To the Editor—We thank DiNubile [1] for the response to our article, and we agree that our data demonstrate that a 2-day staggered discontinuation of treatment with nonnucleoside reverse transcriptase inhibitors (NNRTIs), compared with other components of a multidrug antiretroviral therapy regimen, is not sufficient to completely protect against the development of NNRTI resistance. Two alternative approaches have been suggested to protect against NNRTI resistance when treatment discontinuation can be anticipated: substitution of the NNRTI component of the regimen with a drug from another class, such as a protease inhibitor (as suggested by DiNubile [1]), or staggered discontinuation for a longer period. In a report from the Development of Antiretroviral Therapy in Africa Trial, which is being conducted in Uganda and Zimbabwe, the median times to reach thresholds of 200, 100, and 20 ng/mL (limit of detection) of nevirapine were estimated to be 7.6, 9.3, and 13.2 days, respectively. The investigators concluded that continuation of nucleoside reverse-transcriptase inhibitor treatment for 7–10 days after nevirapine treatment discontinuation may be reasonable to prevent NNRTI resistance in this population [2].

As DiNubile [1] indicated, certain human genetic polymorphisms have been associated with slower clearance of NNRTIs, which might further increase the risk of NNRTI resistance after NNRTI therapy discontinuation. Among our study population, we identified the following variants: CYP2B6 516G→T, ABCB1 (also called MDR1) 2677G→T/A, and ABCB1 3435C→T. We found no association between the development of NNRTI resistance and the presence of allelic variants of either CYP2B6 or ABCB1. This was somewhat unexpected, because CYP2B6 516G→T has been associated with increased steady-state plasma exposure during efavirenz and nevirapine therapy [3–5], and a previous report suggested that ABCB1 position 3435 TT homozygosity was associated with a decreased likelihood of NNRTI resistance during failure of efavirenz-containing regimens [4]. However, the small sample size in the present study may have limited our ability to detect such associations, if present.

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Mycobacterial Disease Attributable to Tumor Necrosis Factor-α Blockers

To the Editor—I read with interest the editorial by Iseman and Fisher [1]. The editorial commented on an article by Winthrop et al. [2], which described the changing epidemiology of tuberculosis and nontuberculous mycobacterial (NTM) disease that is attributable to biologic therapies. Although I agree with regard to the importance of this question, I am concerned that the “broad-brush” comments obscure important differences between drugs and infections.

First, there is no question that patients receiving anti–TNF-α antibodies infliximab and adalimumab experience a greater risk of tuberculosis (TB), compared with patients receiving the soluble TNF-α receptor etanercept (table 1). This is evident across multiple studies that were conducted in the United States and Europe with use of a variety of methods for data collection [15]. The US Food and Drug Administration clearly agrees with this assessment, judging by the language used in the etanercept package insert [16].

The importance of this finding is magnified by the observation that patients experienced a shorter time to TB onset after start of treatment with infliximab than did patients who received etanercept (16 vs. 60 weeks; among 429 patients) [15]. These are important clues with regard to the etiology of TB, because cases considered to be TB reactivation would be expected to cluster shortly after the start of anti–TNF-α therapy. I have used hidden Markov models to examine this question [17]. Such models include state transitions that cannot be directly observed but that are instead deduced from observable phenomena. The modeling exercise revealed (1) that the monthly risk of TB reactivation for patients receiving infliximab was >12 times that for patients receiving etanercept but (2) that patients receiving the 2 drugs experienced equally high risks of progression of new infection to disease. This observation has been confirmed by a study in mice, which found that although both anti–TNF-α antibody and soluble TNF-α receptor had deleterious effects on acute TB infection, only the antibody caused deterioration in mice with chronic infection [18]. Chronic TB infection in the mouse is thought to model latent human infection, because colony-forming unit counts are stable and survival is unimpaired. The lack of effect of soluble TNF-α receptor on established granulo-