any disease-control effort. Global health governance must encourage multisectoral collaboration, including collaboration with the militaries of the world and especially in conflict zones. In fact, where this has occurred, there have been notable successes, including disaster relief, vaccine development, and influenza surveillance.[2]

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The views expressed are those of the author and do not necessarily reflect the official views of the Uniformed Services University of the Health Sciences, the U.S. Navy, or the Department of Defense.

No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1301373

THE EDITORIALISTS REPLY: We agree with Chopra and Hipgrave that the global improvement in child survival "hides uneven progress"; in our editorial, we pointed out that for most global health challenges "the disparities between and within countries are vast." The populations at risk we had in mind are women and children in countries where progress has been minimal or there is still much to be done. Global trends often mask underlying heterogeneity in regional, national, and local disease burdens. Setting priorities is especially complicated in countries with simultaneous growth in noncommunicable diseases and a continuing burden of infectious diseases, maternal death, and death in children.

We agree with Blazes that multisectoral collaboration is important in disease eradication, as it is for responding to most health challenges. The article in the global health series on the topic of global governance elaborates on this issue.[1]

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1301373

Antibody Depletion by Bortezomib through Blocking of Antigen Presentation

TO THE EDITOR: Shortt et al. (Jan. 3 issue)[1] report a case of ADAMTS13 antibody depletion by bortezomib in a patient with thrombotic thrombocytopenic purpura (TTP) and speculate that the clinical improvement was due to depletion of residual autoreactive B cells and plasma cells. However, we would like to add another potential mechanism of bortezomib in the treatment of TTP.

Sorvillo et al.[2] recently reported that the formation of inhibitory autoantibodies against ADAMTS13 depends on the activation of CD4+ T cells, and this process requires endocytosis and subsequent processing of ADAMTS13 into peptides that are presented on major-histocompatibility-complex class II molecules to CD4+ T cells by immature dendritic cells. They showed that uptake and endocytosis of ADAMTS13 was observed after incubation of ADAMTS13 with dendritic cells.[2] Also, Subklewe et al.[3] found bortezomib-induced apoptotic cell death mainly in immature dendritic cells and, to a much lesser extent, in mature dendritic cells.

Therefore, bortezomib might have a beneficial effect on TTP by inhibiting endocytosis of ADAMTS13 through inhibition of maturation of dendritic cells.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1301264

Hepatotoxicity with Combination of Vemurafenib and Ipilimumab

TO THE EDITOR: There has been great interest in testing combination therapy with the BRAF inhibitor vemurafenib and the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4)–blocking antibody ipilimumab, currently the only two agents approved for the treatment of advanced melanoma on the basis of improved overall survival.[1] Vemurafenib and ipilimumab have different mechanisms of action, and preclinical studies have suggested that BRAF inhibitors may enhance immune-cell function and antigen presentation.[2-5] The only clinically significant overlapping toxic effects for these agents are in skin and liver, which rarely limit their use in patients. Therefore, ample rationale exists to investigate combined therapy with these two agents.

Table 1. Data for Patients with Grade 3 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels While Receiving Combination Therapy with Vemurafenib and Ipilimumab.*

Study Cohort and Patient No.	No. of Doses of Ipilimumab before ALT–AST Elevation	Time to Onset of ALT–AST Elevation after First Dose of Ipilimumab	Treatment	Time to Resolution of ALT–AST Elevation	Toxicity Relapse with Repeated Ipilimumab
First cohort					
4	1	21 days	Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab permanently discontinued	4 days	NA
5	2	36 days	Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (2 doses)	6 days	No
6†	1	21 days	Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab continued (1 dose)	6 days	No
8	1	19 days	Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (1 dose)	12 days	Yes
Second cohort					
10	1	15 days	Glucocorticoids; vemurafenib discontinued for 7 days and then restarted with dose reduction; ipilimumab permanently discontinued	10 days	NA
16‡	1	13 days	Vemurafenib and ipilimumab permanently discontinued	20 days	NA

* The first cohort started with a run-in period of 1 month of single-agent vemurafenib (960 mg orally twice daily), followed by four infusions of ipilimumab (3 mg per kilogram of body weight every 3 weeks) and concurrent twice-daily doses of vemurafenib. The second cohort received a lower dose of vemurafenib (720 mg twice daily) together with the full dose of ipilimumab. NA denotes not available.
† This patient also had a grade 2 increase in the total bilirubin level.
‡ This patient also had a grade 3 increase in the total bilirubin level.