

cines and the template described in Anderson and Hanson [2].

Blower falsely claims (e.g., see [3], p. 118) that her 1993 and 1994 articles included, to quote, “the first transmission model of HIV vaccines to assess the potential epidemic-level impact of imperfect vaccines.” This is incorrect—the 1991 *Nature* article by Anderson et al. was the first.

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### Breakthrough Zygomycosis and Voriconazole

**To the Editor**—Zygomycosis is an invasive fungal infection caused by various members of the class Mucorales and usually occurs in patients with ketoacidotic diabetes or hematological disorders. It most commonly occurs in patients with acute leukemia or lymphoma who develop neutropenia as a result of malignancy or chemotherapy and in transplant recipients receiving immunosuppressive treatment [1].

Recently, some reports have suggested an increase in the incidence of zygomycosis in association with prophylactic voriconazole (VRC) use in immunosup-

pressed patients [2–5]. In a recent article, Kontoyiannis et al. reported the results of an observational matched case-control study comparing consecutive patients with zygomycosis and 2 control groups, patients without an invasive mold infection and patients with invasive aspergillosis [6]. The authors identified 27 patients with zygomycosis; 13 (48%) of them had received previous VRC prophylaxis. In a multivariate analysis comparing the patients with zygomycosis and the patients without an invasive mold infection, VRC prophylaxis, diabetes, and malnutrition were found to be independent risk factors for zygomycosis. When the patients with zygomycosis and the patients with invasive aspergillosis were compared, VRC prophylaxis was found to be the most relevant factor favoring the onset of zygomycosis. Kontoyiannis et al. suggest that the increased incidence of zygomycosis might reflect the increasing and prolonged use of oral VRC versus parenteral agents with activity against Zygomycetes. However, it is important to determine whether the increased incidence of zygomycosis is due solely to an increase in oral VRC use or can also be attributed to improvement of the tools of diagnosis and to increased attention to this infection by physicians.

Certainly, an increase in breakthrough infections by opportunistic pathogens is a concern with any antimicrobial agent—VRC is no exception—and it is true that the increased incidence of zygomycosis stands in contrast to the previous breakthrough infections seen when fluconazole or itraconazole were used for prophylaxis [7, 8]. However, an increase in the incidence of zygomycosis over the past 20 years has already been described [9].

In a multicenter retrospective survey conducted over a 15-year period (1987–2001) by Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA), 59 cases of proven or probable mucormycosis in patients with hematological malignancies were registered [1]. It is

noteworthy that 47 (80%) of the 59 patients had received oral antifungal prophylaxis, 35 (59%) of whom had received azole compounds (18 fluconazole, 15 itraconazole, and 2 ketoconazole); none of these patients had received VRC. In addition, in a study by Larkin and Montero in which all cases of zygomycosis in the Collaborative Exchange of Antifungal Research database were analyzed, 13 (23%) of 64 patients with zygomycosis had previously received fluconazole [10]. In an overview of case reports by Gleissner et al., data on previous antifungal prophylaxis were reported for only 12 of 120 patients with zygomycosis and underlying hematological disorders [11]. Prophylaxis with azoles was noted in 7 (58%) of the 12 patients (3 itraconazole, 3 fluconazole, and 1 ketoconazole).

These data suggest that breakthrough zygomycosis could occur with all prophylactic azoles that do not have activity against Zygomycetes. In our opinion, improved diagnostic tools play an important role in the increased incidence of this fungal complication. Finally, we completely agree with Kauffman, who has suggested in an editorial to wait for the results of a blinded, multicenter trial comparing VRC and fluconazole for prophylaxis in patients with hematological disorders before reconsidering the prophylactic use of VRC [4, 5].

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## Reply to Pagano et al.

**To the Editor**—I thank Pagano et al. for their interest in our work [1]. I agree that the increase in the incidence of zygomycosis preceded the introduction of voriconazole (VRC), as my colleagues and I have previously reported [2]. However, I disagree that the increase in reported cases of zygomycosis resulted from the reasons Pagano et al. have set forth. First, I am not aware of any improvement in diagnostic tools specific for the detection of

Zygomycetes that have been widely implemented in clinics during the last decade. Such improvement would be most welcome, given that the yield of conventional culture methods is suboptimal and that early diagnostic markers by which infection with Zygomycetes and infections with other, more common opportunistic molds can be differentiated are not available [3]. Second, I take issue with the assertion that the increase in the number of reported cases of zygomycosis is largely an artifact of an increased awareness of this infection, for the very reasons stated above. The clinical presentation of zygomycosis is frequently indistinguishable from that of aspergillosis, and a definitive diagnosis is often made only via tissue biopsy [4]. In addition to several case series from single institutions reporting an increase in breakthrough zygomycosis in patients receiving VRC during the last 2 years, a recent multicenter prospective surveillance study in transplant recipients has also documented an association between zygomycosis and previous VRC use [5]. I believe that all patients with continuous and intense immunosuppression are at high risk for breakthrough fungal infection, irrespective of the antifungal used. In our study, diabetes mellitus, malnutrition (serum albumin level of  $\leq 3$  g/dL), and VRC use were found to be independent risk factors (along with an initial presentation of sinusitis) that favored an eventual diagnosis of zygomycosis over aspergillosis in our high-risk patient population [6]. Because zygomycosis is uniformly fatal if not accurately diagnosed early, I feel that it is critical for clinicians who are caring for highly immunosuppressed patients to recognize the risk factors associated with breakthrough infections with this multiantifungal-resistant mold. I agree that future prospective studies will help to clarify the roles played by the complex and often interrelated factors that contribute to the epidemiology of zygomycosis in highly immunosuppressed patients with cancer.

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## Questioning Wawer et al.'s Estimated Rate of Sexual HIV Transmission from Persons with Early HIV Infections

**To the Editor**—Wawer et al. [1] use data from a prospective study of HIV incidence in Rakai, Uganda, to estimate rates of HIV transmission per coital act between HIV-discordant heterosexual partners, according to the stage of infection in the index