## REVIEW ARTICLE

# T-cell depletion and immunity to malaria in HIV-infections

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(*Received 9 May 2004; revised 3 August 2004; accepted 9 August 2004*)

SUMMARY

Although early reports on HIV and malaria in co-infected subjects indicated little apparent interaction between the two infections, more recent investigations have found evidence for HIV increasing the risk from malaria. Conversely, increased viral load in susceptible cells occurs in malaria-infected people. However, the overall pattern of results is still somewhat confusing and contradictory. While morbidity from malaria may be greater in HIV-positive patients and in several reports the mortality risk is also higher, major increases in blood-stage parasitaemias that one might expect are not generally observed. The results of surveys are summarized and discussed in the context of what is known of malaria and HIV immunology in the light of recent data from humans as well as animal models.

Key words: malaria, human, rodent, CD4, HIV, AIDS, immunology, cytokines.

## INTRODUCTION

The epidemiological overlap of HIV/AIDS and malaria in tropical regions has been a cause for concern since the 1980s and now that malaria vaccine trials are in progress, some in areas where HIV is frequently a risk factor, this could complicate assessment of their impact. As the virus has spread throughout Africa clinicians needed to know if co-infection with *Plasmodium* increased the rate of progression to serious disease and fatal outcomes for their patients, from either of these infections. Virtually all reports have this question primarily in mind and whether antimalarial prophylaxis is required for those who are HIV positive (HIVP). Tragic though the situation is for people with HIV, not for the first time nature has conducted an experiment that provokes some interesting questions: in this case what are effects of low $CD4^+$ T-cell counts on immunity to human malaria, and does malaria accelerate the progression to AIDS?

Not surprisingly, clinical reports ignore any comparison of malaria-infected HIV/AIDS subjects with malaria in T-cell-deprived animals but despite their limitations most scientists with a broad perspective value experimental data from animal models. The obvious limitations of these must be kept in mind, not least the rapid loss or inherent absence of these cells in immunodeficient mice compared to the gradual loss of $CD4^+$ cells in humans and the relatively clean environment of laboratory animals compared to humans 'in the wild'.

At the time of a previous review (Butcher, 1992) there appeared to be very little evidence for interaction between the two infections, but more recent data indicate that this conclusion requires some revision (Rowland-Jones & Lohman, 2002). Additionally, progress in understanding the relative contributions of different cytokines in both experimental models and human subjects (Artevanis-Tsakonas, Tongren & Riley, 2003) provides a useful basis from which to view the HIV-malaria problem.

## IMMUNITY TO MALARIA IN MICE AND HUMANS

It has been known for many years that, in general, T-cell-deprived mice lose their capacity to control blood-stage malaria infection, experiencing high, prolonged parasitaemias resulting in severe and potentially fatal anaemia (Brown, Allison & Taylor, 1968). The rodent model for human malaria that in my view has been, and continues to be, the most systematically studied is the C57BL/6 mouse infected with *Plasmodium chabaudi chabaudi* (Langhorne, 1989; Taylor-Robinson & Phillips, 1993). The infection overall shows many parallels with human malaria: the initial acute inflammatory response, traditionally described as Th1 type, is followed by production of antibody (Th2 type) and down-regulation of the acute phase. Whilst the other rodent parasites also exhibit features not found in *P. chabaudi*, particularly cerebral malaria in *P. berghei* ANKA, increasingly, aspects of this are being

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*Parasitology* (2005), **130**, 141–150. © 2004 Cambridge University Press
DOI: 10.1017/S003118200400650X Printed in the United Kingdom

https://doi.org/10.1017/S003118200400650X Published online by Cambridge University Press

Table 1. Comparison of malaria data in HIVP and HIVN patients: children

| 1st Author and year | Age* | No. HIVP | No. HIVN | Prevalence | PD† | Dis‡ | Mort§ |
|---|---|---|---|---|---|---|---|
| Nguyen-Dinh (1987) | 3 | 40 | 1006 | 0 | 0 | N.D. | N.D. |
| Müller (1990*b*) | 1 | 206 | 216 | 0 | N.D. | N.D. | N.D. |
| Colebunders (1990) | 7 | 59 | 83 | 0 | 0 | N.D. | N.D. |
| Shaffer (1990) | 3 | 30 | 699 | 0 | +[a] | N.D. | N.D. |
| Greenberg (1991) | <1 | 112 | 508 | 0 | 0 | 0 | N.D. |
| Taha (1994) | <2 | 82 | 540 | 0 | 0 | N.D. | N.D. |
| Kalyesubula (1997) | <4 | 77 | 357 | − | 0 | [b] | − |
| Grimwade (2003) | 7 | 67 | 896 | 0 | 0 | + | N.D. |
| Villamor (2003) | <5 | 44 | 482 | − | N.D. | N.D. | N.D. |

* Mean age of patients.
† Parasite density.
‡ Disease due to malaria.
§ Mortality due to malaria.
[a], Difference not significant; [b], malaria slowed progression to AIDS.
N.D., No data.
0, No difference between HIVP and HIVN patients.
+, HIVP patients show increased malaria prevalence, parasite density, disease or mortality compared to HIVN patients.
−, HIVP patients show decreased malaria prevalence, parasite density, disease or mortality compared to HIVN patients.

reported from *P. chabaudi* in knockout mice (e.g. Sanni *et al*. 2004).

The division of cytokine patterns into Th1 and Th2 *P. chabaudi* infections was an oversimplification and current views reflect the realization that critical cytokines such as IL-10 and TGF-$\beta$ are pleiotropic and, additionally, immunity also involves a regulatory subtype of T cells termed $T_{reg}$ (McGuirk & Mills, 2002). Nevertheless, the early acute/inflammatory response to the parasite particularly involves IFN-$\gamma$, IL-2, TNF-$\alpha$ and thus macrophage activation. This prevents parasitaemias going much over 40% through the generation of cytotoxic factors including nitric oxide and probably other effector molecules. At the peak of infection mice exhibit symptoms of disease (the inflammatory phase) but this gives way to a secondary and longer period with the generation of a different cytokine pattern including IL-4, Il-10 and TGF-$\beta$. The anti-inflammatory properties of the latter enable the mice to recover whilst parasite replication gradually comes under the control of antibody (Langhorne, 1989). The balance between the pro- and anti-inflammatory responses in human malaria infections may be somewhat more complex but old evidence for high levels of macrophage activation in children in malarial areas, gradually declining with increasing age and acquired immunity, (e.g. Reibnegger *et al*. 1987) is broadly consistent with recent views on cytokine patterns (Artevanis-Tsakonas *et al*. 2003).

Since depletion of $CD4^+$ cells in mice leads to high and prolonged parasitaemias it did not seem unreasonable to expect that in humans HIV might cause higher than normal parasitaemias, as in immunosuppressed or splenectomized patients (Warrell, Molyneux & Beales, 1990). At this point, it is worth recalling that though most human infections do not reach the numbers of infected erythrocytes seen in mice some patients with *P. falciparum* have parasitaemias of over 20% (Nguyen-Dinh *et al*. 1987) and over 60% has been recorded (Garnham, 1966*a*); if treated early these unusually high infections are not necessarily fatal.

## REPORTED DATA ON HIV AND ITS EFFECT ON MALARIA

### *Does HIV increase the prevalence, density or risk in patients co-infected with malaria?*

The data from surveys are briefly summarized in Table 1 for children up to age 7, Table 2 for adults, and Table 3 for pregnant women and their offspring, but where observations were mainly restricted to the neonatal period and included data on placental parasitization.

Early studies, from 1988 to 1993, on co-infections in humans found relatively small effects of HIV on malaria, except for one report of 95% red cells infected with *P. vivax* in a patient with AIDS (Katongole-Mbidde, Baruna & Kizito, 1988) and a slightly higher parasite density in HIVP children compared to HIV negative (HIVN) children, though there were no differences in parasite prevalence (Shaffer *et al*. 1990; Table 1). However, these studies have been criticized (Chandramohan & Greenwood, 1998; French & Gilks, 2000) with some justification for a variety of reasons: failure to assess HIV status in detail, especially whether patients had only been HIVP for a short time (Colebunders *et al*. 1990; Greenberg *et al*. 1991, Table 1), small numbers of subjects in some groups, failure to

https://doi.org/10.1017/S003118200400650X Published online by Cambridge University Press

Table 2. Comparison of malaria data in HIVP and HIVN patients: adults

| 1st Author and year | Age* | No. HIVP | No. HIVN | Prevalence | PD† | Dis‡ | Mort§ |
|---|---|---|---|---|---|---|---|
| Simooya (1988) | >12 | 28 | 142 | − | 0 | N.D. | N.D. |
| Müller (1990*a*) | A | 142 | 58 | 0 | 0 | 0 | N.D. |
| Atzori (1993) | A | 62 | 238 | + | 0 | N.D. | N.D. |
| Whitworth (2000) | 35 | 262 | 222 | +[a] | +[a] | +[a] | N.D. |
| French (2000) | 31 | 1392 | 0 | N.D. | N.D. | +[b] | [c] |
| Chirenda (2000) | A | 82 | 155 | N.D. | N.D. | +[d] | + |
| Francesconi (2001) | 26 | 41 | 126 | N.D. | N.D. | + | N.D. |
| Grimwade (2004) | 28 | 180 | 433 | 0 | 0 | + | + |

* Mean age of patients.
† Parasite density.
‡ Disease due to malaria.
§ Mortality due to malaria.
N.D., No data.
0, No difference between HIVP and HIVN patients.
+, HIVP patients show increased malaria prevalence, parasite density, disease or mortality compared to HIVN patients.
−, HIVP patients show decreased malaria prevalence, parasite density, disease or mortality compared to HIVN patients.
[a], Prevalence and parasite density etc increased only with low CD4 counts; [b], Prevalence increased with declining CD4 counts; [c], Patients died of diseases other than malaria; [d], Morbidity and mortality increased, though no correlation with $CD4^+$ counts.

Table 3. Comparison of malaria data in HIVP and HIVN patients: pregnant women and neonates

| 1st Author and year | No. HIVP | No. HIVN | Prevalence | PD† | Dis‡ | Mort§ |
|---|---|---|---|---|---|---|
| Allen (1991) | 965 | 2362 | 0 | 0 | N.D. | N.D. |
| Bloland (1995) | 138 | 2470 | +[a] | N.D. | N.D. | +[b] |
| Steketee (1996) | 162 | 2784 | + | + | N.D. | N.D. |
| Verhoeff (1999) | 159 | 462 | + | N.D. | N.D. | N.D. |
| Ladner (2002) | 228 | 229 | + | + | + | N.D. |
| Van Eijk (2002) | 1268 | 3825 | + | + | N.D. | N.D. |
| Ticconi (2003) | 82 | 904 | + | N.D. | + | +[c] |
| Ayisi (2003*b*) | 567 | 1899 | N.D. | N.D. | +[d] | N.D. |

† Parasite density.
‡ Disease due to malaria.
§ Mortality due to malaria.
0, No difference between HIVP and HIVN patients.
+, HIVP patients show increased malaria prevalence, parasite density, disease or mortality compared to HIVN patients.
−, HIVP patients show decreased malaria prevalence, parasite density, disease or mortality compared to HIVN patients.
N.D., No data.
[a], Placental infection more prevalent in HIVP; [b], Mortality of neonates higher from HIVP mothers; [c], Mortality – more still births of neonates from HIVP mothers, more malaria attacks in mother; [d], Low birth weight in neonates of HIVP mothers.

distinguish rural versus urban situations in regard to their malaria and so forth.

Since 1993, evidence for a greater impact of HIV on malaria has accumulated. Three groups, Atzori *et al*. (1993), Whitworth *et al*. (2000), and French & Gilks (French & Gilks, 2000; French *et al*. 2001), observed up to a 3-fold increased risk of parasite prevalence or of malarial fever in HIVP adults (Table 2), though Whitworth *et al*. and French *et al*. detected this only as $CD4^+$ counts declined to a low level (<200 $CD4^+$ cells/μl of blood). Francesconi *et al*. (2001) found an increased fever risk in HIVP adults with malaria but the differences were not statistically significant (Table 2). Chirenda, Siziya & Tshimanga (2000) (Table 2) also noted a 2-fold increase in mortality but, curiously, the occurrence of severe and complicated malaria did not correlate with a low $CD4^+$ count in HIVP adults. Probably the most significant impact of HIV on malaria reported so far comes from a recent study of non-immune HIVP adults in South Africa: the increase in risk for mortality was finally calculated as nearly 7-fold, but there was no difference in parasite density between HIVP and HIVN subjects (Grimwade *et al*. 2004; Table 2).

Observations on pregnant mothers, sometimes including their new-born children, generally demonstrated an increased risk from malaria, with the

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exception of an older survey (Allen *et al*. 1991; Table 3). In HIVP pregnant women 2 to 4-fold increases were noted in the prevalence of malaria (Steketee *et al*. 1996; Verhoeff *et al*. 1999) and up to a 4-fold higher density of parasites at delivery. Ladner *et al*. (2002, 2003) reported a 2-fold increase in incidence, with a particular risk to mothers post-partum, and Van Eijk *et al*. (2002) reported a similar increase in probability of parasitaemia but malaria was only one of a number of factors involved. In general, the increased risk of high parasitaemia is seen as often in multigravidae as in primagravidae (Steketee *et al*. 1996; Verhoeff *et al*. 1999) indicating that HIV hinders the maintenance of immunity. Seropositivity for HIV was also associated with lower birth weights (Ayisi *et al*. 2003*b*), higher mortality, a 4-fold greater risk of malaria attacks in new-borns and an increase in the probability of having parasitized placentas (Ticconi *et al*. 2003). Higher post-natal mortality for HIVP infants born of mothers with placental malaria was detected by Bloland *et al*. (1995).

The information on children, some of whom were infected from blood transfusions, and who were monitored for varying periods of time, includes many of the earlier, criticized studies in which differences between HIVP and HIVN groups were not significant (see Table 1). However, even more recent studies have not discerned very dramatic effects: Grimwade *et al*. (2003) observed that parasite density in children was unrelated to HIV status, whereas in another investigation, HIVP children aged from 0·5 to 5 years had lower parasitaemias than HIVN children (Villamor *et al*. 2003). Kalyesubula *et al*. (1997) observed HIVP children for up to 4 years but found no significant increase in parasite density and fewer episodes of malaria, although if they did get malaria a higher proportion required hospital treatment. Taha *et al*. (1994), who monitored children for the first 18 months post-partum, observed no differences between the HIVP and HIVN groups.

### *HIV and cause of death in malaria-infected patients*

The pathology of severe and cerebral malaria (CM) is at least in part immunologically mediated, reflected in profound changes in cytokine patterns (Artevanis-Tsakonas *et al*. 2003; Clark & Cowden, 2004): for example, the peak of CM tends to occur after a year or two of malaria experience and non-immune adults moving into a malarial area have a higher risk than children, probably from antigenic cross-reactivity between plasmodial and commonly experienced antigens. The role of parasite cyto-adherence and of strains with a greater potential for precipitating CM are also important considerations and the relative contributions of these are hotly debated (Clark & Cowden, 2004).

The numbers of admissions for CM over a 5-year period in Uganda did not alter with increasing admissions for AIDS (Müller, Moser & Alexander, 1991) and two early small studies also reported no increased CM with HIV (Simooya, Mwendapole & Sikateyo, 1988; Leaver, Hale & Watters, 1990). However, CM may be too rare an occurrence to give sufficient numbers of cases for a precise comparison in the various studies that have been done (Greenwood, Marsh & Snow, 1991). Only Grimwade *et al*. (2004) found a very significantly increased risk of mortality in adults, including death in coma, but without an accompanying rise in parasitaemias that is usually assumed to be a predisposing factor for CM (Warrell *et al*. 1990). If the role of T cells in murine models of CM is any guide there should be *less* CM rather than more in HIVP patients as $CD4^+$ counts decrease (e.g. Marussig, Renia & Mazier, 1996); the immunological evidence in humans points to the same conclusion (see above).

As already mentioned, HIVP neonates are at an increased risk of dying if the mothers had placentas heavily infected with parasites but death was from diseases such as diarrhoea or gastrointestinal disease not malaria (Bloland *et al*. 1995).

If any patients succumbed to overwhelming parasitaemias this is not reported; most post-mortem findings on AIDS patients do not mention malaria as a cause of death (Lucas *et al*. 1993; Chakraborty *et al*. 2002; Kawo *et al*. 2000). It comes fifth in the list of causes of death from retrospective analysis of hospital records of 3667 HIVP people admitted to hospital in Moshi, Tanzania (Ole-Nguyaine *et al*. 2004).

Interestingly, in contrast to the somewhat confusing picture in malaria there has been no difficulty in demonstrating that other protozoan parasites are often major contributors to mortality in AIDS: *Babesia* (Falagas & Klempner, 1996), *Toxoplasma*, *Giardia*, *Cryptosporidium*, *Isospora* (Curry, Turner & Lucas, 1991) and *Leishmania* (Olivier *et al*. 2002).

## THE CHALLENGE OF HIV FOR IMMUNE RESPONSES TO HUMAN MALARIA INFECTION

### *Antibodies in HIVP patients*

In the diseases that lead to AIDS, immunity is thought to be predominantly controlled by cell-mediated responses; in addition to those mentioned above, in developing/tropical countries tuberculosis is probably the most common cause. Thus, as acquired immunity to blood-stage malaria is primarily antibody-mediated one might predict that it will be largely unaffected, particularly as cytokine patterns in HIV are said to be associated with a shift to Th2-type responses (Clerici & Shearer, 1993; Chatt *et al*. 2002) and it is mainly cell-mediated immunity that is impaired (Kedzierska & Crowe, 2001).

https://doi.org/10.1017/S003118200400650X Published online by Cambridge University Press

Further, B cell polyclonal expansion (Shirai *et al*. 1992) and total immunoglobulin concentrations can be at higher or at equivalent concentrations in HIVP patients compared to HIVN controls, including antimalarial antibodies (Wabwire-Mangen *et al*. 1989; Rodriguez *et al*. 2003). In pregnant women seropositive for HIV, antibody levels to malaria are largely maintained (Ayisi *et al*. 2003*a*) until the onset of AIDS when they become significantly lower (Wabwire-Mangen *et al*. 1989). However, for antibody to be effective older data from passive immunity experiments (Cohen, McGregor & Carrington, 1961) suggest that high concentrations are needed, even against very small doses of parasites (Cohen & Butcher, 1969). People with a good acquired immunity to malaria may have the capacity to continue to generate enough antibody to protect them until other infections bring them down with AIDS, but this would not apply to partially immune subjects.

### *Acute/inflammatory responses in HIV-infected non-malaria-immune subjects*

In the investigations on HIVP children (Table 1) there would have been many who were too young to have acquired immunity to malaria (Nguyen-Dinh *et al*. 1987; Müller *et al*. 1990*b*; Shaffer *et al*. 1990; Kaleysubula *et al*. 1997; Grimwade *et al*. 2003). Although some children had parasitaemias over 25% in one study (Nguyen-Dinh *et al*. 1987) this did not correlate with HIV and the recent South African report on non-immune adults also indicated little difference in parasite numbers between HIVP and HIVN patients (Grimwade *et al*. 2004; Table 2). In HIVP adults, decreased lymphocyte IFN-$\gamma$ secretion in response to malaria antigens (Migot *et al*. 1996) combined with a rise in Il-10 and/or TGF$\beta$ that occurs in acute malaria (Li, Corraliza & Langhorne, 1999; Artevanis-Tsakonas *et al*. 2003) may add to depression of macrophage activation and thus increased susceptibility. Further, the activation of TGF$\beta$ by HIV (Wiercinska-Drapalo *et al*. 2004) may enhance that generated by malaria (Omer *et al*. 2003) leading to reduced inflammatory responses; this reinforces the expectation that parasite multiplication in the acute phase would be uncontrolled.

### *Immunity in pregnancy with HIV*

Resistance to malaria declines in mothers in endemic areas during the first pregnancies (Shulman & Dorman, 2003). Cell-mediated responses in the absence of HIV, including IFN-$\gamma$ production in response to malaria antigen, are depressed (Riley *et al*. 1989) and the placenta may be highly parasitized. In addition, mothers may carry multiple parasite strains (Beck *et al*. 2001; see below) and low IFN-$\gamma$ generation in the parasitized placenta is exacerbated if subjects are HIVP (Moore *et al*. 2000; Chaisavaneeyakorn *et al*. 2002). It is not too surprising, therefore, that HIV has an impact in pregnancy, but perhaps more surprising that the differences between HIVP and HIVN mothers are not greater.

Recent data indicate that subsets of parasites adhere to chondroitin sulphate in the placenta (Beeson & Brown, 2004), to which mothers in their first pregnancies lack antibody, but there is no information as yet on this in HIVP mothers.

### *Declining immunity and new infections*

In endemic areas PCR-based diagnostic techniques have revealed that infection with multiple species of *Plasmodium* may be common (Bruce & Day, 2003), in addition to multiple strains of individual species (Beck *et al*. 2001; Franks *et al*. 2001). Persisting chronic infections involving antigenic variation by schizont surface antigens are also characteristic of malaria. Thus, there is a continuing challenge with new species/strains/variants in HIV-infected hosts. Although strain-transcending immunity undoubtedly occurs (Baird, 1994) and non-specific responses to one parasite species suppress a second, both showing evidence of 'crisis forms' (Butcher, Mitchell & Cohen, 1978), any new infectious challenges presumably pose a more serious additional threat in immunosuppressed patients.

### *Immunosuppression and immunostimulation in co-infected hosts*

Immunosuppression by malaria to other antigens and infections during both the acute and chronic phases involves a number of mechanisms including haemazoin-induced defective macrophage function (Scorza *et al*. 1999) and direct parasite action on dendritic cells (Urban & Roberts, 2002). In addition, there is apoptosis of lymphocytes (Balde, Sarthu & Rousshiloun, 1995; Helmby, Junsson & Troye-Blomberg, 2000) and activation of $T_{reg}$ cells (Hisaeda *et al*. 2004). All this is compounded by the loss of immunity caused by HIV and in which apoptosis is also prominent (Brenchley *et al*. 2004).

Equally importantly, malaria infection is a major activator of T cells and macrophages, generating high levels of TNF-$\alpha$ and increased HIV viral load in cells in malarial patients (Hoffman *et al*. 1999; Tkachuk *et al*. 2001; Kapiga *et al*. 2002; Chen *et al*. 2003). Similarly, $CD4^+$ T cells induced increased viral expression in dendritic cells in a transgenic mouse model (Freitag *et al*. 2001). Surprisingly, in view of these data, Kalyesubula *et al*. (1997) claimed progression to AIDS was slower in HIVP children than those who were HIVN. Clearly, immune responses in the co-infected host are dynamic and extremely complex and more research is needed,

https://doi.org/10.1017/S003118200400650X Published online by Cambridge University Press

especially as malaria therapy has been used as an HIV treatment (Heimlich *et al*. 1997), a procedure that most researchers would probably question.

## IN CONCLUSION?

In summary, HIV appears to have less impact on malaria than one might expect, not only from the viewpoint of data from T-cell-deprived mice, but the significant immune responses induced by both infections and the effects of pregnancy even in the absence of HIV. The question remains as to why we do not see a greater rise in parasitaemias as $CD4^+$ counts decrease. In immune subjects depression of the early inflammatory responses might still leave antibody-dependent mechanisms sufficiently intact to control parasite replication. Such an explanation would not, however, account for the relatively low parasitaemias in HIVP subjects not immune to malaria, although more studies, particularly on children, would be desirable. Even if patients die of other infections before they die of malaria, acute attacks might, at least on more than one occasion (Katongole-Mbidde *et al*. 1988), give rise to high parasitaemias.

As discussed previously (Butcher, 1992) with the loss of $CD4^+$ T cells, other cell types – B cells, NK cells, $\gamma\delta$ T-cells and innate resistance factors (see Stevenson & Riley, 2004) may compensate to some extent. Increased IFN-$\gamma$ generation by $CD8^+$ cells in AIDS patients has been reported (Chatt *et al*. 2002) and though this could be sufficient to activate macrophages and neutrophils, both these cell types are rendered less effective by HIV (Kaul *et al*. 2003; Pisell *et al*. 2002).

An aspect of AIDS that might account, at least in part, for people not dying of overwhelming malarial infections is the decline in nutritional status as patients become malnourished (Gorbach, Knox & Roubenoff, 1993). This is a complicated issue since malaria parasites are susceptible to oxidant stress, iron and vitamin deficiencies etc. whilst the immune system is equally vulnerable and any outcome is therefore impossible to predict in general terms.

One observation that does seem to stand out from the various reports is that both mortality and morbidity, apparently due to malaria in HIVP patients, are not necessarily connected with parasite numbers. Although, in general, disease severity and mortality tend to be worse with increasing parasite load (Warrell *et al*. 1999) the correlation is not absolute. Artevanis-Tsakonas *et al*. (2003) have suggested that the timing and balance of pro-inflammatory (IFN-$\gamma$, IL-12 and TNF-$\alpha$) and anti-inflammatory cytokines (TGF-$\beta$ and IL-10) are responsible for disease or resistance. If so, this may be more important than the presence of large numbers of parasites, as argued by Ian Clark in CM (Clark *et al*. 2003; Clark & Cowden, 2004) and exploration along these lines might begin to explain why some HIVP people die from malaria without any major rise in parasitaemia. New data on the effects of quinolinic acid on the brain by both malaria (Medana *et al*. 2002) and HIV (Heyes *et al*. 2001) may also be relevant and need further investigation, as well as other causes of death.

Lastly, inspection of blood films of HIVP patients for the presence of 'crisis form' parasites (Butcher, 1989) would, if found, suggest that non-antibody mechanisms are probably implicated in the control of the infection. Although it is usually claimed these do not occur in human malaria, Garnham suggested they might be present in *P. vivax* infections (Garnham, 1966*b*). This at least could be done when ethical or practical reasons make more sophisticated investigations impossible.

I am grateful to Professor Eleanor Riley and Dr Graham Mitchell for valuable comments, and to Professor Bob Sinden and Imperial College London for the continued use of college facilities.

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