ABS NO: TUPDB104

Epidemiology of malaria in HIV infected patients on ART in Uganda: a prospective cohort study

R.Kasirye [1], J.Levin [1], P.Munderi [1], L.Okell [2], S.Walker [3], A.Mugisha [1], H.Grosskurth [1,2]

[1]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [2]London School of Hygiene and Tropical Medicine, London UK; [3]MRC Clinical Trials Unit, London, UK

Background

There is wide geographical overlap in occurrence between malaria and HIV infection, interaction between these two diseases has major public health implications [WHO 2004].

Among HIV positive patients who are not yet on combination ART (cART), co-infection with malaria has been associated with an increase in HIV1-RNA [Kublin et al, 2005].

Increased rates of malaria have also been associated with declining immune status [French et al, 2001].

We assessed the incidence of malaria and its potential risk factors in a cohort of HIV infected Ugandans on cART, who were enrolled in the DART trial.

Objectives

1. To estimate the incidence of malaria in relation to time on ART.

2. To assess the association between malaria and baseline CD4 count, WHO clinical stage, haemoglobin, body mass index, age, education, gender and use of cotrimoxazole.

Methods

At enrolment into the DART trial; WHO clinical stage, CD4 count, haemoglobin, socio-demographic data, height & weight measurements were recorded on all subjects.

Prescription of cotrimoxazole to prevent opportunistic infections during the study was at the doctors discretion.

Patients were reviewed monthly by a study nurse and every 3 months or whenever acutely ill by a study doctor.

Incident febrile episodes and a recent history of a febrile illness were investigated for malaria as well as for other possible infectious illnesses.

Incident malaria is defined as a febrile illness or recent history of one plus peripheral blood film parasitaemia.

Incidence rates for malaria were calculated overall and separately for each year of follow-up.

We assessed potential risk factors for malaria by fitting unadjusted and adjusted Cox proportional hazard regression models. For continuous explanatory variables, fractional polynomials were fitted (Royston et al. 1999) to allow for non-linear relationships.

Results

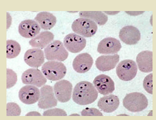
1020 participants enrolled in the DART Trial at the Entebbe site were followed for a median of 4.8 years

51(5%) patients were lost to follow up and mean follow up was 2.3 years.

2013 febrile episodes were reported in 638 patients.

In 1375 febrile episodes (68%), there was also plasmodium parasitaemia on the peripheral blood film.

- Plasmodium falciparum 97.7%
- Plasmodium malariae 1.5%
- Other plasmodium ssp. 0.8%



Plasmodium falciparum on thin blood film

Episodes of malaria (with a range of 0 – 22 episodes) occurred in 524 (51%) of patients

- mean number of episodes experienced per person: 1.3
- median number of episodes experienced per person: 1

Baseline CD4 count, use of cotrimoxazole prophylaxis, level of education and age at enrolment were associated with risk of malaria (see table)

Cotrimoxazole was protective against malaria (adjusted HR 0.40. P<0.001)

There is a non linear association between baseline CD4 count and occurrence of malaria

- Risk of malaria was greatly increased when CD4 was <10 cells/mm^3 (14% of study population).
- At higher baseline CD4 counts the risk of malaria was constant (p<0.001)

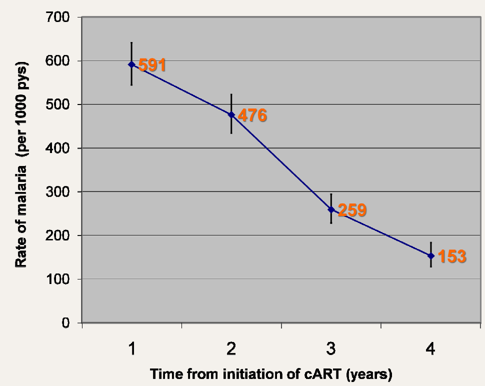
The relationship between age and risk of malaria was also non-linear

- increasing risk up to an age of about 40 and there after decreasing slightly (p=0.042).

Higher education was associated with a lower the risk of malaria (p<0.001)

There was a non significant trend (0.05<p<0.1) towards lower rates in women and those with higher baseline BMI and no effect (p>0.3) of baseline WHO stage or haemoglobin.

Incidence of malaria over time on cART



- The crude malaria rate was 383 episodes per 1000 person years
- Rates of malaria decreased with time on cART

Factors associated with malaria

Factor (levels)		Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95%)	P-value (sequential)
Use of Cotrimoxazole	No	1	1	
	Yes	0.39 (0.32;0.48)	*0.40 (0.33;0.48)	<0.001
Baseline CD4 count	1/CD4	1.33 (1.01;1.75)	**1.54 (1.17;2.02)	<0.001
Age at enrolment	$(age)^3$	1.02 (1.00;1.04)	1.03 (1.01;1.05)	0.042
	Age ^{3} logage	0.99 (0.98;1.00)	0.98 (0.97;0.99)	
Sex	Male	1		
	Female	0.94 (0.84;1.05)		0.079
Education	None	1	1	<0.001
	Secondary	0.70 (0.62;0.79)	0.70 (0.63;0.79)	
	Tertiary	0.57 (0.43;0.70)	0.55 (0.43;0.70)	
Baseline BMI (kg/m^2)	Per unit increase	0.99 (0.97;1.00)		0.097
Baseline hemoglobin (g/dl)	Per unit increase	1.01 (0.98;1.04)		0.37
Baseline WHO stage	Stage 2	1		0.39
	Stage 3	0.97 (0.86;1.10)		
	Stage 4	1.06 (0.91;1.24)		

*not adjusted for time on ART
**HR>1 means higher risk at lower CD4's

Discussion

Initiation of cART, with recovery of the immune system, results in a reduction of rates of malaria.

Concurrent use of cotrimoxazole prophylaxis is protective against malaria (HR 0.40 P<0.001), as previously reported [Mermin et al, 2006] also see DART cotrimoxazole poster (MOPEB020).

At very low CD4 counts (< 10 cells/mm3) there is an increased risk of malaria.

A higher level of education may be a surrogate measure for socioeconomic status and is associated with lower risk of malaria

Implications

In countries where both HIV infection and malaria contribute significantly to disease burden, the indirect effect of ART in combination with other control measures could help reduce this burden.

Before and during ART, additional malaria prevention interventions should be targeted at the more vulnerable patients with advanced immune suppression and low education.

References

1.Kublin JG, Patnaik P, Jere CS et al. (2005) Effect of plasmodium falciparum malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. *The lancet vol.* ***365****,233-240.*
2.Mermin J, Ekwaru JP, Liechty CA et al.(2006) Effect of cotrimoxazole prophylaxis, antiretroviral therapy and insecticide-treated bednets on the frequency of malaria in HIV-1 infected adults in Uganda: a prospective cohort study. *The lancet vol.****367****:1256-61.*
3.Neil F, Nakiyingi J, Lugada E et al.(2001) Increasing rates of malarial fever with deteriorating immune status in HIV-1 infected Ugandan adults.*AIDS,****15****:899-906.*
4.Royston P, Ambler G and Sauerbrei W. (1999). The use of fractional polynomials to model continuous risk variables in epidemiology. *International journal of Epidemiology* **28**; 964 – 974.
5.World Health Organisation. *Malaria and HIV interactions and their implications for public health policy.* Report of WHO technical consultation, Geneva, Switzerland June 2004.

Acknowledgments

We thank all the patients and staff from all the centres participating in the DART trial. **University of Zimbabwe, Harare, Zimbabwe:** A Latif, J Hakim, V Robertson, A Reid, E Chidziva, R Bulaya-Tembo, G Musoro, F Taziwa, C Chimbetete, L Chakonza, A Mawora, C Muvirimi, G Tinago, P Svovanapasis, M Simango, O Chirema, J Machingura, S Mutsai, M Phiri, T Bafana, M Chirara, L Muchabaiwa, M Muzambi. **MRC Programme on AIDS/Uganda Virus Research Institute, Entebbe, Uganda:** H Grosskurth, P Munderi, G Kabuye, D Nsibambi, R Kasirye, E Zalwango, M Nakazibwe, B Kikaire, G Nassuna, R Massa, K Fadhiru, M Namyalo, A Zalwango, L Generous, P Khauka, N Rutikarayo, W Nakahima, A Mugisha, J Todd, J Levin, S Muyingo, A Ruberantwari, P Kaleebu, D Yirrell, N Ndembi, F Lyagoba, P Hughes, M Aber, A Medina Lara, S Foster, J Amurwon, B Nyanzi Wakholi. **Joint Clinical Research Centre, Kampala, Uganda:** P Mugyenyi, C Kityo, F Ssali, D Tumukunde, T Otim, J Kabanda, H Musana, J Akao, , H Kyomugisha, A Byamukama, J Sabiiti, J Komugyena, P Wavamunno, S Mukiibi, A Drasiku, R Byaruhanga, O Labeja, P Katundu, S Tugume, P Awio, A Namazzi, GT Bakeinyaga, H Katabira, D Abaine,J Tukamushaba, W Anywar, W Ojiambo, E Angweng,S Murungi , W Haguma, S Atwiine,J Kigozi. **Infectious Diseases Institute (formerly the Academic Alliance) Makerere University, Mulago, Uganda:** E Katabira, A Ronald, A Kambungu, F Lutwama, A Nanfuka, J Walusimbi, E Nabankema, R Nalumenya, T Namuli, R Kulume, I Namata, L Nyachwo, A Florence, A Kusiima, E Lubwama, R Nairuba, F Oketta, E Buluma, R Waita, H Ojiambo, F Sadik, J Wanyama, P Nabongo. **The AIDS Support Organisation (TASO), Uganda:** R Ochai, D Muhweezi. **Imperial College , London, UK:** C Gilks, K Boocock, C Puddephatt, D Winogron, J Bohannon. **MRC Clinical Trials Unit, London, UK:** J Darbyshire, DM Gibb, A Burke, D Bray, A Babiker, AS Walker, H Wilkes, M Rauchenberger, S Sheehan, L Peto, K Taylor, M Spyer, A Ferrier, B Naidoo, D Dunn, R Goodall. **DART Virology Group:** P Kaleebu (Co-Chair), D Pillay (Co-Chair), V Robertson, D Yirrell, S Tugume, M Chirara, P Katundu, N Ndembi, F Lyagoba, D Dunn, R Goodall, A McCormick. **DART Health Economics Group:** A Medina Lara (Chair), S Foster, J Amurwon, B Nyanzi Wakholi, J Kigozi, L Muchabaiwa, M Muzambi. Independent DART Trial Monitors: R Nanfuka, C Mufuka-Kapuya. Trial Steering Committee: I Weller (Chair), A Babiker (Trial Statistician), S Bahendeka, M Bassett, A Chogo Wapakhabulo, J Darbyshire, B Gazzard, C Gilks, H Grosskurth, J Hakim, A Latif, C Mapuchere, O Mugurungi, P Mugyenyi; Observers: C Burke, S Jones, C Newland, S Rahim, J Rooney, M Smith, W Snowden, J-M Steens. Data and Safety Monitoring Committee: A Breckenridge (Chair), A McLaren (Chair-deceased), C Hill, J Matenga, A Pozniak, D Serwadda. Endpoint Review Committee: T Peto (Chair), A Palfreeman, M Borok, E Katabira. **Funding:** DART is funded by the **UK Medical Research Council**, the **UK Department for International Development (DFID)**, and the **Rockefeller Foundation**. **GlaxoSmithKline, Gilead** and **Boehringer-Ingelheim** donated first-line drugs for DART.

Presented at IAS 2009 in Cape Town - South Africa