

Outer Envelope Protein
 Transmembrane Protein
 Lipid Membrane
 Matrix Protein
 Major Capsid Protein
 RNA
 Protease
 Reverse Transcriptase
 Integrase

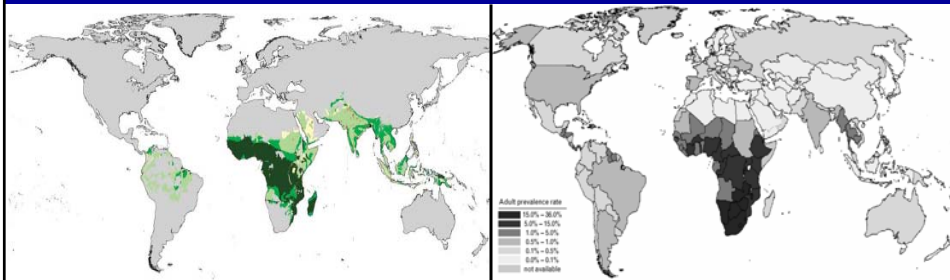
Malaria and HIV infection

Philip Rosenthal
 Dept. of Medicine
 UCSF

The co-epidemics of malaria and HIV infection

- Malaria
 - 300-500 million episodes each year (~90% in Africa)
 - Over 1 million deaths each year
- HIV infection
 - Infects about 33 million persons (~2/3 in Africa)
 - 2.5-3.5 million deaths in 2006

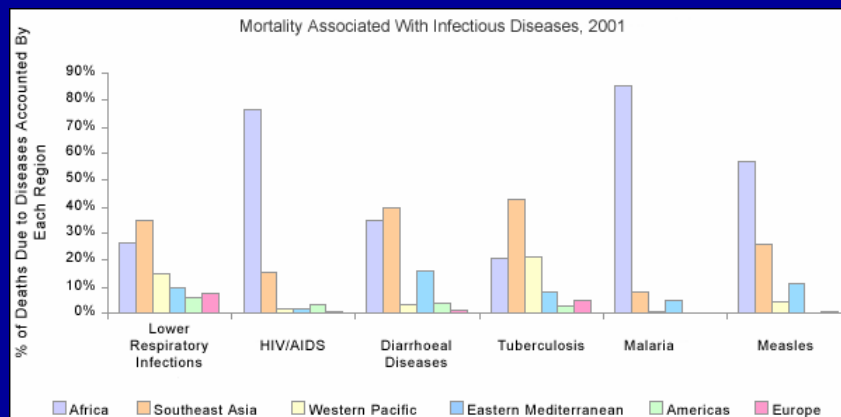
The co-epidemics of malaria and HIV infection



Malaria

HIV

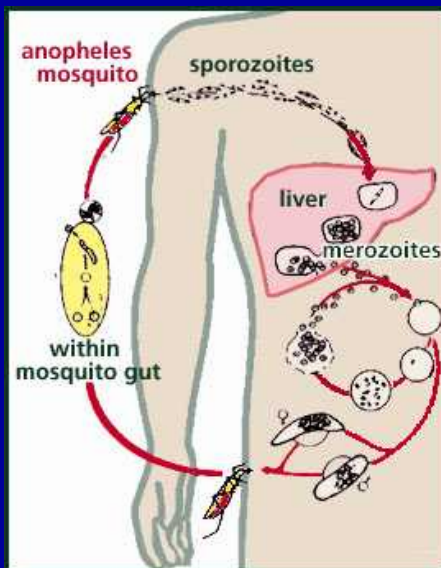
Malaria and HIV infection are of particular importance in Africa



Malaria

- 4 species human malaria parasites
 - *P. falciparum* responsible for nearly all serious morbidity and mortality
 - *P. falciparum* predominates in Africa
- Malaria is an acute illness
- Malaria is a chronic problem

Life cycle of malaria parasites



Malaria

Clinical presentations in endemic countries

- Infection can be very common
- Asymptomatic infection is common
- Most commonly uncomplicated febrile illness
- Severe disease in <1%
 - Cerebral malaria
 - Noncardiogenic pulmonary edema
 - Other acute syndromes
 - Severe anemia

Malaria

Clinical presentations in endemic countries

- Both incidence of disease and severity decrease with increasing age
- Severe disease can occur at any age, especially with decreasing transmission (decreasing immunity)
- Particular risk groups for severe falciparum malaria:
 - Young children
 - Pregnant women



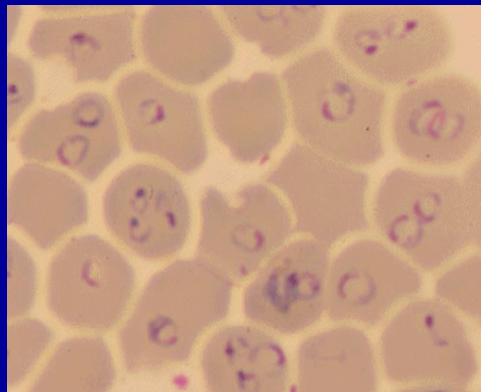
Malaria and HIV infection

Epidemiological differences

- Malaria
 - Primarily disease of young children
 - More common in rural areas
 - Marked geographic variation
- HIV infection
 - Most common in young adults
 - More common in urban areas

Diagnosis of malaria

- Most common means of diagnosis in Africa is clinical (fever = malaria)
- Blood smear is gold standard
- New rapid diagnostic tests are available



Malaria control

- Effective therapy
- Intermittent preventive therapy (IPT)
 - Pregnant women (IPTp)
 - Infants (IPTi)
- Vector control
 - Insecticide treated bednets
 - Indoor residual spraying
- Immunization



Available antimalarial drugs – Developing countries

- Chloroquine
- Amodiaquine
- Sulfadoxine/pyrimethamine (SP, Fansidar)
- Chlorproguanil/dapsone (Lapdap)
- Quinine
- Primaquine
- Artemisinin-based combination therapy (ACT)
 - Artemether/lumefantrine (Coartem)
 - Artesunate/amodiaquine (ASAQ)
 - Artesunate/SP
 - Artesunate/mefloquine
 - Dihydroartemisinin/piperaquine
 - Artesunate/chlorproguanil/dapsone (CDA)

Malaria and HIV

Differences in chemotherapy

- HIV
 - Expensive
 - Often entails toxicity
 - Chronic
 - Requires close supervision and follow-up
- Malaria
 - Short-term (usually 3 days)
 - Must be very cheap and well-tolerated
 - Provision of prompt tx (often outside of health centers) is primary concern
 - Follow-up is a secondary concern

Immune responses to malaria infection

- Young infants (< 6 mo.) relatively protected
 - Maternal antibody
 - Fetal hemoglobin
- Acquired immunity gradually develops with age
 - Cell-mediated immunity
 - Humoral immunity
- Pregnant women are at increased risk, especially with the first pregnancy

Malaria and HIV infection

- The onset of the HIV epidemic in Africa led to an expectation of dramatic changes in malaria epidemiology. Was malaria another major OI?
- Dramatic changes in malaria were not seen.
- Early studies showed only minor associations, if any, between malaria and HIV infection.
- Reexploration of this area over about the last decade has identified many important associations between the two diseases.

Malaria and HIV infection Key questions

- Does HIV infection alter the incidence and severity of malaria?
- Does HIV infection alter malaria treatment outcomes?
- Does malaria impact upon HIV infection?
- Do HIV prevention practices impact upon malaria?
- Do HIV treatment practices impact upon malaria?
- Does co-treatment of malaria and HIV infection entail particular risks?
- Can appreciation of the co-epidemics improve management?

Malaria and HIV infection

Key questions

- Does HIV infection alter the incidence and severity of malaria?
- Does HIV infection alter malaria treatment outcomes?
- Does malaria impact upon HIV infection?
- Do HIV prevention practices impact upon malaria?
- Do HIV treatment practices impact upon malaria?
- Does co-treatment of malaria and HIV infection entail particular risks?
- Can appreciation of the co-epidemics improve management?

Impact of HIV infection on malaria

Adults

- HIV infection diminishes acquired antimalarial immunity
- Cohort studies:
 - Increased frequency of parasitemia and clinical malaria in those with HIV
 - Increasing risk and higher parasitemia with increasing immunodeficiency
- Increases in malarial incidence up to about 2-fold (far below impact on classical OIs)

Effect of HIV on malaria- Uganda

- 484 adults studied 1990-98
- Prevalence parasitemia
 - HIV+ 11.8%
 - HIV- 6.3%
- Clinical malaria more common in HIV+
- Lower CD4 counts associated with higher parasite densities
- Malaria risk increased with falling CD4 count and advancing clinical stage

Whitworth J, et al: Lancet 356:1051, 2000

Effect of HIV on malaria- Malawi

- 349 adults studied 2000-2001
 - HIV positivity associated with parasitemia
 - CD4 and viral load were moderately, but inconsistently associated with parasitemia
- 660 HIV + adults studied 2002-2003
 - Incidence malaria higher in CD4 <200 compared to CD4 >500
 - Parasitemia not associated with CD4

Patnaik, et al., JID 192:984, 2005
Laufer, et al., JID 193:872, 2006

Impact of HIV infection on malaria Children

- Most studies: no increase in malarial incidence in HIV+ children
- Some studies: increased risk severe disease, anemia, transfusion, hospitalization

Van Eijk, et al. AJTMH 67:44, 2002

Summary Impact of HIV on malaria

- HIV is generally associated with more frequent and more severe malaria in adults
- Association is weak in children
- Therefore, the impact of HIV on malaria appears to represent loss of the age-specific immunity normally acquired against malaria

Malaria and HIV infection

Key questions

- Does HIV infection alter the incidence and severity of malaria?
- Does HIV infection alter malaria treatment outcomes?
- Does malaria impact upon HIV infection?
- Do HIV prevention practices impact upon malaria?
- Do HIV treatment practices impact upon malaria?
- Does co-treatment of malaria and HIV infection entail particular risks?
- Can appreciation of the co-epidemics improve management?

Impact of HIV infection on malaria treatment outcomes

- Several reports: HIV infection leads to increased rates of malaria treatment failure
- Was increased rate of treatment failure due to increased risk of recrudescence or new infection?
 - Malaria treatment failures commonly occur late after therapy (up to ~ 4 weeks)
 - Late failures may be due to drug failure (recrudescence) or new infection
 - Recrudescence and new infection can be distinguished by molecular methods

Impact of HIV infection on malaria treatment outcomes

- Uganda- HIV infection associated with >3-fold increased risk treatment failure in adults, but no increased risk in children
 - Treatment failures were primarily due to new infections, not tx failure

- W. Kenya- adults
 - Risk tx failure

HIV + (CD4 <200/ μ l)	HIV -
20.5%	7.7%

- Both total recurrences and recrudescences more common with HIV and most common with low CD4
- Multivariate analysis- risk factors for tx failure: HIV+, CD4 < 200/ μ l, severe anemia

Kanya, et al., JID 193:9, 2006
Shah, et al., JID 194:1519, 2006

Summary

Impact of HIV infection on malaria treatment outcomes

- Malaria treatment outcomes often worse for HIV+ individuals, especially adults
- Much of difference between HIV+ and HIV- outcomes is explained by the increased risk of recurrent malaria in HIV+ adults rather than decreased drug efficacy

Malaria and HIV infection

Key questions

- Does HIV infection alter the incidence and severity of malaria?
- Does HIV infection alter malaria treatment outcomes?
- Does malaria impact upon HIV infection?
- Do HIV prevention practices impact upon malaria?
- Do HIV treatment practices impact upon malaria?
- Does co-treatment of malaria and HIV infection entail particular risks?
- Can appreciation of the co-epidemics improve management?

Malaria and HIV transmission

- Anemia due to malaria is a major reason for blood transfusion in Africa
- Important goals:
 - Improved blood transfusion and testing
 - Avoidance of unnecessary transfusions

Malaria and HIV transmission

- Acute malaria increases HIV viral load (adults)
 - 0.25 log overall
 - 0.89 log with fever, parasite density > 2000/ μ l
- Viral loads returned to baseline within ~8 wks of effective therapy
- Association with CD4 uncertain
- Malaria leads to increased placental HIV
- Does placental malaria lead to increased mother-to-child transmission?
 - Conflicting results

Kublin, et al Lancet 365:233, 2005
Mwapasa, et al AIDS 18:1051, 2004

Overall interaction of HIV infection and malaria - modeling studies

- First model
 - Annual increased malaria attributable to HIV
 - Cases: 3 million
 - Deaths: 65,000
 - Interaction most important in areas with very high HIV seroprevalence and unstable malaria transmission- e.g. Southern Africa
 - Incidence clinical malaria $\uparrow \leq 28\%$
- Second model- Kenya population 200,000
 - Since 1980 disease interaction responsible for:
 - 8500 excess HIV infections
 - 980,000 excess episodes malaria

Korenromp, et al. Emerg Inf Dis 11:1410, 2006
Abu-Raddad, et al. Science 314:1603, 2006

Malaria and HIV infection

Key questions

- Does HIV infection alter the incidence and severity of malaria?
- Does HIV infection alter malaria treatment outcomes?
- Does malaria impact upon HIV infection?
- Do HIV prevention practices impact upon malaria?
- Do HIV treatment practices impact upon malaria?
- Does co-treatment of malaria and HIV infection entail particular risks?
- Can appreciation of the co-epidemics improve management?

TMP/SMX prophylaxis

- Well validated for prevention PCP, toxoplasmosis, bacterial infections
- Becoming the community standard for HIV + individuals in Africa (regardless of CD4 count)
- What is the impact of TMP/SMX prophylaxis on the incidence of malaria?

Antifolates in widespread use

Drug	DHFR inhibitor	DHPS inhibitor	Use
TMP/SMX	Trimethoprim	Sulfamethoxazole	Antibacterial; Prophylaxis in AIDS patients
SP (Fansidar)	Pyrimethamine	Sulfadoxine	Antimalarial
Lapdap	Chlorproguanil	Dapsone	Antimalarial
Malarone	Proguanil (+ Atovaquone)		Antimalarial

Impact of HIV interventions on the incidence of malaria in Ugandan adults

- 1363 HIV+ adults in Tororo, Uganda
- Serial interventions:
 - No intervention →
 - TMP/SMX →
 - ARV tx (usually D4T/3TC/NNRTI) →
 - ITNs
- Incidence of malaria measured

Impact of HIV interventions on the incidence of malaria in Ugandan adults

	Participants	Malaria episodes	Person-years of follow-up	Rate per 100 person-years
Fever and any <i>Pfalciparum</i> parasitaemia				
Phase 1	466	84	165	50.8
Phase 2	399	38	420	9.0
Phase 3	1035	14	398	3.5
Phase 4	989	30	1438	2.1

No intervention

TMP/SMX

ARV tx

ITN

Mermin, et al.: Lancet 367:1256, 2006

Impact of HIV interventions on the incidence of malaria

	Participants	Malaria episodes	Person-years of follow-up	Rate per 100 person-years	Cumulative effect of all interventions compared with no intervention				Additive effect of each intervention compared with preceding intervention			
					Unadjusted IRR (95% CI)	p	Adjusted IRR (95% CI)*	p	Unadjusted IRR (95% CI)	p	Adjusted IRR (95% CI)*	p
Fever and any <i>Pfalciparum</i> parasitaemia												
Phase 1	466	84	165	50.8	--	--	--	--	--	--	--	--
Phase 2	399	38	420	9.0	0.18 (0.12-0.27)	<0.0001	0.24 (0.15-0.38)	<0.0001	0.18 (0.12-0.27)	<0.0001	0.24 (0.15-0.38)	<0.0001
Phase 3	1035	14	398	3.5	0.07 (0.04-0.13)	<0.0001	0.08 (0.04-0.17)	<0.0001	0.38 (0.20-0.75)	0.0049	0.36 (0.18-0.74)	0.0056
Phase 4	989	30	1438	2.1	0.04 (0.03-0.06)	<0.0001	0.05 (0.03-0.08)	<0.0001	0.59 (0.32-1.11)	0.1	0.58 (0.30-1.11)	0.1

• Each intervention sequentially improved the control of malaria in Ugandan adults.

- TMP/SMX: 70% reduction
- ARVs: additional 50% reduction
- ITNs: additional 50% reduction

• Limitations: historical controls, adults, ability to capture episodes malaria not optimal

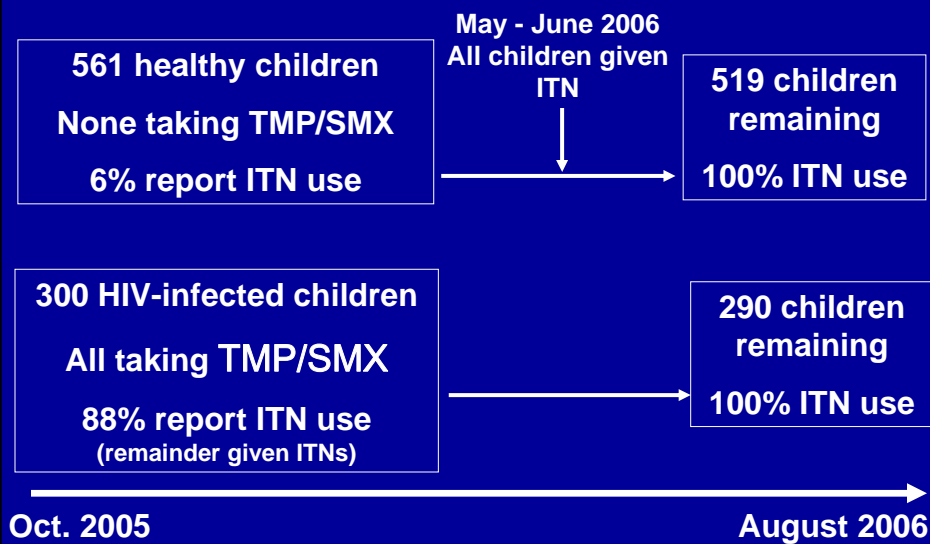
Mermin, et al.: Lancet 367:1256, 2006

Impact of HIV interventions on the incidence of malaria in Ugandan children

- Prospective comparison of malaria incidence in two cohorts in Kampala
 - Healthy children randomly selected from an area adjoining Mulago Hospital, enrolled at age 1-10
 - HIV-infected children enrolled from Mulago Hospital Pediatric ID Clinic, enrolled at age 1-10 (CHAMP)
- Children from both cohorts followed for all health care needs in study clinics open 7 days a week
- CHAMP cohort received standard HIV care
- Incidence of malaria studied
 - Attention to all health care needs
 - Monthly surveillance

Kanya, et al AIDS 21:2059, 2007

Study design



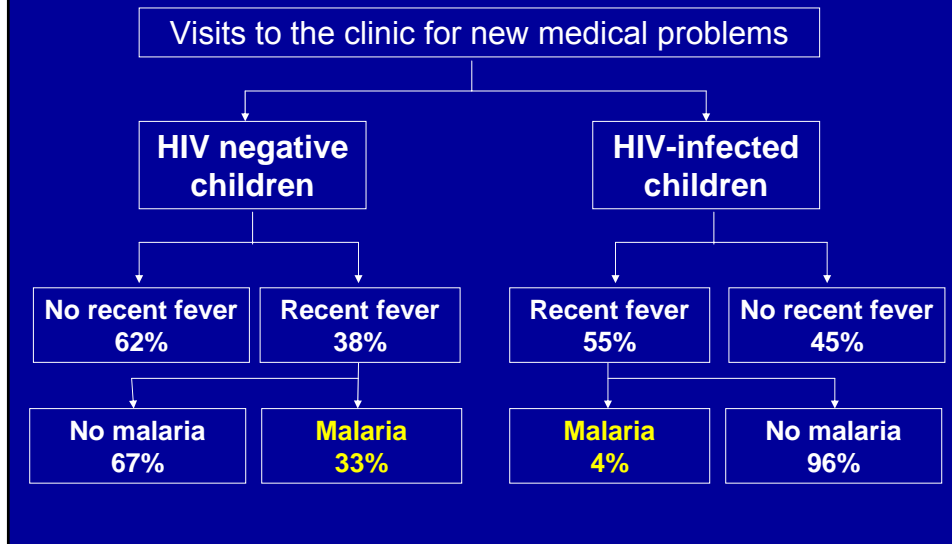
Baseline Characteristics

	HIV-infected children (n=300)	Healthy children (n=561)
Female	162 (54%)	266 (47%)
Mean age yrs (SD)	5.6 (2.6)	6.5 (2.6)
Parasite prevalence (enrollment)	0 (0%)	113 (20%)
% CD4		
Median (IQR)	21% (15-28%)	N/A
< 15%	74 (25%)	
15-20%	64 (21%)	
>20%	162 (54%)	
ARV use	35 (12%)	N/A

Effect of TMP/SMX and ITN use on malaria incidence

Cohort	Exposure group	Episodes of malaria	Person time (yrs)	Incidence (per 100 pyrs)
Healthy children	No TMP/SMX No ITN	356	340.3	104.6
	No TMP/SMX ITN	84	150.0	56.0
HIV-infected children	TMP/SMX No ITN	5	7.8	64.3
	TMP/SMX ITN	4	117.2	3.4

Prevalence of malaria among children with fever



Impact of HIV interventions

- Routine HIV interventions (TMP/SMX, ITNs) markedly diminish incidence malaria in HIV-infected children
- Fever in a child receiving these interventions is very unlikely to be due to malaria
- We must reconsider presumptive therapy in children of all fevers for malaria, especially in HIV+
- **But, does TMP/SMX select for mutations that mediate resistance to sulfadoxine-pyrimethamine?**

Did TMP/SMX use select for dhfr/dhps polymorphisms?

	HIV-infected (n = 9)	Community- based (n = 440)
Mean age (SD)	6.8 (2.6)	6.8 (2.7)
Infection with <i>P. falciparum</i>	9 (100%)	419 (95%)
Geometric mean parasite density	2769/ μ L	11791/ μ L
Mean temperature °C (SD)	37.3 (1.0)	37.7 (1.3)
Prevalence of <i>dhfr/dhps</i> mutations ^b		
<i>dhfr</i> 511	9/9 (100%)	79/80 (99%)
<i>dhfr</i> 59R	9/9 (100%)	65/80 (81%)
<i>dhfr</i> 108N	9/9 (100%)	80/80 (100%)
<i>dhfr</i> 164L	1/9 (11%)	0/80 (0%)
<i>dhps</i> 437G	9/9 (100%)	77/80 (96%)
<i>dhps</i> 540E	9/9 (100%)	76/80 (95%)

Kanya, et al AIDS 21:2059, 2007

Did TMP/SMX use select for dhfr/dhps polymorphisms?

	HIV-infected (n = 9)	Community- based (n = 440)
Mean age (SD)	6.8 (2.6)	6.8 (2.7)
Infection with <i>P. falciparum</i>	9 (100%)	419 (95%)
Geometric mean parasite density	2769/ μ L	11791/ μ L
Mean temperature °C (SD)	37.3 (1.0)	37.7 (1.3)
Prevalence of <i>dhfr/dhps</i> mutations ^b		
<i>dhfr</i> 511	9/9 (100%)	79/80 (99%)
<i>dhfr</i> 59R	9/9 (100%)	65/80 (81%)
<i>dhfr</i> 108N	9/9 (100%)	80/80 (100%)
<i>dhfr</i> 164L	1/9 (11%)	0/80 (0%)
<i>dhps</i> 437G	9/9 (100%)	77/80 (96%)
<i>dhps</i> 540E	9/9 (100%)	76/80 (95%)

Kanya, et al AIDS 21:2059, 2007

Summary

Impact of HIV prevention practices on malaria

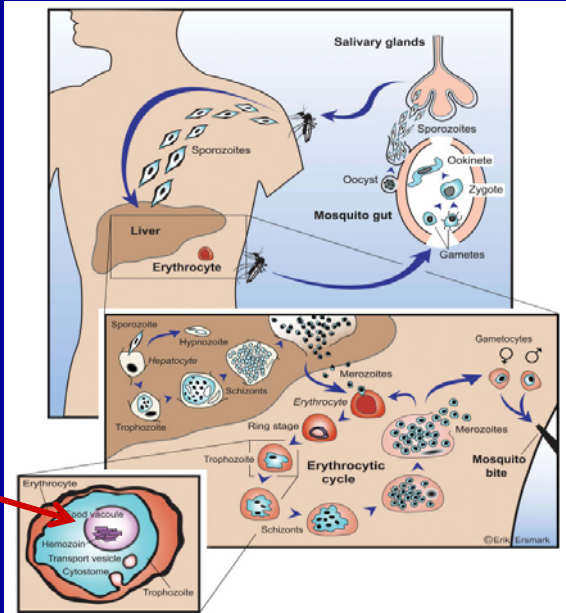
- TMP/SMX prophylaxis highly effective in preventing malaria despite high background prevalence of molecular markers of SP resistance
- Despite selection, due to its marked reduction on overall incidence of malaria, TMP/SMX decreased the overall burden of SP-resistant malaria
- How should these results affect management?
 - TMP/SMX prophylaxis and ITNs should be considered for all HIV-infected children living in malaria endemic areas.
 - With these preventative measures, malaria therapy should only be given after laboratory confirmation.

Malaria and HIV infection

Key questions

- Does HIV infection alter the incidence and severity of malaria?
- Does HIV infection alter malaria treatment outcomes?
- Does malaria impact upon HIV infection?
- Do HIV prevention practices impact upon malaria?
- **Do HIV treatment practices impact upon malaria?**
- Does co-treatment of malaria and HIV infection entail particular risks?
- Can appreciation of the co-epidemics improve management?

P. falciparum life cycle



Proteases
Falcipains
Plasmeprins

Aspartic proteases of *P. falciparum* and HIV

- *P. falciparum*
 - Family of plasmepsins
 - Mediate hydrolysis of erythrocyte hemoglobin
 - Aspartic protease inhibitors exert antimalarial activity
- HIV
 - Protease is key to pathogenesis and an important drug target
 - Aspartic protease inhibitors are leading antiretroviral drugs

In vitro antimalarial activity of HIV PIs

Drug	<i>P. falciparum</i> IC ₅₀ (μM)				Serum concentration with standard dosing (μM)		Serum concentration with boosted dosing (μM)	
	HB3	D6	Dd2	W2	C _{max}	C _{min}	C _{max}	C _{min}
Saquinavir	5.6	4.8	4.3	1.1	3.7	0.3	5.5	0.6
Ritonavir	4.7	7.9	6.9	1.2	15.5	5.1	NA	NA
Indinavir	5.8	15.6	31.2	4.1	10.3	0.3	17.2	0.4
Nelfinavir	15.2	23.0	19.1	6.5	6.0	3.3	NA	NA
Amprenavir	51.9	25.0	17.4	33.3	15.2	0.6	14.1	3.8
Lopinavir	1.4	2.0	2.1	0.9	NA	NA	15.6	8.8
Atazanavir	6.8	11.6	7.1	2.5	3.3	0.2	8.7	1.7

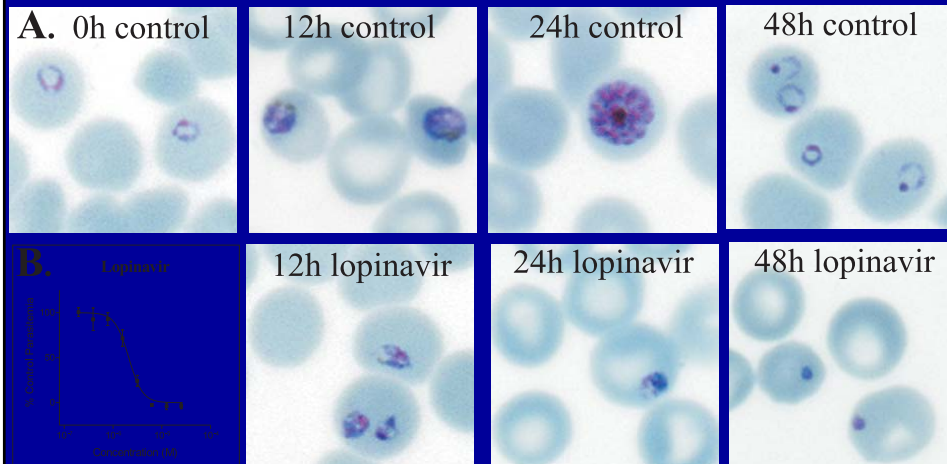
Parikh, et al., AAC 49:2983, 2005

In vitro antimalarial activity of HIV PIs

Drug	<i>P. falciparum</i> IC ₅₀ (μM)				Serum concentration with standard dosing (μM)		Serum concentration with boosted dosing (μM)	
	HB3	D6	Dd2	W2	C _{max}	C _{min}	C _{max}	C _{min}
Saquinavir	5.6	4.8	4.3	1.1	3.7	0.3	5.5	0.6
Ritonavir	4.7	7.9	6.9	1.2	15.5	5.1	NA	NA
Indinavir	5.8	15.6	31.2	4.1	10.3	0.3	17.2	0.4
Nelfinavir	15.2	23.0	19.1	6.5	6.0	3.3	NA	NA
Amprenavir	51.9	25.0	17.4	33.3	15.2	0.6	14.1	3.8
Lopinavir	1.4	2.0	2.1	0.9	NA	NA	15.6	8.8
Atazanavir	6.8	11.6	7.1	2.5	3.3	0.2	8.7	1.7

Parikh, et al., AAC 49:2983, 2005

Effect of lopinavir on cultured *P. falciparum* parasites



Parikh, et al., AAC 49:2983, 2005

HIV PIs have antimalarial activity

- Similar findings showing inhibition of parasite development by a number of other groups
- Activity also seen against malaria in a mouse model
- Serum from patients treated with PIs had antimalarial activity

Skinner-Adams, et al, 190:1998, 2004
Andrews, et al, AAC 50:639, 2006

HIV PIs have antimalarial activity

- PIs might be lead compounds for new antimalarial drugs?
- An advantage of a PI based antiretroviral regimen might be prevention of malaria.

Malaria and HIV infection Key questions

- Does HIV infection alter the incidence of malaria?
- Does HIV infection alter the severity of malaria?
- Does HIV infection alter malaria treatment outcomes?
- Does malaria impact upon HIV infection?
- Do HIV prevention practices impact upon malaria?
- Do HIV treatment practices impact upon malaria?
- Does co-treatment of malaria and HIV infection entail particular risks?
- Can appreciation of the co-epidemics improve diagnostic practices?

Drug interaction concerns

Table 4. Selected Drug Interactions Involving Antimalarials and ARVs or Other Selected Medications Commonly Used in the Care of HIV-Infected Patients in Sub-Saharan Africa

Antimalarial	ARVs and Other Medications ^a	Drug-Drug Interactions ^b
Amodiaquine	Efavirenz, saquinavir, lopinavir, tipranavir	Decreased metabolism of amodiaquine as a result of inhibition of CYP2C8; likely increased risk of amodiaquine-related hepatic and hematologic toxicity ^{26,27} ; hepatotoxicity has been observed in healthy volunteers given efavirenz and amodiaquine ²⁸
Artemisinin	Ketoconazole	Antagonism observed in vitro; clinical significance unknown ²⁹
Aloquone	Atazanavir sulfate Lopinavir Rifampin Ritonavir, tipranavir	Combination may decrease level of aloquone; clinical significance unknown ^{22,29}
Aloquone	Zidovudine	Decreases oral clearance of zidovudine; clinical significance unknown ³⁰
Dapsone	Rifampin	Decreases level of dapsone ³¹
Dapsone	Stavudine	May increase risk of peripheral neuropathy ³²
Dapsone	Co-trimoxazole ^a	May increase level of dapsone ³³
Doxycycline hydrochloride	Rifampin	May decrease level of doxycycline ³⁴
Halofantrine hydrochloride	PIs, NNRTIs	ARV effects on cytochrome P450 3A4 metabolism may cause inhibition of halofantrine metabolism with risk of significant cardiotoxicity ³⁵
Lumefantrine	PIs, NNRTIs	Controversial; theoretically, combination may cause Q-T interval prolongation; manufacturers recommend against combining others, including WHO, refute recommendation as not supported by evidence ^{31,34,37,38,39,40}
Proguanil hydrochloride	Ritonavir	Ritonavir may inhibit conversion of proguanil to cycloguanil; clinical significance unknown ⁴¹
Quinine	Ritonavir, delamanid mesylate, ritonavir-based PI regimens	Quinine levels may be increased by ARV-provoked inhibition of cytochrome P450 3A4 activity; risk of cardiac toxicity (Q-T interval prolongation) ⁴²
Quinine	Nevirapine, efavirenz	ARV-related induction of CYP 3A4 activity may decrease levels of quinine to subtherapeutic range ⁴³
Quinine	Rifampin	Increased clearance of quinine resulting in 5-fold increase in likelihood of malaria recrudescence after treatment ⁴⁴
Sulfadoxine-pyrimethamine	Co-trimoxazole Zidovudine	Combination may further increase risk of bone marrow toxicity ⁴⁵
Sulfadoxine-pyrimethamine	Co-trimoxazole	Known malaria cross-resistance between pyrimethamine and trimethoprim ⁴⁶

Brentlinger, et al. Arch Int Med 167:1827, 2007

Potential toxicity concerns Drug interactions

- 10 normal controls treated with artemether/lumefantrine (AL) without and then with concomitant lopinavir/ritonavir (Kaletra)
- Kaletra led to significant (~ 2-fold) increases in lumefantrine levels
- Interaction might be harmful (toxicity) or helpful (improved activity)
- Should we use artemether/lumefantrine to treat those with malaria while on ARV tx?

German, et al., CROI 2008

Unexpected toxicity of AS/AQ in HIV-infected children

- AS/AQ standard tx for malaria in ~15 African countries
- AS/AQ back-up tx in Uganda after artemether/lumefantrine
- Cohort of HIV+ children in Uganda
 - Treatment for uncomplicated malaria with AS/AQ
 - AQ has old concerns regarding hepatic and bone marrow toxicity

Neutropenia after treatment of uncomplicated malaria with AS/AQ

- HIV- cohort: 15/253 (6%) neutropenic
- HIV+ cohort: 14/31 (45%) neutropenic
- 16% of neutropenic episodes in the HIV+ cohort and none in the HIV- cohort were severe or life threatening ($<750/\text{mm}^3$)
- Risk of neutropenia significantly higher in those receiving ARV tx (usually included AZT)
- Therefore, AS/AQ, a standard new antimalarial regimen, entails increased toxicity risk in HIV-infected patients

Malaria and HIV infection

Key questions

- Does HIV infection alter the incidence and severity of malaria?
- Does HIV infection alter malaria treatment outcomes?
- Does malaria impact upon HIV infection?
- Do HIV prevention practices impact upon malaria?
- Do HIV treatment practices impact upon malaria?
- Does co-treatment of malaria and HIV infection entail particular risks?
- Can appreciation of the co-epidemics improve management?

Can appreciation of malaria and HIV epidemiology improve our ability to identify HIV-infected individuals?

- 1965 children and adults randomized to different antimalarial txs at 7 sites in Uganda (presented to clinics with fever)
- HIV seroprevalence
 - < 18 yrs: 45/1802 (2.5%)
 - ≥ 18 yrs: 50/163 (31%)
- Malaria in an adult is a red flag suggesting HIV infection

Can appreciation of malaria and HIV epidemiology improve our ability to identify HIV-infected individuals?

- Evaluation of 1000 consecutive patients referred for malaria microscopy (generally due to presentation with fever) at each of 7 health centers in Uganda
- Children (≤ 16 yrs)
 - 77 (1.7%) HIV+
 - A *negative* blood smear was associated with a higher odds of HIV infection (OR 1.9, CI 1.2-3.1)
- Adults
 - 270 (10.7%) HIV+
 - A *positive* blood smear was associated with a higher odds of HIV infection (OR 1.4, CI 1.0-2.0)
- **Fever with a negative blood smear in children and presentation with malaria in adults are both concerning for HIV infection in those presenting with fever.**

Bebell, et al, JAIDS, in press

Malaria in the HIV+ traveler

- Risks similar to those for general population
- Falciparum malaria is major risk for all non-immune individuals
- Standard precautions for travelers
 - Avoidance night-biting anopheline mosquitoes
 - Bednets (ITNs)
 - Insect repellent
 - Long sleeves in evening
 - Chemoprophylaxis

Bhadelia, et al, Am J Med, 120:574, 2007

Malaria chemoprophylaxis in the HIV+ traveler

- Chloroquine- only areas without resistant *P. falciparum* (Central America, Haiti)
- Mefloquine- neuropsych. toxicity
 - May confound Efavirenz effects
 - Decreases Ritonavir levels
 - MQ levels might be decreased by NNRTIs
- Malarone (Atovaquone/Proguanil)
 - Minimal drug interaction concerns
 - Simplest choice for most HIV-infected travelers
- Doxycycline
 - Photosensitivity, GI tox, Candidiasis
 - No known drug interactions

Bhadelia, et al, Am J Med, 120:574, 2007

Summary

Malaria and HIV infection

- Two very common infections in Africa and other developing countries
- Associations are relatively modest
- Importance of co-infection is profound

