

High risk of neutropenia in HIV-infected children following treatment with artesunate-amodiaquine for uncomplicated malaria in Uganda

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Abstract

Background: Artemisinin-based combination therapies are rapidly being adopted for the treatment of malaria in Africa, yet there are limited data on safety and efficacy among HIV-infected populations.

Methods: We compared malaria treatment outcomes between cohorts of HIV-infected and HIV-uninfected children in Uganda followed for 29 and 18 months, respectively. Malaria was treated with artesunate plus amodiaquine and outcomes assessed using standardized guidelines. HIV-infected children received trimethoprim-sulfamethoxazole prophylaxis and antiretroviral therapy according to current guidelines.

Results: Thirty-five malaria episodes among 26 HIV-infected participants and 258 malaria episodes among 134 HIV-uninfected children were included. Twelve HIV-infected children were receiving antiretroviral therapy with 11 receiving zidovudine. Malaria treatment was highly efficacious in both the HIV-infected and HIV-uninfected cohorts (28-day risk of recrudescence 0% and 3.6%, respectively) however, there was a trend towards increased risk of recurrent malaria in the HIV-uninfected children (2.9% vs. 13.2% respectively, $p=0.08$). Importantly, the risk of neutropenia 14 days after treatment with artesunate plus amodiaquine was higher in HIV-infected compared to HIV-uninfected children (45% vs. 6%, respectively, $p<0.001$). All neutropenia episodes in HIV-uninfected children were of mild to moderate severity while 16% of neutropenia episodes in the HIV-infected cohort were severe or life-threatening ($<750/\text{mm}^3$). Among HIV-infected children, the risk of neutropenia was significantly higher in those receiving antiretroviral therapy (75% vs. 26%, $p=0.001$). We compared the risk of significant clinical events in HIV-infected children during the period of neutropenia to HIV-infected controls not treated with AS/AQ over the same time. There was a trend towards a higher risk of any significant clinical event in subjects treated with AS/AQ compared to those not treated with AS/AQ (57% vs. 35%, $p=0.16$).

Conclusions: Artesunate plus amodiaquine was highly efficacious for malaria treatment in HIV-infected children, but associated with a high risk of neutropenia, especially in the setting of concurrent antiretroviral use. Our findings highlight an urgent need for evaluation of alternative antimalarial therapies in HIV-infected individuals.

Background

- Control interventions for HIV and malaria are expanding in sub-Saharan Africa
- Access to cotrimoxazole (CTX) prophylaxis and antiretroviral therapy (ART) for HIV populations is increasing
- Artemisinin-based combination therapies (ACT) now recommended as 1st line anti-malarial therapy in most African countries
 - Artesunate + amodiaquine (AS/AQ)
 - Artemether-lumefantrine (AL)
- Limited data on interactions between HIV and antimalarial therapy in the era of ACT, CTX prophylaxis, and ART
 - Are the ACTs as efficacious in HIV-infected populations?
 - Are ACTs safe in HIV-infected populations?
 - Concern about overlapping toxicity profiles
 - Concern about pharmacological interactions

Objective

- To compare the efficacy and safety of AS/AQ for the treatment of uncomplicated malaria in HIV-infected and HIV-uninfected children in Kampala, Uganda

Study design

- Prospective study comparing efficacy and safety of AS/AQ for the treatment of uncomplicated malaria in 2 cohorts at Mulago Hospital, Kampala, Uganda
 - 601 healthy children 1–10 yrs randomly recruited from the community in Nov 04–Apr 05
 - 300 HIV-infected children aged 1–10 yrs enrolled from a designated HIV clinic in Oct 05–Aug 06
- All HIV-infected children on CTX prophylaxis, insecticide-treated bed nets (ITNs) and, if eligible, on ART
- Healthy children given ITNs in June 06 and HIV-tested in Feb 07

Follow-up

- Standard evaluation for clinical malaria
 - Blood smear for patients with fever (subjective or $T \geq 38^\circ\text{C}$) in previous 24 hrs
 - Malaria: fever + malaria parasites
- HIV-uninfected cohort randomized to receive AS/AQ, AL, or AQ/SP
 - Receive the same treatment for all subsequent episodes
- HIV-infected cohort treated with AS/AQ
- AS/AQ 3-day therapy directly observed

Follow-up (cont'd)

- 28-day treatment outcomes classified according to WHO 2005 criteria
- Clinical and laboratory adverse events graded using DAIDS toxicity guidelines
 - CBC and ALT measured on days 0 and 14
 - Asymptomatic lab abnormalities monitored 3 monthly as part of routine assessment
- Comparison groups
 - HIV-infected: all treatments with AS/AQ between Oct 05 and Apr 07 ($n=35$, 1–3 treatments per patient)
 - HIV-uninfected: up to the first 3 treatments with AS/AQ ($n=258$)

Results

Baseline characteristics

Variable	HIV-uninfected cohort (n=258)	HIV-infected cohort (n=35)
AS/AQ treatment %		
1 st	134 (54%)	26 (74%)
2 nd	76 (29%)	7 (20%)
3 rd	48 (19%)	2 (6%)
Mean age in yrs (SD)	6.3 (2.5)	7.2 (3.2)
ITN use, n(%)	42/258 (16%)	31/35 (89%)
Mean Day 0 temperature (SD)	37.9C (1.2)	38.2C (1.1)
Day 0 GMPD	10,152pa/ul	6,810pa/ul
P. Falciparum	245/258(95%)	30/35 (86%)
Hemoglobin g/dl, mean	11.7 (1.4)	11.8 (1.3)
Neutrophils per mm ³ , mean	4302 (2806)	3487 (2428)
ALT, mean (SD)	21.2 (17.0)	30.3 (27.1)

Response to AS/AQ therapy

28-day WHO outcomes	HIV-uninfected cohort (n=258)	HIV-infected cohort (n=35)	P value
ACPR	217/258 (84%)	33/35 (94%)	
ETF	2/258 (1%)	0	
LCF	19/258 (7%)	0	
LPF	12/258 (5%)	1/35 (3%)	
No outcome	8/258 (3%)	1/35 (3%)	
Risk of early failure or recurrent malaria	13.2% (9.6-18%)	2.9% (0.4-18.6%)	0.08
Risk of early failure or recrudescence	3.6% (1.9-6.9%)	0	0.25

ACPR=adequate clinical and parasitological response; ETF=early treatment failure; LCF=late clinical failure; LPF=late parasitological failure

Association between HIV and neutropenia 14 days following treatment with AS/AQ

	HIV-uninfected cohort	HIV-infected cohort	P value
Risk of neutropenia*	15/253 (6%)	14/31 (45%)	<0.001
Association between HIV and neutropenia			
Outcome	OR (95% CI)	P-value	
Neutropenia of mild severity or greater (< 1300/mm ³)	7.6 (3.9-15.0)	<0.001	
Neutropenia of moderate severity or greater (< 1000/mm ³)	24.6 (6.8-89.1)	<0.001	

*All patients had normal neutrophil counts on the day malaria diagnosed

Risk factors and clinical consequences of neutropenia among HIV-infected children

Risk factors for neutropenia among HIV-infected children		
Risk Factor	OR (95% CI)	P-value
Antiretroviral use*	2.3 (1.4-3.6)	0.001
Prior treatment with AS/AQ	1.6 (0.9-2.6)	0.04

*11/12 of children on ART were receiving AZT containing regimens, 8/12 on EFV

- Clinical consequences on neutropenia
 - Nested case-control study comparing clinical events in HIV-infected children treated with AS/AQ with neutropenia and age, CD4-matched HIV-infected controls
 - Risk of pneumonia higher in those with neutropenia (43% vs. 19%, $p=0.008$)

Summary

- AS/AQ efficacious for treatment of malaria in HIV-infected and uninfected children
- Trend towards lower risk of recurrent malaria due to re-infection among HIV-infected children
 - CTX prophylaxis and widespread ITN use
- AS/AQ associated with remarkably higher risk of neutropenia in HIV-infected children
 - Increased risk of clinical events
- Neutropenia in HIV was likely due to:
 - Additive effects of HIV, AQ, CTX, AZT-related bone marrow suppression
 - Increased AQ exposure due to CYP2C8 inhibition by trimethoprim and efavirenz
- AS/AQ should be avoided in HIV-infected individuals, particularly those on AZT
- Alternative antimalarial therapies should be identified for HIV individuals if these findings are confirmed

