Correspondence

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Long-term efficacy after switch from protease inhibitor-containing highly active antiretroviral therapy to abacavir, lamivudine, and zidovudine

We present the extended follow-up of patients switching from protease inhibitor-containing therapy to abacavir/lamivudine/zidovudine. After median of 3.1 years, 16 virological failures occurred among 84 patients during 252 patient-years. The incidence of virological failure per 100 patient-years was 3.4 in patients without versus 13.5 in those with a history of zidovudine mono/dual therapy ($P = 0.008$). After achieving viral suppression, a switch to abacavir/lamivudine/zidovudine maintains long-term antiviral efficacy in patients without previous episodes of incomplete viral suppression on nucleoside analogues.

Several studies have shown that successful protease inhibitor (PI)-containing highly active antiretroviral therapy (HAART) can be switched to regimens containing efavirenz or nevirapine. Such a switch is associated with the continued control of viral replication and in some studies with higher adherence and an improvement in blood lipid levels. Similar data have also been generated for switching from a PI to abacavir, but continued viral suppression is only assured in patients who do not harbour archived resistance mutations against nucleoside analogue reverse transcriptase inhibitors (NRTI) [1,2]. All published switch studies had a maximum follow-up of 1.5 years, and therefore long-term data on the virological efficacy of this strategy are lacking. Because the triple NRTI combination abacavir/lamivudine/zidovudine has recently been shown to be inferior to efavirenz-containing regimens when used as initial therapy in treatment-naive patients [3], an assessment of its long-term efficacy is important for those patients who use it as maintenance therapy.

After closing our previous randomized trial that compared the continuation of a PI-containing HAART with the simplification to abacavir/lamivudine/zidovudine [1], patients in the simplified arm were offered to continue this treatment (except those with virological failure, and for logistic reasons all patients from Milan). Patients in the PI-containing arm were then also offered to switch if they had never received zidovudine mono or dual therapy before the initiation of HAART, in accordance with the conclusions of the study. In the extended part of the study, patients were prospectively monitored every 3 months in the first year, and thereafter every 3–6 months within the Swiss HIV Cohort Study. The study protocol was approved by all local ethics committees, and all patients gave written informed consent.

Patients were evaluated as long as they stayed on study medication (administered as Trizivir®, one tablet twice a day). The substitution of abacavir, lamivudine, or zidovudine with another NRTI (but not tenofovir) was permitted for toxicity reasons. Patients with suppressed HIV-1-RNA levels who underwent a scheduled treatment interruption or received another antiretroviral drug were censored at that time. Virological failure was defined as an HIV-1-RNA level greater than 400 copies/ml in two consecutive samples. Statistics were performed using GraphPad Prism version 4 for Windows (GraphPad Software, San Diego, CA, USA).

Out of the 84 patients of the original trial, 47 patients continued to take abacavir/lamivudine/zidovudine, contributing 122 additional patient-years of observation. The median follow-up for all 84 patients was 3.1 years (interquartile range 1.4–4.8 years). The baseline characteristics of patients with extended treatment did not differ from the entire group (Table 1). Twelve patients had virological failure during the original randomized part of the study (on treatment analysis). Four additional virological failures occurred during the extension phase, between 3.1 and 3.8 years after the original switch, without noticeable problems with adherence and without concurrent diseases. Nine patients underwent scheduled treatment interruptions, four patients changed their regimen for different reasons, and one patient died of anal carcinoma.

When patients were stratified by their exposure to zidovudine mono or dual therapy before the initiation of HAART, those without a history of zidovudine before HAART (group 1) failed virologically in 11% (6/53), whereas 32% of patients (10/31) with zidovudine before HAART (group 2) failed. The incidence of virological failure was 3.4 per 100 patient-years in group 1 versus 13.5 per 100 patient-years in group 2 ($P = 0.008$). The Kaplan–Meier proportional estimates of virological failure in group 1 were 5.7% after one year, 7.8% after 3 years, and 14.5% after 5 years.

When patients with virological failure were compared with those without, the overall duration of antiretroviral therapy (median 2.8 versus 1.7 years, $P = 0.006$) and

Table 1. Demographic data at time of switch from protease inhibitor-containing highly active antiretroviral therapy to abacavir/lamivudine/zidovudine and virological outcome.

	ABC/3TC/ZDV in the original trial		
	All, including extended follow-up (N = 84)	Subgroup with extended follow-up (N = 47)	Original PI arm, then switch to ABC/3TC/ZDV (N = 28)
Male sex – no. (%)	66 (80%)	38 (81%)	23 (82%)
HIV risk factor – no. (%)			
Homosexual activity	43 (51%)	28 (60%)	18 (64%)
Heterosexual activity	18 (21%)	11 (23%)	6 (21%)
Intravenous drug use	21 (25%)	7 (15%)	4 (14%)
Blood products or undetermined	2 (2%)	1 (2%)	0
Age, median – years (IQR)	38 (34–47)	39 (34–47)	40 (37–51)
Duration of suppressed HIV-1 RNA, median – years (IQR)	1.1 (0.8–1.4)	1.2 (0.8–1.5)	2.9 (2.6–3.3)
Previous therapy, median – years (IQR)			
ART total duration	1.8 (1.3–2.5)	1.6 (1.3–2.4)	3.5 (3.0–3.8)
PI-containing ART	1.5 (1.2–1.9)	1.5 (1.2–1.7)	3.5 (2.9–3.8)
NRTI before start of PI – no. (%)			
Any NRTI	35 (42%)	15 (32%)	0
Including ZDV	31 (37%)	12 (26%)	0
Including 3TC (all with previous ZDV)	13 (15%)	3 (6%)	0
CD4 lymphocytes – cells/mm^3, median (IQR)	512 (345–778)	448 (314–696)	636 (501–851)
Duration of follow-up			
Median – years (IQR)	3.1 (1.4–4.8)	4.6 (3.4–5.1)	3.0 (1.8–3.3)
Total patient-years	252	204	71
Virological failures – no. (%)	16/84 (19.0%)	5/47 (10.6%)	0
No previous ZDV mono/dual therapy[a]	6/53 (11.3%)	3/35 (8.6%)	0
History of ZDV mono/dual therapy[a]	10/31 (32.3%)	2/12 (16.7%)	No such patients

ABC, Abacavir; ART, antiretroviral therapy; IQR, interquartile range; NRTI, nucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; 3TC, lamivudine; ZDV, zidovudine.
[a]Stratification based on history of ZDV mono/dual nucleoside analogue therapy.

the duration of NRTI therapy before the initiation of HAART (median 0.8 versus 0 years, $P = 0.033$) were significantly longer in patients who failed, but other baseline parameters did not differ, such as sex, risk group, AIDS stage, CD4 lymphocytes at nadir or at the time of switch, or highest HIV-1-RNA level, duration of HAART, or duration of suppressed viraemia before the switch.

After a median of 1.7 years in the original PI-containing arm and with continued viral suppression, 28 patients without a history of zidovudine before HAART switched to abacavir/lamivudine/zidovudine at the end of the original trial (group 3). No virological failure occurred among them during a median of 2.1 years after this switch. Seven out of 28 decided to undergo a scheduled treatment interruption, and two changed the treatment regimen as a result of toxicity (including one case of abacavir hypersensitivity); these patients were censored at the time they stopped study medication. When groups 1 and 3 were combined, the incidence of virological failure was 2.45 per 100 patient-years (95% Poisson confidence interval 0.90–5.33 per 100 patient-years).

This prospective long-term follow-up of patients on triple NRTI maintenance extends the validity of our original randomized trial and other studies for a median duration of over 3 years. Patients who must be assumed to harbour archived resistance mutations against NRTI, approximated in our trial as having had previous zidovudine-containing mono or dual NRTI therapy, have a high risk of virological failure with this strategy [1,2]. On the other hand, a switch to abacavir/lamivudine/zidovudine maintains viral suppression in patients never exposed to zidovudine mono or dual therapy, and the incidence of virological failure of 2.5% in our combined groups 1 and 3 compares favourably with that of approximately 5% per year observed with the best reported HAART regimens that have a prolonged duration of follow-up [2,4,5]. The strategy of switching only those patients who are unlikely to harbour NRTI resistance mutations has been validated by the results of group 3 in a prospective way. Maintenance with abacavir/lamivudine/zidovudine holds the advantages of preserving other classes of antiretroviral drugs that will thus be available for second-line treatment, to lower blood lipids [1,2], and to be cost effective and simple to administer. Furthermore, a switch to abacavir/lamivudine/zidovudine after the body viral load has been dramatically reduced seems to represent a different situation than its use for treatment of a fully productive HIV infection.

Milos Opravil[a], Doris Baumann[a], Jean-Philippe Chave[b], Hansjakob Furrer[c], Alexandra Calmy[d], Enos Bernasconi[f], Monika Blasko[e], Pietro Vernazza[g], Bruno Ledergerber[a], Luc Perrin[d], and the Swiss HIV Cohort Study, *[a]Division of Infectious Diseases, University Hospital, Zurich, Switzerland; [b]Private practice, Lausanne, Switzerland; Divisions of Infectious Diseases, University Hospitals, [c]Bern, [d]Geneva and [e]Basel, Switzerland; and Divisions of Infectious Diseases, Cantonal Hospitals, [f]Lugano and [g]St Gallen, Switzerland.*

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Reactive iris lymphoid proliferation presenting as the AIDS-defining event in an HIV patient with systemic lymphoma

A 54-year-old man presented with a 2-week history of left eye pain, redness and blurred vision, 2 years after cataract surgery that was complicated by retinal detachment. His left eye examination revealed 20/400 vision and anterior granulomatous uveitis with mild hypopyon. The iris pattern was normal. Vitreous cells were absent and fundus was normal. His right eye was normal.

Low-grade postoperative endophthalmitis was suspected, and intravitreal vancomycin was given after performing vitreous tap. Vitreous culture grew coagulase negative *Staphylococcus* on blood and chocolate agar. He improved symptomatically on topical and systemic antibiotics, but developed increasing hypopyon with thickened nodular iris (Fig. 1), confirmed by ultrasound biomicroscopy. The posterior segment remained uninvolved. Vitreous culture repeated a month later was negative for microorganisms. He had no constitutional symptoms and was otherwise well. He was started on prednisolone 60 mg a day.

A week later he was admitted for high fever, dysuria and mild right-sided loin pain with persisting ocular symptoms. It was at this stage that he revealed that he had been treated for a sexually transmitted disease 5 years earlier. Systemic examination showed diffuse maculopapular rash, small cervical lymphadenopathy and penile warts. Investigations revealed normocytic normochromic anemia, lymphocytosis and reactive lymphocytes with an absolute CD4 cell count of 150

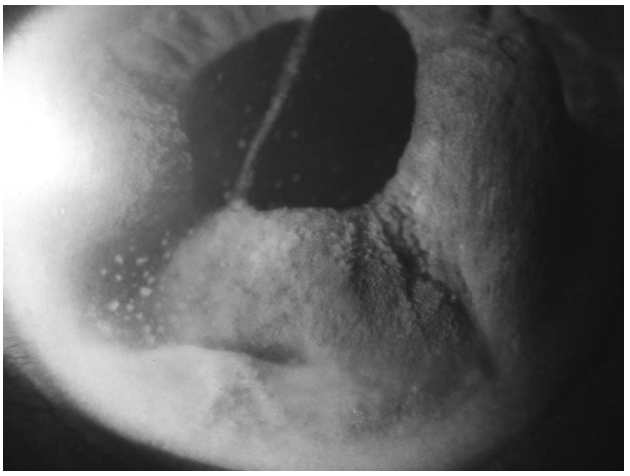

Fig. 1. Left eye shows mutton fat keratic precipitates and hypopyon with thickened nodular iris.

cells/μl, reactive *Treponema pallidum* hemagglutination antibody and HIV seropositivity. Computed tomography (CT) of the abdomen demonstrated right hydronephrosis with mild dilation of the ureter but no lymphadenopathy. Investigations for tuberculosis or other secondary infections were negative.

In view of unrelenting anterior uveitis and systemic illness, an iris biopsy was obtained, which revealed intense lymphoid infiltration, a few prominent nucleoli and a single mitosis. Microdissection of the iris tissue did not verify IgH gene rearrangement, and was negative for Epstein–Barr virus by polymerase chain reaction. Immunohistochemical markers for lymphoid cells could not be interpreted because of heavy iris pigmentation. Meanwhile, he developed dysphagia as a result of esophageal candidiasis. He was treated empirically with systemic vancomycin and nystatin and his fever resolved.

Two days later, he developed sudden painless loss of vision to no light perception in his right eye and counting fingers in his left eye. A right afferent pupillary defect and partial left sixth nerve palsy were noted. CT and magnetic resonance imaging of the brain and orbit were normal. In view of the rapid worsening of vision and ocular findings, the patient underwent another round of comprehensive systemic examination. A right iliac fossa mass was palpable at this stage. A repeat CT of the abdomen and pelvis showed a circumferential mass around the sigmoid colon involving the right ureter. Diagnostic colonoscopy biopsy revealed a high grade, diffuse, large B-cell malignant non-Hodgkin's lymphoma. Urine cytology detected highly atypical lymphocytes but no malignant cells. Immunophenotyping of the cerebrospinal fluid established lymphoproliferation; however, no evidence of central nervous system lymphoma was found. Bone marrow aspirate and trephine biopsy were suggestive of reactive marrow but negative for malignancy. In view of the cerebrospinal fluid findings and normal magnetic resonance imaging scan, ocular signs were attributed to infiltrative optic neuropathy or basal meningitis. Although chemotherapy and intrathecal methotrexate resulted in marginal visual improvement, iris infiltration resolved completely. Despite the institution of highly active antiretroviral therapy the patient died. The patient's next of kin did not consent to autopsy.

Lymphomas are increasingly common cancers in HIV patients, although with dismal survival despite therapy. Most HIV-related lymphomas occur at an advanced stage of immunosuppression. In 3.2% of patients, HIV-related lymphoma is the AIDS-defining event in the era of highly active antiretrovital therapy [1,2] The incidence of AIDS-associated non-Hodgkin's lymphoma is reported to be 10–20%, but the eye is seldom the primary site of presentation of systemic lymphoma [3]. Anterior segment intraocular lymphoma in the presence of a normal fundus is even rarer [4]. Our patient masqueraded as having chronic postoperative endophthalmitis (two positive solid media cultures), with features of severe anterior uveitis, iris lymphoid proliferation, leading to a diagnosis of HIV as well as AIDS-related systemic lymphoma. This, to the best of our knowledge, is the first such reported case in the literature.

Ranjana Mathur[a,b], Wee-Kiak Lim[a,b], Chi-Chao Chan[d] and Soon-Phaik Chee[a,b,c], *[a]Singapore National Eye Centre, Singapore; [b]Singapore Eye Research Institute, Singapore; [c]National University of Singapore, Singapore; and [d]National Eye Institute, National Institutes of Health, MD, USA.*

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HIV treatment optimism and high-risk sexual behaviour among gay men: the attributable population risk.

Stolte *et al.* [1] examined the relationship between HIV treatment optimism and high-risk sexual behaviour in a cohort of 146 gay men in Amsterdam whom they interviewed every 6 months for 2.5 years. The strength of their investigation is that they were able to monitor changes in sexual behaviour at an individual level in relation to beliefs about new treatments recorded before the change occurred. Consequently, they were in a position to consider cause and effect.

They found that most men in the cohort were quite realistic about highly active antiretroviral therapy

(HAART). Only a minority were optimistic, as reported in a number of other studies [2–6]. However, perceiving HIV or AIDS to be less of a threat in the light of new treatments predicted a change to high-risk behaviour over the following 6 months. The associated odds ratio was 1.60 [95% confidence interval (CI) 1.16, 2.22]. The authors wrote 'although causality is difficult to establish even with longitudinal data, the findings in this study are supportive of the hypotheses that perceiving less HIV/AIDS threat since HAART is a cause of the change to high risk behaviour'. They concluded that the decreased threat of HIV/AIDS since the advent of HAART explains at least part of the increase in risk behaviour and sexually transmitted diseases seen at the population level among gay men since HAART became available.

Their paper marks an important advance. The odds ratio derived from this longitudinal study allows us to estimate, at a population level, how much of the increase in high-risk behaviour can be attributed to HIV treatment optimism. We can do this using standard epidemiological methods that estimate the proportion of the total population risk that is attributable to a given factor (known as the 'population attributable risk') [7]. The population attributable risk (AR) is a function of both the proportion of the population with the factor as well as the relative risk (or odds ratio) associated with that factor. The population AR is calculated using the formula: $AR = [p\,(RR - 1)]/[p\,(RR - 1) + 1]$, where p equals the proportion of the population with the factor and RR is the relative risk associated with the factor.

In the Amsterdam study, the authors gave median scores for optimism rather than percentages. However, inspection of the median scores suggests that between 15 and 25% of men in their study could be classified as optimistic (i.e. they scored 5, 6 or 7 on the 'perceiving less HIV/AIDS threat' scale) as has been reported elsewhere [2–6]. In the Amsterdam cohort, optimistic men were 1.6 times more likely to switch to high-risk sexual behaviour than other men. Using these estimates for p (15%) and the RR (1.6), the population AR works out to be 8% $[0.15\,(1.6 - 1)/0.15\,(1.6 - 1) + 1]$ with a 95% CI of 2–15%. In other words, 8% of the change to high-risk behaviour in the Amsterdam cohort can be explained by HIV treatment optimism when 15% of the men are optimistic. The remaining 92% of the change can not be explained in this way. Increasing the proportion who are optimistic from 15 to 25% increases the population AR from 8 to 13% (95% CI 4–23%). Nearly 90% of the change in risk still remains unexplained.

The longitudinal study by Stolte *et al.* [1] demonstrates that, even when a causal association exists, the contribution of HIV treatment optimism to the overall increase in high-risk sexual behaviour remains extremely modest at a population level. This is not entirely surprising. Numerous studies have demonstrated that only a minority of gay men are optimistic in the light of HAART [2–6]. This low proportion exerts a strong influence on the magnitude of the population AR [7]. It appears, therefore, that the findings from the Amsterdam cohort study do not differ substantially from those recently reported in London [8], Glasgow [9] and Sydney (P. Rawthorne, personal communication) based on behavioural surveillance time series data. Namely, that at a population level, HIV optimism is unlikely to explain the recent increase in high-risk sexual behaviour among gay men. Regardless of this debate, we all agree that priority should now be given to research that helps us better understand the factors that underlie high-risk sexual behaviour among gay and bisexual men at risk of HIV infection.

Jonathan Elford, *City University, Institute of Health Sciences, St Bartholomew School of Nursing and Midwifery, 24 Chiswell Street, London EC1Y 4TY, UK.*

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Cryptococcosis in HIV-infected individuals

We read with interest the recent article by Dromer *et al*. [1] on behalf of the French Cryptococcus Study Group on the Epidemiology of HIV-associated cryptococcosis in France (1985–2001). The authors found that in the era after the introduction of highly active antiretroviral therapy (HAART) (1997–2001) being of African origin, older age, heterosexual risk, no previous HIV diagnosis or AIDS-defining illness were predictors of cryptococcosis. We now report on our experience with cryptococcosis in HIV-infected patients admitted in the HAART era to Cook County Hospital, Chicago, USA, a large urban, public hospital, which serves mostly uninsured, ethnic minorities. In the HAART era we continue to have an active inpatient HIV service with approximately 800–900 admissions per year. A prospective observational database that captures demographic and clinical information on all HIV-infected individuals admitted to the HIV service was established in September 1999.

All patients with cryptococcosis between September 1999 and July 2002 were identified from the database and included in this analysis. Of 1562 patients (2736 admissions), 37 patients (65 admissions) were admitted for cryptococcosis. Cryptococcosis was defined as the detection of cryptococcal antigen from serum or the cerebrospinal fluid, or a positive culture for *Cryptococcus neoformans* from the cerebrospinal fluid, blood or bronchoscopy specimens.

The incidence of cryptococcosis as an admission diagnosis over time was as follows: August 1999–June 2000 9/853 (1.05%); July 2000–June 2001 13/939 (1.4%); July 2001–July 2002 15/924 (1.6%). Data on all the patients, stratified by cryptococcal antigen status, are presented in Table 1.

Our study population differed from the French study [1] in two aspects, first we looked at hospitalized HIV patients with similar access to care in a different geographical area (Chicago), and second our study population was mostly African American.

Table 1. Demographic and clinical characteristics of 1562 HIV-infected individuals admitted to the Cook County Hospital HIV service, September 1999-July 2002, stratified by cryptococcal antigen status.

Characteristic	HIV-infected patients CRAG-positive ($N = 37$)	HIV-infected patients CRAG-negative ($N = 1525$)
Male sex (%)	31 (84%)	1098 (72%)*
Mean age, years (± 2SD)	40 (8.3)	41 (8.2)
Race		
African American	28 (76%)	1220 (80%)
Hispanic	9 (24%)	183 (12%)
Caucasian		122 (8%)
HIV risk group (%)		
IDU	10 (27%)	656 (43%)
MSM	6 (15%)	229 (15%)
Heterosexual	14 (38%)	305 (20%)*
Unknown/not documented	7 (20%)	335 (22%)
Substance abuse	52%	67%
Mean/median CD4 cell count	50/20	199/105*
CD4 cell count < 50 cells/mm^3	64%	37%*
HIV RNA > 50 000 copies/ml	92%	65%*
Number on HAART (%) (self report)	17 (46%)	763 (43%)
New HIV diagnosis (%)	11 (30%)	198 (13%)
Cryptococcosis diagnosed		
Positive antigen test	37 (100%)	
(Serum ± CSF)	(1 : 2–1 : > 8192)	
Positive blood culture	10 (27%)	
Positive CSF culture	17 (46%)	
Positive bronchial culture	2 (5%)	
Meningitis/fungemia	35 (95%)	
Pneumonia	2 (5%)	
Treatment (first 2 weeks)		
Amphotericin + flucytosine	15 (41%)	
Amphotericin	19 (51%)	
Fluconazole	3 (8 %)	
Mortality	3 (8 %)	20 (1.3%)

*P values < 0.05.

CRAG, Cryptococcal antigen; CSF, cerebrospinal fluid; HAART, highly active antiretroviral therapy; IDU, injection drug users; MSM, men who have sex with men.

As in the study by Dromer *et al.* [1], most patients with cryptococcosis were men and had advanced HIV disease. Cryptococcosis was the initial HIV presentation in 30% of our study group as in their study. Most patients with cryptococcosis were African American, but we were unable to find the association between African American race and cryptococcosis that was found in the French study and a large USA study by Mirza *et al.* [2]. This is probably caused by the fact that 80% of our entire cohort was African American.

We found that 46% of the patients reported being on HAART at the time of the first admission for cryptococcosis; 24 (65%) had been seen at the outpatient HIV clinic within 6 months before admission, but the median CD4 cell count on admission was only 20 cells/mm^3. The high percentage of patients with self-reported use of HAART with active cryptococcosis suggests either an ineffective HAART regimen, lack of adherence, or patients receiving HAART only a minimal duration of time before their presentation with cryptococcosis. It is also known that cryptococcosis can induce or increase CD4 lymphopenia and could have contributed to the lymphopenia.

Morbidity from cryptococcosis was significant in our population as 43% of patients were admitted two or more times; five (14%) were discharged to a skilled nursing/rehabilitation facility; and two lost their eyesight. We observed a mortality rate of 8%, which is similar to the 11% mortality reported by Mirza *et al.* [2].

Outpatient follow-up information was available for 20 patients, with a median duration of 12 months after hospital discharge (5–39 months). The median CD4 cell count was 75 cells/mm^3 (3–273) and nine (45%) of 20 had viral loads less than 1000 copies/ml.

In conclusion, we found that a low but steady percentage of our HIV-infected patients continued to present with cryptococcosis in the HAART era. All patients were from ethnic minorities, most were heterosexual and although most cases occurred in African Americans, we are unable to make any associations between cryptococcosis and ethnicity, because our entire cohort was 80% African American.

Patients had advanced HIV disease that was newly diagnosed in a third of the patients, and many of our patients reported HAART use, suggesting inadequate response or more likely non-adherence to therapy. These findings emphasize the need for more prevention and testing programmes in ethnic minorities, especially in heterosexuals who may not consider themselves at risk, and the need for improved efforts on adherence counseling to patients initiating HAART.

Oluwatoyin M Adeyemi[a,b], Joseph Pulvirenti[a,b], Sindhu Perumal[a], Uma Mupiddi[a], Becky Kohl[a] and Todd Jezisek[a], *[a]Section of Infectious Diseases, Department of Medicine, Cook County Hospital, Chicago, IL, USA; and [b]Rush Medical College, Chicago, IL, USA.*

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