observation made in the HIV-1/HCV–
coinfected (P = 0.38) and the HIV-1–un-
infected (P = 0.008) HGDS participants
[2] as well as by others [4–8]. Antonucci et al. reported that they did not observe a
difference in HCV RNA load by HCV ge-
genotype in the I.Co.N.A. Furthermore, they
showed that the difference in CD4+ T cell
load by HCV genotype remained un-
changed even when adjusted for HCV RNA
load. Because we had previously shown in
the HGDS cohort an independent relation-
ship between HCV RNA load and HIV-
1 disease progression [9]—an observation
subsequently confirmed by Herrero-Marti-
nez et al. [5]—we also considered this
possibility. In our article, we described how the
addition of HCV RNA load to the Cox
proportional hazards model minimally in-
fluenced the relationship between HCV ge-
genotype 1 and AIDS-related mortality [2].
Moreover, we have since reanalyzed the da-
ta and have found that adjusting for HCV
RNA load does not alter the significant asso-
ciation between HCV genotype 1 and de-
creased absolute (P = 0.35) and percentage
(P = 0.03) CD4+ T cell measurements.

We agree with Núñez and Soriano and with
Antonucci et al. that the observed relation-
ship between HCV genotype and CD4+ T cell
count in HIV-1–infected individ-
uals requires further exploration.
In their editorial commentary, Núñez and
Soriano suggested several mechanisms that
might explain these findings, including
the possibility that HCV has a direct ef-
effect on CD4+ T cells [10], as we had pro-
posed in our original study [2]. Although this
possibility cannot be excluded, our
data suggest that the relationship between
HCV genotype and CD4+ T cell count is
specific to those coinfected with HIV-1 and
HCV, because no relationship be-
 tween HCV genotype and either absolute
or percentage CD4+ T cell measuremen-
t was identified in the HIV-1–uninfected par-
ticipants in the HGDS cohort [2]. Further
investigation is needed, to better define
both the interactions between HIV-1 and
HCV infection and how HCV RNA load
and genotype influence the natural history
of HIV-1 disease.

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Antimalarial Effects of HIV Protease Inhibitors: Common Compounds but Structurally Distinct Enzymes

To the Editor—The brief report by Skin-
nner-Adams et al. [1] on the antimalarial
effects of HIV protease (referred to as
“protease” by Skinner-Adams et al.) inhibi-
tors is of great interest and potential
therapeutic importance in areas where ma-
laria and HIV infection are coendemic.
We were interested by the views expressed
by these authors, as well as those expressed
by Savarino et al. in their cor-
respondence [2], regarding the aspartic
proteinases of Plasmodium falciparum
(plasmepsins) as likely targets for inhibi-
tion by these compounds. The work of both
groups in this field is valuable, but
greater caution should be exercised in the
discussion of structural and sequence sim-
ilarities between the 2 enzymes, because
an appreciation of the molecular intric-
cacies of the aspartic protease family
will be essential for the proper interpre-
tation of the antimalarial effects of HIV
protease inhibitors.

The plasmepsins belong to aspartic pro-
tease family A1 [3], in which the 2 cata-
lytic aspartate residues are contributed by
different domains, generally formed from
a single amino acid chain in a monomeric
enzyme. A1 enzymes have long active site
trenches overarched with a single β hair-
pin loop (the flap) and are underlaid by
a symmetrical active site trench with 2 flaps.
The active site trench of A2 enzymes is
approximately parallel to and beneath the active
site of the antimalarial effects of HIV
protease inhibitors. The work of Savarino et al. in their cor-
respondence [2], regarding the aspartic
proteinases of Plasmodium falciparum
(plasmepsins) as likely targets for inhibi-
tion by these compounds. The work of both
groups in this field is valuable, but
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lytic aspartate residues are contributed by
different domains, generally formed from
a single amino acid chain in a monomeric
enzyme. A1 enzymes have long active site
trenches overarched with a single β hair-
pin loop (the flap) and are underlaid by
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The active site trench of A2 enzymes is

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much shorter than that of A1 enzymes, and the dimer is held together on a base of 4 interdigitating strands, forming a β sheet perpendicular to the active site trench. Thus, although there may be some important similarities in architecture between HIV proteinase and plasmepsins, to discuss them as being structurally similar is, in reality, misleading. Consequently, we do not share Savarino et al.’s surprise that no plasmodial homologue of the HIV protease was found, because there is no true equivalent: the *P. falciparum* aspartic proteinases and the closely related histoaspartic proteinase [4] are members of the A1 protease family and are quite distinct from the A2 retroviral-type dimeric enzymes.

Furthermore, the sequence alignment of HIV proteinase and plasmepsin II presented by Savarino et al. shows no more similarity than would be expected for 2 diverse members of the aspartic protease superfamily. The regions surrounding the active site motifs of aspartic proteinases are highly conserved, with a characteristic hydrophobic–hydrophobic–aspartic acid–threonine-serine–glycine sequence. In fact, comparison of the leucine–aspartic acid–threonine–glycine–serine sequence (plasmepsin II) with the isoleucine–aspartic acid–threonine–glycine–alanine sequence (HIV proteinase) illustrates the differences between the enzymes as much as the similarities, because the serine in plasmepsin II is within hydrogen-bonding distance of the catalytic aspartic acid, whereas the alanine in the equivalent position in HIV proteinase cannot form such a bond.

The overall importance and interest of these structural distinctions is that, assuming the antimalarial activity of the anti-retrovirals is mediated via the plasmepsins, the inhibitors described are actually interacting with active site trenches with very different architectures—even if the model produced by Skinner-Adams et al. indicates that some HIV proteinase inhibitors may adopt similar conformations on binding to both enzymes. These differences in the characteristics of the active site trenches are illustrated by distinct ligand-binding affinities—for example, the general aspartic proteinase inhibitor isoaverlyl pepstatin inhibits plasmepsins with subnanomolar *K*ᵢ values [5] but shows a *K*ᵢ of 400 nmol/L against HIV proteinase [6].

The inhibition of plasmepsins by the HIV proteinase inhibitor ritonavir may not be surprising, because interactions between this drug and nonretroviral aspartic proteinases have been known for almost 10 years, with *K*ᵢ values against human cathepsins D and E of 20 and 8 nmol/L, respectively (see Kempf et al. [7], whose work significantly predated that cited by Savarino et al. in showing such interactions). The plasmepsins are much more closely related to human cathepsin D than to HIV proteinase, so, when the development of antimalarial therapy based on HIV protease inhibitors is considered, the potential interactions with human aspartic proteinases may need to be minimized. For ritonavir in particular this may be of clinical relevance, because cathepsin D is a lysosomal enzyme and, thus, is present in most cell types and because cathepsin E is found in epithelial cells lining the gut (which are exposed to orally administered drugs) and is also present in red blood cells—the clinically significant site of malarial infection. Saquinovir, by contrast, achieves potent inhibition of HIV proteinase with negligible inhibition of the human aspartic proteinases [8], demonstrating the selectivity that can be achieved between these types of enzymes. Ultimately, it may be the structural differences governing the interactions between inhibitors and the plasmepsins (on the one hand) versus the human aspartic proteinases (on the other) that hold the key to the development of existing drugs that target HIV proteinase as antimalarial agents.

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