Malaria and HIV infection

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 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?
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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


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


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

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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
  - 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/μl, severe anemia

<table>
<thead>
<tr>
<th></th>
<th>HIV + (CD4 &lt;200/μl)</th>
<th>HIV -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk tx failure</td>
<td>20.5%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

Kamya, et al., JID 193:9, 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

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• 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?
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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/μl
- 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

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 ↑ ≤ 28%
- Second model- Kenya population 200,000
  - Since 1980 disease interaction responsible for:
    - 8500 excess HIV infections
    - 980,000 excess episodes malaria

Malaria and HIV infection
Key questions

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• 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?
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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

<table>
<thead>
<tr>
<th>Drug</th>
<th>DHFR inhibitor</th>
<th>DHPS inhibitor</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP/SMX</td>
<td>Trimethoprim</td>
<td>Sulfamethoxazole</td>
<td>Antibacterial; Prophylaxis in AIDS patients</td>
</tr>
<tr>
<td>SP (Fansidar)</td>
<td>Pyrimethamine</td>
<td>Sulfadoxine</td>
<td>Antimalarial</td>
</tr>
<tr>
<td>Lapdap</td>
<td>Chlorproguanil</td>
<td>Dapsone</td>
<td>Antimalarial</td>
</tr>
<tr>
<td>Malarone</td>
<td>Proguanil (+ Atovaquone)</td>
<td></td>
<td>Antimalarial</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Participants</th>
<th>Malaria episodes</th>
<th>Person-years of follow-up</th>
<th>Rate per 100 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No intervention</td>
<td>466</td>
<td>84</td>
<td>165</td>
<td>50.8</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>399</td>
<td>38</td>
<td>420</td>
<td>9.0</td>
</tr>
<tr>
<td>ARVs</td>
<td>1035</td>
<td>14</td>
<td>398</td>
<td>3.5</td>
</tr>
<tr>
<td>ITNs</td>
<td>989</td>
<td>30</td>
<td>1438</td>
<td>2.1</td>
</tr>
</tbody>
</table>


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

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


Study design

Oct. 2005 August 2006

<table>
<thead>
<tr>
<th>561 healthy children</th>
<th>May - June 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>None taking TMP/SMX</td>
<td>All children given ITN</td>
</tr>
<tr>
<td>6% report ITN use</td>
<td>519 children remaining</td>
</tr>
<tr>
<td>100% ITN use</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>300 HIV-infected children</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All taking TMP/SMX</td>
<td></td>
</tr>
<tr>
<td>88% report ITN use</td>
<td>(remainder given ITNs)</td>
</tr>
<tr>
<td>290 children remaining</td>
<td></td>
</tr>
<tr>
<td>100% ITN use</td>
<td></td>
</tr>
</tbody>
</table>
## Baseline Characteristics

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

## Effect of TMP/SMX and ITN use on malaria incidence

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Exposure group</th>
<th>Episodes of malaria</th>
<th>Person time (yrs)</th>
<th>Incidence (per 100 pyrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy children</td>
<td>No TMP/SMX</td>
<td>356</td>
<td>340.3</td>
<td>104.6</td>
</tr>
<tr>
<td></td>
<td>No ITN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No TMP/SMX</td>
<td>84</td>
<td>150.0</td>
<td>56.0</td>
</tr>
<tr>
<td></td>
<td>ITN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-infected children</td>
<td>TMP/SMX</td>
<td>5</td>
<td>7.8</td>
<td>64.3</td>
</tr>
<tr>
<td></td>
<td>No ITN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TMP/SMX</td>
<td>4</td>
<td>117.2</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>ITN</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prevalence of malaria among children with fever

Visits to the clinic for new medical problems

HIV negative children
- No recent fever: 62%
  - No malaria: 67%
  - Malaria: 33%
- Recent fever: 38%
  - Malaria: 33%

HIV-infected children
- Recent fever: 55%
  - Malaria: 4%
  - No malaria: 96%
- No recent fever: 45%

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?**

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

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
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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**

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

Parikh, et al., AAC 49:2983, 2005
Effect of lopinavir on cultured *P. falciparum* parasites

A. 0h control  12h control  24h control  48h control

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

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

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.

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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 |
| Antimalarials | ARVs and Other Medications* | Drug Drug Interaction* |
| Artemether | Lopinavir/ritonavir (Kaletra) | Significant increases in lumefantrine levels (2-fold) |
| Lumefantrine | Lopinavir/ritonavir (Kaletra) | Significant increases in lumefantrine levels (2-fold) |


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/mm³)
- 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

Gasasira, et al, CID, in press
Malaria and HIV infection
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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

Kamya, et al. JID 193:9; 2006
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

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


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