Correspondence

Investigating New Antiretroviral Combinations

To the Editor—Kuritzkes, in his commentary on the study by Gallant et al. [1], suggests that overlapping barriers to resistance may have been responsible for the extremely high rates of virological failure observed with an antiretroviral regimen comprising tenofovir, lamivudine, and abacavir [2]. These overlapping resistance pathways were thought to be possible, however, before the study began [3].

I agree with Kuritzkes that randomized trials should precede the use of an untried antiretroviral combination in clinical practice. I would, however, take this approach a step further. I believe that a more ethical approach is to undertake at least 1 small pilot study before such a randomized trial, to determine whether it is reasonable, on safety and efficacy grounds, to expose a much larger number of subjects (171 in the present trial) to such a combination, especially when existing data suggest that a regimen might be virologically inadequate. There is a long precedent for this approach; for example, drug-interaction studies precede a regulatory agency’s recommendation that an antiretroviral drug and a commonly prescribed drug, such as an antibiotic, antidepressant, or statin, can be coadministered. Alternatively, a large study should have a pilot phase in which the short-term outcomes in 20–30 subjects are analyzed before further recruitment. Use of either of these approaches in the study by Gallant et al. may well have spared ~150 patients from substandard treatment and spared many of those from acquiring permanently drug-resistant HIV.

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References

Reply to Carr

To the Editor—we concur with Carr [1] that caution is warranted in designing large clinical trials and that pilot studies may be more appropriate in settings in which supportive data are unavailable. At the time when our study of tenofovir, abacavir, and lamivudine was designed and conducted [2], clinical data were accruing on combinations of abacavir and lamivudine with several third agents that had diverse patterns of and barriers to resistance [3–8]. Tenofovir had demonstrated potency both as short-term monotherapy without selection for the K65R mutation and (with lamivudine) as a nucleoside backbone in antiretroviral-naive subjects [9, 10]. Furthermore, neither pharmacokinetic nor virologic data precluded the use of tenofovir, abacavir, and lamivudine together, and there was no evidence of or plausible reason to expect antagonism or negative interactions among these agents.

Although pilot studies may sometimes help to protect patients from participation in larger studies that ultimately fail, they may also allow flawed or equivocal conclusions to be drawn from underpowered data. These studies may then discourage delay either the conduct or recruitment of the large, definitive studies that should be used to guide practice. During the conduct of our study, the combination of tenofovir, abacavir, and lamivudine was already being utilized in clinical practice. The rapid identification of a virologic nonresponse signal in our study, public dissemination of these results, and prompt protocol management minimized negative outcomes for many study participants and prevented further use of this regimen outside of our study by clinicians worldwide. A pilot study might not have had the same broad impact, considering the ready availability of all 3 regimen components and the theoretical attractiveness of the regimen. Moreover, a smaller, pilot study might have failed to detect a problem with this regimen, had the decreased efficacy been less dramatic than it turned out to be.

Carr correctly notes that the overlapping resistance profiles of the drugs used in this regimen were understood before the study was begun. However, as Kuritzkes points out in his editorial commentary accompanying our article [11], the reason for virologic nonresponse while receiving this regimen is still not understood and may be unrelated to the low genetic barrier to resistance. Only 54% of patients with therapy failure had K65R detectable by population sequencing; this would have been expected in virtually 100% of patients if resistance had been the cause of failure. Moreover, the relationship between treatment efficacy and the genetic
barrier to resistance is not straightforward, as is evidenced by the success of the combinations of efavirenz plus either lamivudine or emtricitabine plus either abacavir or tenofovir disoproxil fumarate [6, 7, 10, 12], which have demonstrated outstanding efficacy despite the fact that resistance to each drug requires only a single mutation.

There are several key findings from our experience that should inform future trials. First, pilot studies should be considered, especially when no data are available or for studies of novel paradigms. Second, active clinical oversight and vigilance, without compromising study integrity, is essential. This includes oversight at the level of the investigator, sponsor, and/or central coordinating center or, in some instances, by an independent data-monitoring committee. Finally, rapid dissemination of study results, both positive and negative, and timely implementation of protocol amendments to ensure subject safety are critical for maintaining the trust of our subjects, investigators, and the patient and research communities.

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References

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No Role for Thalidomide in the Treatment of Leprosy

To the Editor—Haslett et al.’s assertion [1] that thalidomide is the drug of choice for treatment of erythema nodosum lepromatous (ENL) is not supported by the World Health Organization (WHO). Indeed, the WHO recommends that the drug no longer be used in the management of this complication of leprosy [2]. The WHO’s conclusion is based on the fact that ENL is not a serious complication, thus confirming my own observations made >30 years ago [3]. When the US Food and Drug Administration considered approving thalidomide as treatment for ENL, no evidence was produced that thalidomide is the drug of choice for treating ENL.

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that ENL could cause “neuritis, iritis and nephritis,” as Haslett et al. claim [4].

Presumably, both the patients with ENL and the control subjects in Haslett’s study were receiving multidrug therapy (MDT). The presence of clofazimine, which has an anti-inflammatory action, in the MDT regimen has reduced the frequency and severity of ENL [2]. Small doses of prednisone can also be used. It is not mentioned whether any ENL lesions were “blistered, pustular or had ulcerated,” but lowering the dose of dapsone can reduce the severity of these complications [3]. There is little risk of dapsone resistance, since most patients with ENL have masses of dead bacteria. Therefore, recording the percentage of nonviable bacteria by use of the morphological index would be more revealing than recording it by use of the bacillary index (BI). Fifteen of the 20 patients had a BI >3, which may give the impression that the disease is still active. Because ENL is a very chronic condition, any treatment has to be prolonged. If treatment with thalidomide is continued over a longer period, there is a danger of neuropathy occurring that can be severe and irreversible [5]. Although not a single case of neuropathy has been recorded in a patient with leprosy who has been given the drug [6], the frequency of nerve damage in patients with nonleprosy disorders is at least 21% [7]. In patients with multiple myeloma who are treated with thalidomide, the frequency of neuropathy varies between 50% and 80% [8]. Fortunately, new cases of leprosy and, hence, new cases of ENL are declining very rapidly [9, 10], and so there is even less need for thalidomide to be used.

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References

Reply to Crawford
To the Editor—Crawford [1] rejects our assertion [2] that thalidomide is the treatment of choice for erythema nodosum lepromatous (ENL), arguing that prednisone and clofazimine are sufficient and relatively safe treatments for acute and chronic ENL, respectively. Indeed, he is correct in pointing out that the World Health Organization holds the same view, one that weighs the potential benefits of thalidomide against the very real concern of widespread treatment with this agent in settings where its use cannot be effectively controlled. However, our intent in our study was not merely to support the data showing that thalidomide is an effective therapy for ENL, as it is in a wide range of other diseases caused by destructive immunopathologic processes. Rather, our investigation was an attempt to use the dramatic efficacy of thalidomide in ENL as a tool to provide insights into the immunopathogenesis of this poorly understood condition, as well as into the mechanisms of action of thalidomide.

Crawford also argues that there is no evidence that ENL is associated with iritis, neviritis, or neuritis. We suggest that patchy ascertainment in the field may have resulted in the inconsistent observation of these complications, which have, nonetheless, been extensively reported [3–9]. It is also possible that the severity of lepra reactions may vary by geographic region as a result of genetic and/or environmental factors. For example, the Lucio phenomenon, a poorly defined ulcerating reactional state that complicates lepromatous leprosy, is common in Mexico but is rarely observed in other parts of the world [10]. Similarly, ENL is frequently very severe in South America, perhaps more so than in Nepal, necessitating the use of thalidomide as a specific and potent treatment when corticosteroid therapy has failed or is not tolerated. Indeed, we suggest in our article [2] that such regional differences in disease severity may account for the differences in levels and response patterns of inflammatory mediators observed in different studies of ENL.

Crawford implies that the apparent absence of neurotoxicity of thalidomide in patients treated for ENL should be viewed with suspicion, given the high frequency of nerve damage seen in patients with other diseases treated with the drug. We agree that the lack of thalidomide-induced neurotoxicity in ENL is surprising. We support the idea that it may be due, in part, to the lack of sophisticated assessment tools in field settings, as well as to the difficulty of detecting drug-induced changes against the background of leprosy-associated neuropathy. We suggest that the use of thalidomide should therefore be reserved for cases of moderate or severe ENL and agree that availability of this drug should be constrained by strict controls, to avoid the tragic toxicities observed in the past. Finally, we would point
out that efforts to elucidate the mechanism of action of thalidomide, motivated by the indubitable efficacy of the drug in defined clinical settings, has led to the development of putatively nonteratogenic and nonneurotoxic analogs of thalidomide that may provide safe alternatives to the parent drug in the future.

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References


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