CD4 T-Cell Count and HIV-1 Infection in Adults With Uncomplicated Malaria

Jean-Pierre Van Geertruyden, MD, MSc, Modest Mulenga, MD, PhD,† Webster Kasongo,† Katja Polman, PhD,* Robert Colebunders, MD, PhD,‡§ Luc Kestens, PhD,¶ and Umberto D'Alessandro, MD, PhD**

Background: HIV-1–negative children with malaria have reversible lymphocyte and CD4 count decreases. We assessed the impact of malaria parasitemia on the absolute CD4 count in both HIV-1–infected and non-HIV–infected adults.

Methods: In Ndola, Zambia, at the health-center level, we treated 327 nonpregnant adults for confirmed, uncomplicated, clinical malaria. We assessed HIV-1 status, CD4 count, and HIV-1 viral load (if HIV-1–infected) at enrollment and at 28 and 45 days after treatment.

Results: After successful antimalarial treatment, the median CD4 count at day 28 of follow-up increased from 468 to 811 cells/μL in HIV-1–negative and from 297 to 447 cells/μL in HIV-1–positive patients (paired *t* test, $P < 0.001$ for both). CD4 count increment was inversely correlated with CD4 count at day 0 in both HIV-1–negative ($P < 0.001$) and HIV-1–positive patients ($P = 0.03$). After successful treatment, the proportion of patients with CD4 count $<200/\mu L$ at day 45 decreased from 9.6% to 0% in HIV-1–negative and from 28.7% to 13.2% in HIV-1–positive malaria patients ($P < 0.001$ for both). In patients with detectable but mostly asymptomatic parasitemia, CD4 count and, if HIV-1–infected, viral load at day 45 of follow-up were similar to those observed at enrollment.

Conclusion: Interpretation of absolute CD4 count might be biased during or just after a clinical malaria episode. Therefore, in malaria-endemic areas, before taking any decision on the management of HIV-1–positive individuals, their malaria status should be assessed.

Key Words: HIV-1, malaria, CD4 count, viral load, HIV-1 monitoring

(*J Acquir Immune Defic Syndr* 2006;43:363–367)

Epidemiological overlap of HIV/AIDS and malaria in tropical regions, and particularly in Eastern and Southern Africa, has been a reason for concern since the 1980s, as any interaction between these two diseases could be of great public-health importance, even if the statistical link is small. Some interactions between HIV and malaria have already been reported.[1] HIV-1–infected individuals with decreased CD4 count have an increased incidence of clinical and asymptomatic malaria,[2,3] a higher risk of malaria treatment failure,[4] and more severe malaria attacks.[5] CD4 cell involvement is probably essential for development of malaria immunity.[6] This is not surprising because CD4 cells help B cells to produce antimalarial antibodies and indirectly support the control of parasitemia through production of cytokines and activation of macrophages.[7]

The impact of malaria on HIV-1 is less clear. Efficient reverse transcription and integration of HIV genome into the host DNA does not occur until the immune cells are activated.[8] Because malaria infection is associated with strong CD4 cell activation and up-regulation of proinflammatory cytokines,[9] it provides an ideal microenvironment for the spread of the virus among the CD4 cells and thus for rapid HIV-1 replication. This has been described for malaria in an in vitro model.[10] In vivo, HIV-1 viral load first increases in malaria-infected patients[11] and then partially decreases 4 weeks after antimalaria treatment.[12,13] Furthermore, because of the selective HIV infection, the antigen-specific memory CD4 cells are lost.[14] Therefore, malaria may have an impact on the progression of HIV-1 infection toward AIDS.[15]

Next to the impact on HIV-1, malaria may also have a direct effect on CD4 cells. Indeed, a reversible decrease in lymphocytes and the absolute and relative CD4 counts have been observed in HIV-1–negative patients with malaria,[16,17] although the pathophysiology behind these findings is still unclear.[18] As such, malaria parasitemia may thus be an important confounding factor for the correct evaluation of the degree of immune depression in HIV-1–infected individuals.

Received for publication May 22, 2006; accepted August 31, 2006.

From the *Department of Parasitology, Institute of Tropical Medicine, Antwerp, Belgium; †Department of Clinical Sciences, Tropical Disease Research Center, Ndola, Zambia; ‡Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium; §Faculty of Medicine, University of Antwerp, Belgium; and ¶Department of Microbiology, Institute of Tropical Medicine, Antwerp, Belgium.

This study was funded by the Belgian Development Co-operation in the framework of an institutional collaboration between the TDRC in Ndola and the ITM in Antwerp. The funding source was not involved in any aspect of the study.

Contributors: Jean-Pierre Van geertruyden contributed to the study design, analysis plan, data interpretation, produced the final dataset, did the analysis, and wrote the paper. Modest Mulenga organized the collection of data, supervised the trial, and contributed to the data interpretation and writing the paper, Webster Kasongo analyzed the HIV-related parameters. Katja Polman and Robert Colebunders reviewed the paper. Luc Kestens contributed to the study design and data interpretation and helped to write the paper. Umberto D'Alessandro contributed to the study design, the analysis plan, data interpretation, and the writing of the paper.

Reprints: Jean-Pierre Van geertruyden, MD, MSc, Department of Parasitology, Unit of Epidemiology, Institute of Tropical Medicine, Nationalestraat 155, B-2000 Antwerp, Belgium (e-mail: JPVangeertruyden@itg.be).

We assessed the impact of malaria parasitemia on the absolute number of peripheral CD4 cells in both HIV-1–positive and HIV-negative adults treated for uncomplicated confirmed malaria.

METHODS

The study was carried out between October 2004 and June 2005 at four peri-urban health centers in Ndola, Zambia, an area of meso- to hyperendemic malaria. This study was nested into an ongoing randomized clinical trial with patients receiving either sulfadoxine/pyrimethamine (SP) or artemether/lumefantrine (AL).[19] Although these antimalarial drugs are not expected to have an immunomodulatory effect, treatment was assessed as a possible confounding factor for changes in the CD4 counts. All individuals of age 15 to 50 years attending any of the four peri-urban clinics and presenting with fever (body temperature $\geq$37.5°C) and/or history of fever in the previous 48 hours and without any other obvious disease were screened for malaria infection (thick and thin blood film in duplicate for parasite density and species identification) and pregnancy (if applicable). Patients with a *Plasmodium falciparum* density of 1000 parasites/μL or more were included. Exclusion criteria were as follows: (a) pregnancy; (b) severe *P. falciparum* malaria;[20] (c) documented intake of SP or AL 2 weeks before recruitment; (d) other cause of fever; (e) evidence of underlying chronic diseases (cardiac, renal, hepatic, malnutrition); (f) history of allergy to study drug or known allergy to other sulfa drugs, such as cotrimoxazole; (g) nonresident in the study area. Malaria parasites, CD4 cell counts, and viral load (if HIV-1 infected) were assessed at enrollment and after 28 and 45 days of follow-up.[20] This study was approved by the ethics and scientific committees of the Institute of Tropical Medicine, Antwerp, Belgium, and of the Tropical Disease Research Center, Ndola, Zambia.

Laboratory Investigations

All laboratory technicians were blinded to the patient's identity and all patient-related parameters. Thin blood films were fixed with methanol and thin and thick blood films were stained with 10% Giemsa. The number of asexual *P. falciparum* parasites per 200 white blood cells (WBC) multiplied by the actual WBC count divided by 200 was used to estimate the parasite density per μL. Internal quality control was organized as recommended by WHO.[20] After patient consent had been obtained, HIV-1 testing followed an "unlinked anonymous" procedure: blood samples were sent to the central laboratory within a couple of hours, where they were processed anonymously. Neither the study staff nor the patient had access to the HIV test results. Patients wanting to know their HIV-1 status were offered voluntary counseling and testing (VCT), located in the same clinic but independent to the study. Samples were first tested with Abbott Determine® (Abbott Laboratories, Tokyo, Japan). If the result was negative, the patient was considered to be HIV-1 negative. If the result was positive, a second test, Genie II® (Sanofi Diagnostics Pasteur, Marne La Moquette, France), was carried out. If this test was positive, the individual was considered to be HIV-1 positive. If the second test was negative (discordant), a final test, Capillus® (Cambridge Diagnostics, Galway Ireland), was performed and considered as the final result. CD4 count was performed on all individuals with a direct volumetric absolute CD4 counting instrument (Cyflow® Counter, Partec, Münster, Germany) at enrollment and at days 28 and 45 after treatment.[21] A FACSCount® instrument (Becton, Dickinson and Company, Franklin Lakes, NJ) was used to validate the Cyflow data and served as a quality control and back-up instrument for the Cyflow. Blood samples (at least 2 mL) for CD4 count and viral load (VL) were collected between 11 and 12 AM and analyzed within 3 hours. HIV-1 VL was determined from 200 μL of frozen plasma collected. The Roche Amplicor Monitor 1® technique was used to amplify and quantify viral RNA according to the manufacturer's instructions. The range of VL detection was between 400 and 750,000 copies/mL. At the time the study was carried out, antiretroviral therapy was not available in this setting.

Statistical Analysis

Data were double entered and cleaned in Epi-info (version 6.04b; Centers for Disease Control and Prevention, Atlanta, GA). Proportions were compared using the χ^2 or Fisher's exact test (when required); Student's *t* test was used for continuous variables. Paired *t* test was used for within patients' comparisons. Nonparametric tests (Wilcoxon or Kruskal-Wallis) were used for non-normally distributed variables. Linear regression modeling was used to assess the risk factors of CD4 count change after malaria treatment. Non-normally distributed variables, such as CD4 count and parasite density, were log-transformed. Risk factors with a P value <0.10 and modifying the model were retained. All reported P values are two-sided. All analyses were performed using a STATA statistical analysis software package.[29]

RESULTS

A total of 327 patients with laboratory confirmed uncomplicated malaria were included in the study. At enrollment, HIV-1 infection prevalence was 32.1% (105/327). HIV-1–infected and –uninfected patients had different demographic and clinical characteristics (Table 1). Compared to HIV-1–negative patients, positive ones were older (mean age 29.4 vs. 24.4 years, $P < 0.001$), had a lower mean Hb (126 vs. 140 g/L, $P < 0.001$), and women were more represented (63.8% vs. 43.9%, $P = 0.001$). Body temperature tended to be higher in HIV-1–positive patients and was associated with increasing parasite density ($P = 0.006$). The median CD4 count was significantly higher ($P < 0.001$) in HIV-1–negative (459 cells/μL; CI 95%: 425 to 517) than in HIV-1–positive patients (274 cells/μL; CI 95%: 234 to 347), but both were significantly lower than an expected average of 830 cells/μL (both $P < 0.001$).[22] Furthermore, among HIV-1–positive patients, 53.9% had a CD4 count below 300/μL and 28.7%, below 200/μL. No significant correlations were found between CD4 count and other variables, such as parasite density, fever, age, or sex.

The geometric mean viral load in HIV-1–infected patients was $10^{4.86}$ (95% CI: $10^{4.71}$ to $10^{5.00}$). Eight patients (8%) had an undetectable viremia (<400 RNA copies/μL) whereas 11 patients (11%) had >750,000 RNA copies/μL. No significant correlation between viral load and parasite density was found.

TABLE 1. Baseline Characteristics of Enrolled Study Population According to HIV-1 Status (Zambia 2006)

	No HIV-1 Infection (n = 222)	HIV-1 Infected (n = 105)	*P* Value*
Mean weight, kg (SD)	56.8 (9.8)	57.5 (13.7)	0.63
Number of women, %	97 (43.9)	67 (63.8)	0.001
Mean age, years (SD)	24.4 (8.7)	29.4 (7.3)	<0.001
Mean body temperature, °C (SD)	37.2 (1.3)	37.4 (1.3)	0.14
Mean white blood cell count, $\times 10^9$/L (SD)†	5.3 (1.9)	5.1 (1.7)	0.40
Mean Hb, g/L (SD)	140 (21)	126 (25)	<0.001
Mean (geometric) parasite density, per μL (range)†	10,334 (378–120,960)	10,035 (390–158,894)	0.84
Gametocytes prevalence, *n* (%)	4 (1.8)	3 (2.9)	0.53
Median CD4 count, per μL (95% CI)‡	459 (425 to 517)	274 (234 to 347)	<0.001
Number of CD4 < 200/μL, %‡	18 (9.6)	32 (28.7)	<0.001
Number of CD4 < 300/μL, %‡	49 (22.6)	55 (53.9)	<0.001
Mean (geometric) HIV-1-1 RNA copies, per μL (SD)§	$10^{4.86}$ ($10^{0.65}$)	4.86 (0.65)	

**P* value based on Chi square, Kruskal-Wallis, or one way-ANOVA as required.
†Data on WBC were missing in 2 patients in the non-HIV-1–infected group and in 2 in the HIV-1–infected group.
‡Data on CD4 cells count were missing in 5 patients in the non-HIV-1–infected group and in 3 in the HIV-1–infected group.
§Outside the detection area for 8 (8%) patients (<400 copies/μL) on day 0, and >750,000 copies/μL in 11 (11%) patients.

Before day 45, 61 (18.6%) had been lost to follow-up, 8 (2.4%) were excluded (3 withdrew, 2 hospitalized for non-malaria–related reasons, 3 for protocol violations), and 26 (8.5%) were classified as treatment failures and were consequently removed from the cohort during follow-up. Baseline data of patients who completed the follow-up visits were compared with those who did not: no significant difference was found in HIV-1 status, age, sex, CD4 count, and HIV-1 RNA VL. At day 45, 22 patients had recurrent parasitemia (recrudescence or new infection); a blood sample for all the laboratory tests was available for 20 (90.1%) of them; 210 patients responded adequately to treatment, and blood samples for all laboratory tests (HIV, CD4 count, and viral load if HIV infected) were available from 188 (89.5%) of them.

In 190 successfully treated patients at day 28, the absolute CD4 count after treatment had increased significantly in both HIV-1–infected (median: 447 CD4 cells/μL, CI 95%: 378 to 521; paired *t* test, $P < 0.001$) and HIV-uninfected patients (median: 811 cells/μL, CI 95%: 779 to 888; paired *t* test, $P < 0.001$) (Fig. 1A). As compared to day 0, the absolute (117 CD4 cells/μL vs. 292 CD4 cells/μL; $P < 0.001$) and relative (42% vs. 61%; $P = 0.04$) increment of CD4 count was significantly lower in HIV-1–positive than in HIV-1–negative patients. At day 28, 28.7% of HIV-1–positive patients had CD4 count <300 cells/μL and 13.4%, <200 cells/μL (Fig. 1B). After successful treatment, HIV-1 RNA concentration had decreased by 0.1 log unit at day 28 of follow-up (n = 68; paired *t* test, $P = 0.34$). CD4 count ($P = 0.67$) and HIV-1 RNA concentration ($P = 0.48$) were similar at days 28 and 45 of follow-up.

We analyzed risk factors for CD4 count change between day 0 (before antimalarial treatment), and days 28 and 45. We only report the changes between days 0 and 45 as we observed no difference between days 28 and 45. By univariate analysis, body temperature, CD4 count at day 0, and HIV-1 status were significantly associated with CD4 count change (Table 2). Body temperature was excluded from the multivariate analysis because it did not contribute significantly to the final model. As HIV-1 status influenced the correlation between CD4 count change and CD4 count at day 0, we present a linear regression model by HIV-1 status (Fig. 2). The CD4 count change was significantly and inversely correlated with CD4 count at day 0 for both HIV-1–negative (slope −0.669, $P < 0.001$) and HIV-1–positive patients (slope −0.236, $P = 0.03$). Due to effect modification (difference between slopes, $P < 0.001$), HIV-positive patients with lower CD4 counts at enrollment returned to lower values than the HIV-1–negative patients.

Patients With Treatment Failure at Day 45

In these patients (all with detectable parasitemia), CD4 count and viral load at day 45 were similar than those at day 0. In HIV-1–negative patients, the CD4 count at day 45 was significantly lower (median 598 cells/μL, CI 95%: 420 to 674) than that in the successfully treated patients (median 831 cells/μL, CI 95%: 791 to 875) ($P < 0.001$). In HIV-1–positive patients, such differences did not reach statistical significance because of low statistical power ($P = 0.24$).

DISCUSSION

After successful antimalarial treatment, absolute CD4 count increased significantly in adult patients with uncomplicated malaria, regardless of their HIV-1 status. For both for HIV-1–infected and non-HIV-1–infected individuals, this increase was inversely related with the baseline values before treatment. However, in HIV-1–infected patients with low CD4 count at enrollment, the increase was significantly lower than in non-HIV–infected patients. Therefore, the overall difference in CD4 count between HIV-1–negative and –positive patients became larger after malaria treatment, both at day 28 and day 45.

The temporarily loss of T cell in the peripheral circulation, described in non-HIV-1–infected patients with acute *Plasmodium falciparum* is probably due to a temporary disease-induced reallocation of malaria-specific T cells.[23] The lower increase of CD4 count after successful antimalarial treatment, observed in HIV-1–positive patients with low CD4 count is probably due to a lower number of malaria-specific

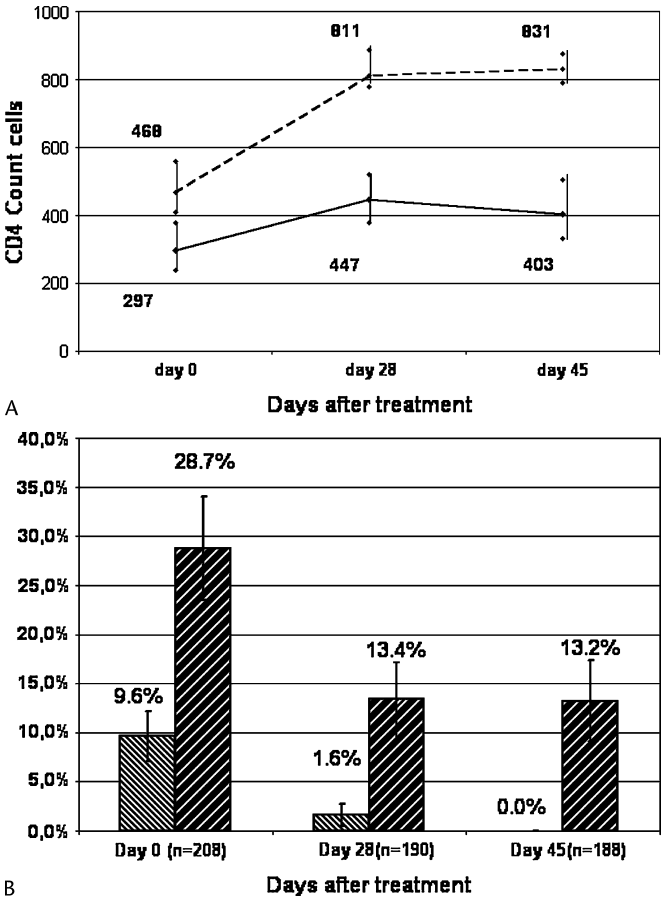

FIGURE 1. A, Median CD4 count (cells/μL) at days 0, 28, and 45 in patients successfully treated for malaria according to HIV-1 status (Zambia 2006). Values shown with 95% CIs. Day 28 or day 45 versus day 0: both $P < 0.001$ (paired t test). Only patients with measurements on day 0 and day 28 or day 45 were included in the analyses. B, Percentage of patients with CD4 count <200 cells/μL at days 0, 28, and 45 according to HIV-1 status (Zambia 2006): ▨ HIV-1–negative or ▨ HIV-1–positive (values shown with 95% CIs). Only patients successfully treated and with at least 2 measurements were analyzed. Differences between day 0 and day 28 or day 45: $P < 0.001$.

CD4 cells removed from the peripheral circulation during the clinical episode. This is compatible with the observed higher risk of clinical malaria[2,3] and recrudescence[4] in individuals with low CD4 counts.

Our study did have some limitations. First, CD4 cells were assessed only 4 weeks after antimalarial treatment. However, these levels could have been reached earlier after treatment. Indeed, previous studies in HIV-negative children have reported normal CD4 cells levels 7 to 10 days after successful treatment.[17,24] Second, we did not assess CD4 counts before the malaria episode. In HIV-infected patients with clinical malaria, activated CD4 cells, which are more susceptible to HIV than naïve T cells, could be readily lost and the CD4 count could return to lower level.[14] However, it is most likely that several malaria episodes are needed to observe a destruction of CD4 cells and a faster progression toward full-blown AIDS.

TABLE 2. Univariate Linear Regression of Risk Factors for Log 10 CD4 Count Change at Day 45 After Successful Antimalarial Treatment (Zambia 2006)

	All Univariate	
Risk Factor	**Slope**	***P* Value**
Male	−0.01125	0.74
Weight, kg	−0.00038	0.78
Age, years	−0.00375	0.06
Body temperature at enrollment, °C	0.08135	<0.001
Log_{10} parasite count/μL, log units	0.00338	0.91
Log_{10} CD4/μL at day 0, log units	−0.33090	<0.001
Log_{10} HIV-1 RNA copies/μL, log units	0.46567	0.27
HIV-1 status	−0.12810	<0.01
Drug taken	0.00087	0.98

*Only CD4 and HIV-1 status were retained in the final model. HIV-1 modified the result.

Patients with recurrent parasitemia at day 45 had similar CD4 counts as during the clinical episode, indicating that not only clinical malaria but also asymptomatic malaria parasitemia could alter CD4 count. As microscopy only detects a total parasite load above 10^8 in adults, this might even apply to patients with microscopically undetectable parasitemia.

Former reports mention that HIV-1 patients with a CD4 count <200/μL have a higher risk of parasitemia or clinical malaria compared to those with a higher CD4 count.[2,25]

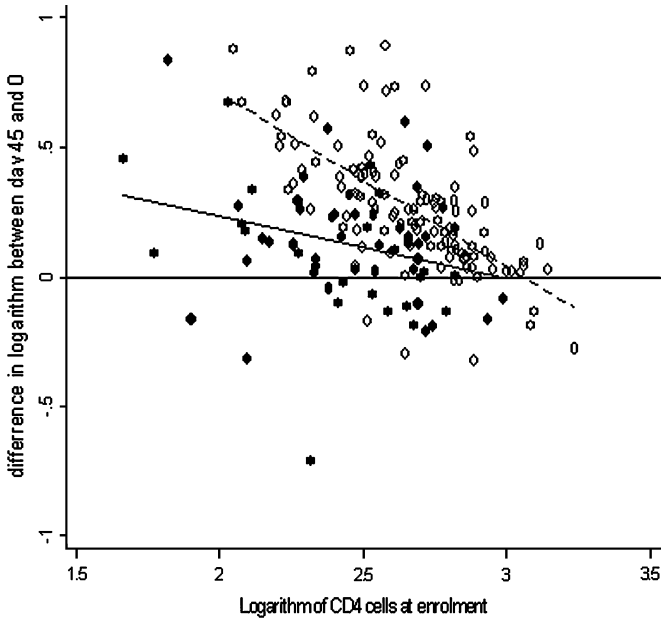

FIGURE 2. Log 10 difference on day 45 after successful antimalarial treatment versus log 10 CD4-cell count at day 0 (Zambia 2006). CD4 count change was significantly and inversely correlated with CD4 count at day 0 for both HIV-1–negative (slope, −0.669; $P < 0.001$) and HIV-1–positive patients (slope, −0.236; $P = 0.03$) (difference between slopes: $P < 0.001$). ○ = HIV negative (—: regression line); ● = HIV positive (—: regression line).

However, CD4 count in these patients was assessed during or just after the malaria episode. HIV-1–infected patients with CD4 count <300/μL were reported to have an increased risk of treatment failure, recrudescence, and new infections.[4,26] As malaria by itself causes a reversible decrease in CD4 count, HIV-1–infected individuals might be at risk for clinical malaria and malaria treatment failure at higher CD4 levels than reported so far. Considering that HIV-1–infected patients with CD4 <300/μL at enrollment had mean increase of 134 CD4/μL after successful treatment, the threshold for an increased risk of malaria treatment failure (new infections or recrudescence) probably lies ~400 CD4 cells/μL. This is consistent with a recent study that reported the an increased risk for clinical malaria when CD4 count was below 400/μL.[27]

No change in viral load was observed at day 45 in parasitemic patients; after successful treatment, we observed a non-significant decrease. This is in contrast with previous reports of a substantial change of the viral load after successful malaria treatment.[12,13]

In countries with limited resources, CD4 count is the chosen marker to monitor the progression of HIV-1 infection, to decide on antiretroviral treatment, and to assess its impact.[28] The results of our study clearly indicate that the interpretation of the absolute CD4 count may be biased during or just after a clinical malaria episode. Therefore, caution is necessary when applying this method in malaria-endemic areas. Before making any decision on the management of HIV-1–positive individuals, their malaria status should be assessed.

ACKNOWLEDGMENTS

We thank all the patients and their families who contributed to this study. Sincere thanks also to the staff of the health centers where the study was carried out. We are also grateful to all the staff of the Tropical Disease Research Centre, Ndola. The study was funded by the Belgian Development Cooperation in the framework of an institutional collaboration between the TDRC in Ndola and the ITM in Antwerp. The funding source was not involved in any aspect of the study.

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