from Barbados (*4*) indicates a net sea level rise since LGM that is essentially identical to that delivered by the ICE-4G model, it is unclear as to whether even this small adjustment to the model will be required.

My article included a further characterization of the continuous meltwater redistribution that accompanies glacial isostatic adjustment. The theory tuned to fit the raw *rsl* record at Barbados also predicted an *rsl* history at the Huon Peninsula that fit the (raw) record there also. Because there is a significant offset between the *rsl* records at Barbados and Huon [the Huon record indicating a lower *rsl* rise, at the same age, than that at Barbados (by about 10 m at LGM)], and because this offset was predicted, it seemed that the theory could be accurately predicting the redistribution of meltwater driven by glacial isostatic adjustment. The predicted (*1*) net *rsl* rise at Huon since LGM is near 108 m (close to the 105.2 m eustatic value), whereas the predicted value at Barbados is near 118 m, so that, according to the theory, water depth increased by 10 m more at Barbados than at Huon, and both sites received more water than eustatic. If one were to accept the standard correction for tectonic uplift at the Huon site of 1.9 mm year^{-1}, then the Barbados and Huon curves could be brought into closer coincidence (figure 1 of the comment by Edwards), which would imply that meltwater redistribution during the adjustment process had zero differential impact at these two sites. The fact that the theory (*1*) predicts the differential impact recorded in the raw *rsl* data would then have to be seen as fortuitous. An equally tenable interpretation is that the tectonic rate of uplift at Huon (or Barbados, or both) has not in fact been constant. Current estimates of the site-specific rates of tectonic uplift eliminate the discrepancy between the sea level records at these two sites, but Edwards does not provide an estimate of the accuracy with which these rates have been inferred.

Deviations from the eustatic *rsl* rise at ocean basin sites might conceivably be reduced from those predicted by my analyses (*1*) if the radial viscoelastic structure of the model were modified in a way that did not violate the constraints used to derive this structure. Before suggesting that the usual constant rate of tectonic uplift assumed for the Huon Penninsula might be in error, this alternative possibility should be investigated. As one plausible flaw in the assumed radial viscoelastic structure (*5*, *6*) concerns lithospheric thickness, I have investigated for comparative purposes the result on the predicted *rsl* histories of doubling this thickness.

This maximum plausible increase of the thickness of the elastic lithosphere decreases the offset between the predicted *rsl* histories at Barbados and Huon, as expected on physical grounds, but only by about 1 m at LGM (Fig. 2). Although some modification of the radial viscosity profile in the sub-lithospheric mantle (or perhaps the influence of gravitational disequilibrium at LGM or of lateral viscosity variations) may allow the reconciliation of the theoretical prediction of the model with a constant rate of tectonic uplift of 1.9 mm year $^{-1}$ at Huon, it seems equally plausible that this rate has not been constant. The question of the origin of this offset does not affect the main conclusion (*1*) that the LGM ice sheets contained significantly less ice than posited in the CLIMAP MAX reconstruction. The topography of these ice sheets was therefore significantly lower than that previously calculated. Computations of climate state that use the revised LGM topography as a lower boundary condition for the atmospheric general circulation model are therefore expected to be significantly different from those previously derived.

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T_H2 Downregulation of Macrophage HIV-1 Replication

Acquired immunodeficiency syndrome (AIDS) is a disease characterized by infection of T cells and macrophages and a decline in the number of CD4 T cells (*1*). Mechanisms that mediate the resulting immunodeficiency in AIDS and regulate viral load continue to be a primary focus of human immunodeficiency virus–type 1 (HIV-1) research. Cytokines have been postulated to play a major role in pathogenesis with particular emphasis on the viral and immunological consequences of a proposed polarization into a T_H1 (cell-mediated), or T_H2 (humoral) host response (*2*). Although the T cell is primarily involved in secretion of both types of cytokines, cytokines derived from macrophages have also been recognized to play a central role in determining induction and effector pathways of immunity. Likewise, for HIV-1 infection and replication, macrophages provide viral reservoirs that may be subject to regulation by T cell–derived cytokines (*1*). These possible consequences of altered T cell cytokine expression in AIDS have meaning for recent reports by E. Maggi *et al.* (*3*) and by C. Graziosi *et al.* (*4*).

Maggi *et al.* studied preferential viral production in T_H2 T cell clones. We and others have found that T_H2-type cytokines produce opposite results in isolated macrophages (*5*–*8*). We also believe that the reported in vitro data concerning macrophage and T cell viral regulation by T_H2-type cytokines, not discussed in the report by Maggi *et al.*, bear on their findings.

T_H2-type cytokines [interleukin-4 (IL-4), -10, and -13], while not inhibiting the establishment of infection, induce a potent virostatic latent state in infected macrophages in vitro (Table 1). By contrast, IL-4 upregulates viral production in T cells, unlike other T_H2-type cytokines tested. We postulate that the finding by Maggi *et al.* of preferential replication of HIV-1 in T_H0 and T_H2 clones might result from in vitro positive feedback mediated by endogenous IL-4. In this macro-

Table 1. HIV replication in T cells and tissue culture-derived macrophages (TCDM) treated with T_H2 cytokines (IL-4, IL-10, and IL-13) in vitro. T cell and macrophage cultures were prepared as described (*5*) and infected with HIV-1 RF (MOI 0.03) and HIV-1 ADA (MOI 0.12), respectively. Treatment with 20 ng/ml of IL-4 (Genzyme, Kent, United Kingdom), IL-10 (DNAX, California), and IL-13 (Sanofi-Elf, Labege, France) was started 72 hours before infection and replenished with cytokine every 3 days. Samples for viral production were obtained every day for T cells and every 2 days for TCDM until the end of culture on day 10 and 16, respectively. T cell values indicate virus production following the first round of replication (2 to 5 days after infection). Viral production was measured by in-house adapted enzyme-linked immunosorbent assay (ELISA) as described (*5*), which is one-tenth as sensitive as commercial ELISA kits. Results are the average of duplicate independent cultures and representative of multiple experiments where cytokines have been tested in different donors.

Cell type	Control	p24 (ng/ml) HIV			
		Control	IL-4	IL-10	IL-13
T cell*	0	1.39	9.11	1.30	1.12
Macrophage†	0.08	3.73	0.23	0.11	0.38

*Day 10 after infection. †Day 16 after infection.

phage-free system, the increase of IL-4 in the T_H0 and T_H2 clones isolated from seronegative peripheral blood mononuclear cells would enhance T cell proliferation and consequently HIV-1 replication. As their data show that presence of endogenous interferon γ (INF-γ) in T_H0 clones does not seem to affect viral replication, we suggest that the factor determining absence of viral replication in the T_H1 clones might be the lack of IL-4 and not actions of other T_H1 soluble factors acting in concert with INF-γ. Evidence arising from the studies of Maggi *et al.* of CD4 purified cultures suggests that IL-4 is the determining cytokine. If IL-4–producing T cells are major viral-producing T cells in vivo, they may also mediate a cycle of viral persistence by shutting down, but not eradicating, viral expression in newly infected macrophages. According to this scenario, any effective immune clearance of viral-producing T_H0 and T_H2 cells would be followed by a decrease in T_H2-type cytokines and renewed viral expression from latent newly infected macrophages. Our in vitro observations about the reversibility of T_H2 viral regulation in macrophages are compatible with this hypothesis.

The conclusion drawn by Maggi *et al.* that progression to disease is favored by a "high and continuous HIV replication in $CD4^+$ T cells activated in vivo in response to the sustained production of T_H2-type cytokines . . ." (p. 248) is also questionable because it does not account for the potential consequences of T_H2-type cytokine action on macrophages. Specifically, IL-4 and IL-13 increase IL-1 receptor antagonist secretion by macrophages, while all T_H2-type cytokines inhibit production of TNF-α, IL-1β, and IL-6, proinflammatory cytokines known to upregulate virus replication (*9–11*). Therefore, T_H2-type cytokines might reduce viral load as well as viral-induced cytokine secretion by macrophages, thus preventing a positive cycle of viral replication in T cells and macrophages. These and other variables would be absent when studying macrophage-free models of HIV-1 infection in vitro.

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Response: The comment by L. J. Montaner and S. Gordon to our report (*1*) is appropriately addressed. The model based on the in vitro infection of established T cell clones allows one to investigate HIV replication in T cells, but does not provide information about the possible effects of T_H cell–derived cytokines on HIV replication in macrophages. So, in principle, our data do not exclude the possibility that T_H2 cytokines and particularly IL-4 can favor HIV replication in $CD4^+$ T cells and inhibit at the same time HIV replication in macrophages. The effects of this possible dichotomy in vivo, however, are difficult to evaluate. Our recent data suggest the existence of a more complex scenario than that provided by the classical model of T_H1 or T_H2 cytokines in the regulation of HIV replication. For example, CD30, a member of TNF receptor superfamily (*2*), appears to be preferentially expressed on both $CD4^+$ and $CD8^+$ T cells producing T_H2-type cytokines (that is, T_H2- and T_H0-like cells) (*3*). High amounts of soluble CD30, found in the serum of HIV-infected individuals, appear to behave as a prognostic factor independent of other prognostic parameters, including the initial number of circulating $CD4^+$ T lymphocytes (*4*). On the basis of recent results of several in vitro and in vivo experimental approaches (*5*), we believe that CD30 triggering in T_H2 and T_H0 cells, rather than production of T_H2-type cytokines, plays a critical role in promoting HIV replication and $CD4^+$ T cell death.

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