of circulating Vδ1 T cells. *D,* Absolute number of circulating Vδ2 T cells. Bars, Medians and interquartile ranges. Comparison between GBV-C–infected and GBV-C–uninfected HIV patients groups was made by a nonparametric Mann-Whitney test (Prism 4; GraphPad Software). NS, *P* not significant.

editorial commentary [7] suggested that GBV-C coinfection may trigger a γδ T cell immune response that, in turn, may induce a slower HIV replication rate and/or a more effective anti-HIV Th1 immune response.

Since we previously observed that a subset of γδ T cells expressing the Vδ2 T cell receptor may play a protective role during HIV infection by producing noncytolytic antiviral factors [8], and that this γδ T cell subset is generally depleted in HIV-infected patients [9], we have investigated whether GBV-C coinfection was associated with altered frequencies of γδ T cell subsets in a cohort of HIV-infected patients, which may account for the beneficial influence of GBV-C coinfection on the course of HIV disease. The frequency of circulating γδ T cells and their subset composition was analyzed by flow cytometry in 47 HIV-infected patients (28 male and 19 female; median age, 41 years; age range, 28–66 years) attending the outpatient facility at the National Institute for Infectious Diseases "Lazzaro Spallanzani" in Rome. In our cohort, 41 subjects (87.2% of 47) had been receiving successful antiretroviral treatment for at least 2 years prior to the study. The presence of GBV-C RNA in plasma was determined by nested RT-PCR, according to a previously established method [1]. γδ T cell distribution in such subjects was compared according to their GBV-C infection status (figure 1). The 2 study groups were similar with respect to their demographic characteristics (data not shown). To establish reference values for γδ T cell distribution in peripheral blood, 50 blood samples from healthy donors were obtained from the Immunohaematology Laboratory at the Forlanini-San Camillo Hospital in Rome.

As shown in figure 1, the γδ T cell subset distribution was significantly altered by HIV infection, as expected (figure 1, panels C–D). In fact, the Vδ1 T cell subset was significantly augmented in the peripheral blood of HIV-infected subjects [9, 10]. Furthermore, the increase of Vδ1 T cells was concomitant with a decrease of Vδ2 T cells [9, 11, 12]. However, comparison of γδ T cell subset distribution in HIV-infected subjects, grouped according to their GBV infection status indicated that the increase in γδ T cells occurred independently of GBV-C coinfection (figure 1, panel C) and that GBV-C coinfection had no role in the specific deletion of T cell receptors (figure 1, panel D).

In our cohort of HIV-infected subjects, we observed that Vδ2 T cell exhaustion and Vδ1 T cell increase are not correlated with GBV-C coinfection. Thus, other mechanisms are likely to be involved in interactions between GBV-C and HIV infections.

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Reply to Martini et al.

Sir—We read with interest the findings of Martini et al. [1] regarding the influence of GB virus type C (GBV-C) coinfection of $\gamma\delta$ T cells in human immunodeficiency virus (HIV)–infected patients. The use of direct human-to-human microbial transmission as therapy for infectious diseases may seem anachronistic, but several studies have suggested that infection with 1 microbe can alter the disease expression of another pathogen, including HIV [2]. To date, 11 clinical studies have associated GBV-C coinfection with slower progression to acquired immunodeficiency syndrome, longer life, and improved response to antiretroviral therapy in HIV-infected individuals [3–6]. Several mechanisms have been proposed: namely, the induction of anti-HIV cytokines and chemokines [3, 4, 7], the stimulation of anti-HIV cytotoxic T lymphocyte response [8], and the preservation of Th1 lymphocyte response [9]. In our limited observational study [10], we reported no significant differences in lymphocyte subsets between HIV-infected African mothers coinfected with GBV-C and those not coinfected (table 1). We observed no significant difference in absolute $\gamma\delta$ T cell counts between HIV-infected mothers coinfected with GBV-C and those not coinfected. However, we reported a marginally significant difference ($P < .052$) between the relative $\gamma\delta$ T cell counts of the 2 groups (table 1). On the basis of this observation and the cognizance of the potential role of $\gamma\delta$ T cells in HIV infection [11], we hypothesized that another anti-HIV mechanism may be associated with GBV-C infection. Martini et al. [1], on the other hand, re-

Table 1. Comparison of mean lymphocyte subset indices in HIV-infected patients with and without GB virus type C infection.

	Mean value ± SD		
Lymphocyte subset	Infected subjects (n = 22)	Uninfected subjects (n = 33)	P
CD4			
Percentage	26.70 ± 8.30	26.64 ± 8.67	NS
Count, cells/μL	461.12 ± 163.28	478.42 ± 181.22	NS
CD8			
Percentage	48.47 ± 10.08	48.70 ± 10.78	NS
Count, cells/μL	680.83 ± 320.36	862.52 ± 354.48	NS
CD4:CD8 ratio	0.58 ± 0.25	0.59 ± 0.28	NS
CD3			
Percentage	80.0 ± 4.17	70.99 ± 19.76	.015
Count, cells/μL	1395.45 ± 366.79	1451.29 ± 571.37	NS
CD30			
Percentage	35.45 ± 17.86	50.59 ± 9.20	.041
Count, cells/μL	577.75 ± 307.64	823.88 ± 392.00	NS
$\gamma\delta$ T			
Percentage	3.22 ± 1.30	2.15 ± 1.08	.052
Count, cells/μL	53.11 ± 18.35	39.15 ± 29.12	NS

NOTE. NS, not significant.

port a marginally significant difference ($P < .05$) in absolute $\gamma\delta$ T cell counts [1, figure 1B] and no significant difference in relative counts [1, table 1A] between the 2 groups. Although Martin et al. [1] reports a significant difference in $\gamma\delta$ T cell subsets between the study groups, we did not measure $\gamma\delta$ T cell subsets. In addition, there are other differences between our respective studies. In their study [1], 41 (87.2%) of 47 HIV-infected subjects had been receiving successful antiretroviral treatment for a period of 2 years. In our study [10], all HIV-infected African mothers were antiretroviral-naive; the only criterion that determined whether patients could participate was HIV infection status; the study populations are composed of different racial groups; and the majority of HIV and GBV-C infections in KwaZulu Natal are clade C and genotype 5, respectively. Our data concurs with the observations reported by Martini et al. [1], and we agree that some other factor or factors besides GBV-C infection may play a role in altering the $\gamma\delta$ T lymphocyte subsets in HIV-infected individuals.

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Coinfection with HIV and Human T Lymphotropic Virus Type 1: What Is the Real Impact on HIV Disease?

Sir—We read with interest the article by Beilke et al. [1] summarizing their findings of an observational study of a group of HIV-infected patients, some of whom were coinfected with human T lymphotropic virus types 1 (HTLV-1) and/or 2 (HTLV-2). The authors focus the clinical outcomes and survival probabilities among coinfected patients, and the final conclusions reinforce previous evidence of the absence of a significant impact of HTLV-2 coinfection on AIDS progression [2, 3]. They conclude that HTLV-2 coinfection is associated with some degree of protection against disease progression for such patients, with a consequent greater duration of survival. Other findings include the increased incidence of some clinical events among coinfected patients, such as myelopathy, urinary tract infection, peripheral neuropathy, thrombocytopenia, and bronchitis, compared with persons who were infected with HIV alone. In addition, Beilke et al. [1] confirm already-reported data on higher $CD4^+$ cell counts among coinfected patients [4].

However, the absence of an impact of HTLV-1 coinfection on survival was an unexpected finding. Our previous experience in evaluating a similar population with a similar duration of follow-up yielded the opposite result. We evaluated the duration of survival for 132 HIV-infected patients (63 of whom where coinfected with HTLV-1) who were observed at our clinics, with a significant difference in the time to death that favored HIV-monoinfected subjects, which remained after adjustment for injection drug use [5]. One possible explanation for such discrepancies could reside in the population studied: our study included mainly patients in the pre-HAART era. The use of antiretroviral drugs probably modifies the natural history of coinfection, because the proper therapy for HIV infection could mask the potentially additive effects of HTLV-1 coinfection on disease progression. Beilke et al. [1] stated that they adjusted the analysis for the use of antiretroviral drugs, but there is no description in the article on the duration of therapy or follow-up or on the time that therapy was started for monoinfected and coinfected patients. In addition, the stratification of $CD4^+$ cell counts into 3 groups (<200, 200–500, and >500 cells/μL) can mask some important difference between HIV-monoinfected and HIV-HTLV–coinfected patients. The range of $CD4^+$ cell counts in the 3 groups is large enough to include some quite different patients.

Another important question regards the matching of patients by $CD4^+$ cell count: if Beilke et al. [1] conclude that this parameter is modified by coinfection, then we do not think it is the best approach to compare groups. Because $CD4^+$ cell counts are expected to be higher in HIV-HTLV–

coinfected patients, and because coinfection can be associated with immune dysfunction, matching patients by immune markers is not a good strategy. The authors recognize that they were not able to define the best threshold point to recommend the commencement of HIV therapy for such patients for these reasons.

The study is very important because it raises this and other questions. The statistical analysis is quite strong and well designed, but some of the study's points remained unclear. Although the authors recognize some limitations of the study, they affirm the absence of a clinical impact of coinfection on AIDS progression. We believe that the available data are still too weak to confirm that theory. As correctly stated at the end of the article, these questions probably will be answered only through prospective studies.

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Reply to Brites et al.

Sir—We appreciate the correspondence by Brites et al. [1] and would like to provide additional clarification concerning several points they raised. Our study [2], which focuses on clinical outcomes and survival probabilities among patients coinfected with HIV and human T lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2, respectively), actually arrives at conclusions that are somewhat different than those of the previous studies cited by Brites et al. [1]. In contrast to the reports of Hershow et al. [3] and Giacomo et al. [4], who found no differences in survival outcomes, our findings indicate improved duration of survival and delayed progression to AIDS among patients coinfected with HIV and HTLV-2. A similar trend was observed among patients coinfected with HIV and HTLV-1, but the results did not reach statistical significance. Several reasons may exist for observed differences among various cohort studies. First, treatment effects at different study sites could have an impact on survival trends and rates of disease progression. In the New Orleans cohort analysis, we were careful to generate a matched cohort study, in which exposure to antiretroviral therapy and $CD4^+$ cell count was controlled for at baseline, as well as over time. The mean durations ($\pm$SD) of exposure to antiretroviral therapy among HIV–HTLV-1–coinfected patients, HIV–HTLV-2–coinfected patients, and HIV-monoinfected patients were 20.02 ± 30.10, 24.21 ± 37.03, and 22.79 ± 34.23 months, respectively. The year of initiation of antiretroviral therapy did not differ significantly among the 3 groups.

Second, the prior studies did not report whether there was control for baseline $CD4^+$ cell count or viral load. We found no differences in baseline plasma HIV RNA levels (although viral load data were only available for patients who entered the cohort after 1996), and our case-control cohort was matched for baseline $CD4^+$ cell count. We elected to stratify by $CD4^+$ cell count category (i.e., <200, 200–500, and >500 cells/μL). Brites et al. [1] expressed concern that these ranges might be too wide. Therefore, we examined the mean and median $CD4^+$ cell count range among the 3 strata, and we found almost identical results among the groups. In the $CD4^+$ cell count stratum of 200–500 cells/μL, for example, the mean ($\pm$SD) $CD4^+$ cell counts were 345.3 ± 77.1 cells/μL (median, 362.0 cells/μL; range, 212–497 cells/μL) for HIV–HTLV-1–coinfected patients, 344.7 ± 84.8 cells/μL (median, 340.0 cells/μL; range, 200–500 cells/μL) for HIV–HTLV-2–coinfected patients, and 350.0 ± 83.7 cells/μL (median, 340.1 cells/μL; range, 202–494 cells/μL) for HIV-monoinfected patients. Although coinfected and monoinfected patients were matched with respect to $CD4^+$ cell count at baseline, the $CD4^+$ cell count could have changed over time (which we also demonstrated), and, therefore, the $CD4^+$ cell count over time was also controlled for in the survival analyses. We contend that matching for baseline $CD4^+$ cell count is a rational method to compare survival and disease progression, because there may be qualitative and quantitative differences in $CD4^+$ cell count that account for divergences in outcomes.

In our analysis of mortality and duration of AIDS-free survival, we attempted to account for potential survivor-treatment selection bias by matching for $CD4^+$ cell count at baseline/time of clinic entry. This is one approach that is commonly used in observational studies [5] to eliminate potential survival bias, because the final model compares persons in the different treatment or exposure groups who started in similar physical conditions and (theoretically) survive to

the same time point or have similar options for treatment and prolonged survival or AIDS-free time [5–7]. Survivor-treatment bias should be accounted for when interpreting the results of HIV cohort studies.

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Fatal *Salmonella* Pulmonary Arteritis in a Patient with Eisenmenger Syndrome

Sir—Arterial infection is the most serious complication of salmonellosis [1]. *Salmonella* arterial infections can involve the thoracic and abdominal aortas and the peripheral arteries. Infection of the pulmonary trunk or its major branches is rare [2, 3]. The mortality rate for patients with mycotic pulmonary aneurysm (pulmonary arteritis) is reported to be >50%, and most of the causative pathogens are gram-positive bacteria, including *Staphylococcus aureus* and streptococci [3]. To our knowledge, *Salmonella* species have never been reported as a cause of pulmonary arteritis in the English-language literature.

The patient was a 61-year-old woman who had received a diagnosis of atrial septal defect with Eisenmenger syndrome. She was admitted to a regional hospital (hospital A) because of fever, severe cough, and dyspnea. The patient was treated for asthma with secondary infection. Intravenous cefazolin (1 g q8h) was administered. On the eighth day of hospitalization at hospital A, the patient developed hemoptysis and severe chest pain and was transferred to our hospital.

Physical examination revealed a body temperature of 37°C, blood pressure of 120/70 mm Hg, a regular pulse rate of 90 beats/min, and a respiratory rate of 18 breaths/min. There was a grade III/VI systolic murmur heard along the left sternal border and apex. Chest palpation revealed a right parasternal heave. Except for clubbing fingers and cyanosis, the remainder of the findings of the examination were unremarkable. Laboratory data revealed a WBC count of 17.45×10^3 cells/μL (with 92.8% neutrophils), a hemoglobin level of 16.4 g/dL, and a platelet count of 154×10^3 platelets/μL. Blood chemistry examination revealed a urea nitrogen value of 9.3 mg/dL, a creatinine level of 0.7 mg/dL, an albumin level of 3.2 g/dL, and a C-reactive protein level of 10.37 mg/dL. Chest radiographs revealed cardiomegaly and a bulging pulmonary conus. The bilateral pulmonary arteries were also dilated (figure 1). A hazy, ill-defined shadow extending upward from the pulmonary conus was noted. Chest CT with contrast enhancement revealed markedly dilated pulmonary trunk and bilateral central pulmonary arteries (figure 1). An abnormal consolidation around the left pulmonary artery near the hilar area was demonstrated. The consolidation consisted of inhomogeneous masses with irregular peripheral enhancement, which was consistent with mural thrombus and peri-arterial inflammation. There was an irregular tract extending from the pulmonary artery into the consolidation mass, suggesting extravasation of the infected pulmonary artery. Echocardiography demonstrated a secundum atrial septal defect of 22 mm in diameter and no evidence of infective endocarditis.

The patient developed fever, repeated hemoptysis, and hypotension during the initial 3 days of hospitalization. The infected pulmonary arteritis (pulmonary mycotic pseudoaneurysm) was considered to have an impending rupture with a hemorrhage that was probably life-threatening. Surgical resection was necessary but risky because of pulmonary hypertension with Eisenmenger syndrome. The patient was considered to be a candidate for combined heart-lung transplantation.

Intravenous ceftriaxone (1 g q12h) was administered on the first day of hospitalization, because 2 sets of blood cultures from hospital A were positive for *Salmonella* serogroup D (nontyphoid). The isolate was susceptible to ampicillin, ceftriaxone, and ofloxacin but resistant to trimethoprim-sulfamethoxazole, as determined by the disk diffusion method. The patient was afebrile and in stable clinical condition (subsidence of chest pain and absence of hemoptysis) on the fourth day of hospitalization. Unfortunately, the patient developed a sudden onset of intractable pulmonary hemorrhage and died on the seventh day of hospitalization, despite immediate and vigorous resuscitative efforts.

Pulmonary hypertension with Eisen-

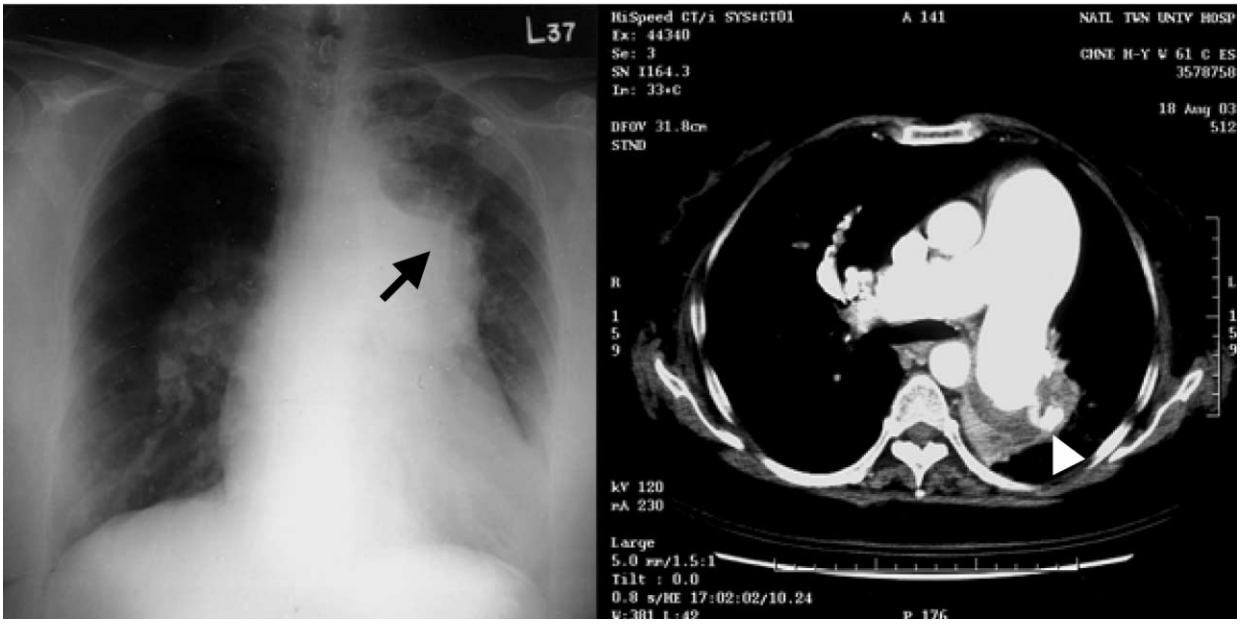

Figure 1. *Left,* Chest radiograph showing cardiomegaly and a bulging pulmonary conus, with a hazy, ill-defined shadow extending upward from the pulmonary conus *(arrow). Right,* Chest CT with contrast enhancement revealing an abnormal consolidation around the dilated left pulmonary artery near the hilar area. There was an irregular tract extending from the pulmonary artery into the consolidation mass, suggesting extravasation *(arrow head)* of the infected pulmonary artery.

menger syndrome leads to exposure of the pulmonary vasculature to systemic arterial pressure and results in aneurismal dilation. The responsible microorganism has an inclination toward diseased vascular walls, and mural thrombi would provide an ideal environment for the seeding and growth of the microorganisms. The clinical course and management of infected pulmonary arteritis is not well documented because of the rarity of cases. From experience with the management of aortic aneurysms infected with *Salmonella* species [4–6], survival rates appear to improve among patients who receive combined medical treatment and surgical intervention. In the collective case study by Hsu et al. [4], none of the 20 patients who had combined medical and surgical treatment died. However, 2 of the 4 patients treated with antibiotics alone died.

Complex congenital heart disease with indolent *Salmonella* infection exposed our patient to a life-threatening situation. Early surgical interventions, including resection of the infected left pulmonary artery and wide debridement of adjuvant tissue, followed by combined heart-lung or lung transplantation [7], were crucial in our case because of the impending rupture with probable life-threatening hemorrhage. Unfortunately, the patient had intractable pulmonary hemorrhage and died, despite administration of appropriate antibiotic treatment 1 week before death.

In conclusion, *Salmonella* species should be included in the list of pathogens that can cause pulmonary arteritis. Aggressive antibiotic treatment and intensive surgical intervention are essential to avoid death due to rupture of the aneurysm.

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Background for Different Use of Antibiotics in Different Countries

SIR—We read the article about the quantitative and qualitative differences in antibiotic prescribing between British Columbia and Denmark [1] with great interest. We agree with the authors that the increasing use of fluoroquinolones and new macrolides is worrying, because it may increase the risk for emergence of a greater number of resistant microorganisms. With use of a different method, we performed a study that compared the prescribing of antibiotics in Spain and Denmark [2]. In Spain, a similar phenomenon to the one in British Colombia was observed, with an increase in the use of new antibiotics.

We agree that among the main reasons for the difference in antibiotic use are the different opinions and traditions regarding how to treat infections that exist in different countries. We have verified this by comparing, for example, the existing general practice guidelines for the treatment of streptococcal tonsillitis or of the exacerbation of chronic obstructive pulmonary disease in Denmark and Spain. In Denmark, narrow-spectrum penicillin is recommended for both infections, whereas in Spain, only broad-spectrum antibiotics are recommended. A vicious circle is thus created. In an attempt to cover these pathogens, the prescribing of broad-spectrum antibiotics favors a more rapid expansion of resistant microorganisms. In Denmark, where rates of resistance are very low, narrow-spectrum antibiotics are still the most frequently used antibiotics in primary health care, thus perpetuating a low prevalence of resistant microorganisms.

We would like to emphasize the fact that different methods of organizing health care services may have a considerable influence on the pattern of antibiotic prescribing. Variables such as the type of health care financing system, the number of doctors per inhabitant, and the average time spent with the patient may lead to different prescribing habits. It is known, for example, that countries with a greater number of doctors per inhabitant use more antibiotics than do countries with a smaller number of doctors per inhabitant [3], and that doctors who spend more time with their patients prescribe fewer antibiotics [4]. The permissive policy of the sale of antibiotics without a prescription (i.e., over-the-counter policy), which exists in Spain but not in Denmark, is another potential reason for the difference. Other factors to take into account are the number of pharmacies per inhabitant (10 times greater in Spain than in Denmark), the pressures from the pharmaceutical industry, and the antibiotics available. In Spain, penicillin V is only marketed in doses of 200 mg and 600 mg, a fact about which the pharmaceutical industry's representatives do not inform doctors. Different policies concerning subsidization of antibiotics may also have an influence. In Denmark, fluoroquinolones and cephalosporines are not subsidized by the national health care service.

In conclusion, we believe that different methods of organizing health care services, different subsidization policies, and different impacts of pharmaceutical marketing should be taken into account when trying to explain differences in the pattern of antibiotic prescribing. These factors may indeed explain some of the differences that exist between neighboring countries, such as between Belgium and The Netherlands [5]. Antibiotic resistance may spread across borders. Countries with a high prevalence of resistance may serve as a source of bacterial resistance for countries with low prevalence. Studies comparing consumption of antibiotics in different countries are therefore important, and the article by Patrick et al. [1] contributes to our understanding in this field. However, more knowledge about the background of these differences is needed to stem the increasing use of new antibiotics and the increasing prevalence of resistant microorganisms.

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False-Positive Results of *Aspergillus* Enzyme-Linked Immunosorbent Assays for a Patient with Gastrointestinal Graft-versus-Host Disease Taking a Nutrient Containing Soybean Protein

SIR—A direct double antibody sandwich ELISA (Platelia *Aspergillus;* BioRad) for galactomannan antigen has a sensitivity of 67%–100% and a specificity of 81%–99% for the diagnosis of invasive aspergillosis (IA) [1]. The mechanism of reported false-positive results remains to be clarified [2, 3]. We describe a patient who had consecutive positive galactomannan ELISA results without any signs of IA.

A 31-year-old woman with acute lymphoblastic leukemia underwent hemato-

poietic stem cell transplantation from an HLA-identical sibling in December 2003. She received busulfan and cyclophosphamide for conditioning, as well as cyclosporin and short-term methotrexate for graft-versus-host disease (GVHD) prophylaxis. Engraftment occurred on day 14 of transplantation. Diffuse erythema and diarrhea developed, and grade 3 acute GVHD was diagnosed after skin biopsy. We initiated methylprednisolone therapy (1 mg/kg) on day 20, to which GVHD gradually responded.

The patient had persistent appetite loss and taste disturbance. On day 44, we started giving the patient the liquid nutrient Racol (Otsuka Pharmaceutical; 200 mL q.d.), which contains the lowest amount of fiber among our formulary nutrients. Because acute GVHD that requires corticosteroid treatment is associated with a significant risk of IA, we monitored the galactomannan ELISA results, which were negative on day 24. On day 47, the optical density index (ODI) was >4.0 (normal value, <1.5) (figure 1). The patient had no fever or respiratory symptoms. Chest CT and blood culture results were negative.

We suspected that Racol was the culprit in the false-positive galactomannan ELISA results. After Racol was withheld for 3 days, the ODI decreased to 1.7. To identify the association, we administered Racol to the patient on day 66 and to a healthy control subject. The patient experienced a subsequent increase in the ODI, whereas the findings of serial monitoring examinations remained normal for the control subject. After the use of Racol was discontinued, the ODI normalized again in the patient. She never received herbal medicines or piperacillin-tazobactam, which is associated with a high rate of false-positive galactomannan antigen test results [4]. Racol and its constituents (i.e., soybean protein, lactic acid casein, maltodextrin, and water) were submitted to galactomannan ELISA testing. Racol, soybean protein, and lactic acid casein yielded positive results, with ODIs of >5.0, >5.0, and 4.8, respectively. Cultures of the products did not yield *Aspergillus* species.

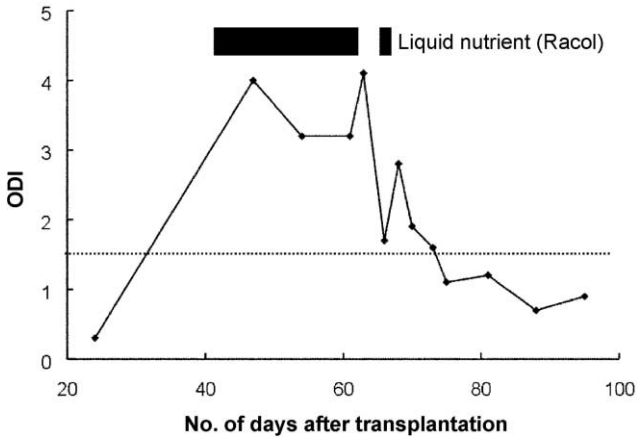

Figure 1. Optical density index (ODI) for galactomannan ELISA. The dotted line indicates an ODI of 1.5, which is the cutoff for the normal value. The thick black bar denotes the period during which Racol (Otsuka Pharmaceutical) was administered.

Galactomannan contained in soybean may have entered the patient's circulation, thus leading to the positive galactomannan ELISA result; however, galactomannan has high molecular weight (range, 0.3–4 million Da) and is not absorbed through an intact intestinal mucosa, as shown in our control subject. Galactomannan become digestible after hydrolysis by α-1,6-galactosidase and β-1,4-mannanase, which humans do not produce. The 2 possible ways to gain these enzymes are external supplementation and production by intestinal bacteria. Although experiments involving pigs have shown that the administration of the enzymes improved the digestibility of soybean meal [5], Racol is not supplemented with the enzymes. The other possibility is that the antibiotic treatments increased galactosidase- and mannanase-producing intestinal bacteria, such as *Bacteroides, Bifidobacterium,* and *Lactobacillus* species, to enable digestion of galactomannan.

The disrupted intestinal mucosal barrier secondary to GVHD in our patient may have contributed to the translocation of a larger amount of galactomannan-degraded products than in the control subject. Clinicians should be alert to the possible false-positive results of galactomannan ELISAs for patients with gastrointestinal GVHD who are taking nutrients containing soybean protein.

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