Outline

• Brief Introduction
• Influence of malaria on HIV disease
• Effect of HIV infection on malaria in children and non-pregnant adults
• Effect of HIV infection on malaria in pregnancy
• Effect of HIV on response to antimalarial therapy
• Prevention of malaria among people with HIV
• Antiretroviral-antimalarial drug interactions
• Conclusions
Burden of malaria

- Over 243 million clinical cases and 1.24 million deaths annually (80% in SSA)

- Accounts for 25-40% of outpatient visits and 20-50% of hospital admissions
HIV and Malaria in Sub-Saharan Africa

HIV distribution

Malaria distribution
Epidemiological overlap: Why does this matter?

• Any interaction could be of great public health importance:
  – Malaria could accelerate HIV disease progression and facilitate HIV transmission
  
  – HIV infection could disrupt immune responses to malaria and may increase incidence and severity of malaria
  
  – Routine interventions for HIV may impact upon the incidence of malaria
  
  – Therapies for each infection may impact upon the other, leading to unanticipated effects on drug efficacy or toxicity
Plausibility of interaction: Malaria affecting HIV

Antigen stimulation → Immune activation

↑

Faster disease progression

↓

Increased viral replication
HIV Viral load changes during malaria.

Influence of malaria on HIV disease

• Increased viral load during malaria might be sustained for long enough to increase risk of HIV transmission and accelerated disease progression.

• Parasitemia and clinical malaria are associated with 0.25-0.89 log increase in viral load for about 9 weeks

• Treatment of malaria in HIV-infected adults is associated with decreased viral load (190000 to 120000 copies/ml), and increased CD4 cell count (297 to 447 cells/µL) after 28 days

Influence of malaria on HIV disease

• Malaria associated with more rapid decline in CD4 cell count

• Mean difference in CD4 cell decline per additional episode of malaria was 40 cells/µL/year
  – Mermin et al, *JAIDS* 2006;41:129-130

• However evidence that malaria has an impact on HIV disease progression is limited

• Transient and repeated increases in HIV viral load from recurrent co-infection with malaria may contribute to promoting the spread of HIV in sub-Saharan Africa.
  – Modelling in Kisumu, Kenya indicated a 2.1% increase in HIV prevalence since 1980 translating to 8,500 excess HIV infections.

*Abu-Raddad, et al, Science 2006;314:1603-1606*
Rates of clinical malaria by HIV status, CD4 count and WHO stage (Ugandan study, Lancet 2000)
HIV and malaria in pregnancy

- Pregnant women are at increased risk for malaria, especially in their first 2 pregnancies.

- Estimated that the HIV epidemic results in an additional 500,000 to 1 million women per year who have malaria during pregnancy.

- HIV infected pregnant women are at increased risk of:
  - Symptomatic malaria and placental malaria
  - Severe malaria: present with higher parasite densities
  - Maternal anemia
  - Adverse birth outcomes

Diagram:

- Malaria infection → placental malaria → low birth weight → infant mortality
- Maternal anemia
Gravidity-related pattern of Malaria in pregnancy is altered by HIV

Total n = 414: Similar trends for delivery peripheral parasitemia and placental parasitemia

Kisumu, Kenya, 1994-1996 (CDC Studies)
SP- IPT versus CTX for prevention of malaria in pregnancy
Response to ACTs in HIV infected children with uncomplicated malaria

- 2007-2009, 205 episodes of malaria in 55 Children
- Artemether-lumefantrine (co-artem or Al) vs. Dihydroartemisinin-piperaquine (DP) followed for 28 days
- Both treatments were 100% efficacious in preventing recrudescent parasites.
- Higher risk of Recurrent parasitemia due to new infection in AL (34%) compared to DP (7.1%)
“Combination prevention” for malaria in HIV infected populations.

- Cotrimoxazole prophylaxis (CTX)
- Insecticide treated bed nets (ITNs)
- ART
Malaria incidence among HIV-infected adults

- 95% reduction in malaria with all 3 interventions

![Bar chart showing malaria incidence per 100 person-years for different interventions: Cotrim, Cotrim and ART, Cotrim, ART, and bednets. The chart shows a significant reduction in malaria incidence with the combination of all three interventions.]
### Effect of CTX and ITN use on malaria incidence (Kamya et al. AIDS 2007)

<table>
<thead>
<tr>
<th>Exposure Group</th>
<th>IRR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CTX, No ITN</td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>CTX prophylaxis alone</td>
<td>0.65 (0.27-1.57)</td>
<td>0.34</td>
</tr>
<tr>
<td>ITN alone</td>
<td>0.56 (0.45-0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both CTX and ITN</td>
<td>0.03 (0.01-0.11)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Is CTX needed for those with antiretroviral immune reconstitution?

- Adult patients on ART with CD4 counts >200 cells/µL, those discontinuing CTX had a 32.5 fold increased risk of malaria over a 4-month follow up period.

- In a large retrospective cohort study in Malawi, investigators reported a 41% reduction in mortality during the first 6 months after ART.

- In the DART trial, CTX prophylaxis after ART initiation in adults reduced mortality and the incidence of malaria for at least 18 months.
Prophylactic effect of CTX against malaria in contrasting transmission settings

<table>
<thead>
<tr>
<th>Site</th>
<th>CTX use</th>
<th>Episodes of malaria</th>
<th>Person time</th>
<th>Incidence of malaria (PPY)</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kampala*</td>
<td>No CTX</td>
<td>389</td>
<td>727</td>
<td>0.54</td>
<td>0.20 (0.13-0.30)</td>
</tr>
<tr>
<td></td>
<td>CTX</td>
<td>49</td>
<td>423</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Tororo‡</td>
<td>No CTX</td>
<td>121</td>
<td>44.1</td>
<td>2.74</td>
<td>0.27 (0.19 -0.40)</td>
</tr>
<tr>
<td></td>
<td>CTX</td>
<td>45</td>
<td>66.3</td>
<td>0.68</td>
<td></td>
</tr>
</tbody>
</table>

*low-medium transmission site; ‡ very high transmission site
Clinical implications

- Malaria is rarely the cause of fever in individuals receiving CTX

- Malaria accounted for only 4% of febrile episodes in an HIV-infected cohort compared to 33% in the HIV-uninfected cohort (p < 0.0001). Kamya et al, AIDS, 2007

- Presumptive therapy for malaria in these groups should be avoided and careful evaluation for other causes of fever should be done
Are we creating resistance?

![Graph showing mutation frequencies in different locations and conditions.](image-url)
HIV and Malaria Interactions

DON’T FORGET THE DRUGS!
Moderate to severe neutropenia

Lumefantrine exposure

Lumefantrine exposure

Lopinavir / ritonavir

Healthy Volunteers & HIV+ with or without malaria

Non Malaria HIV+

Nevirapine

Healthy Volunteers

HIV Infected Children

Antiretrovirals (nucleoside analogues)

Lumefantrine

Exposure

Liver Function Tests

AQ Exposure

<table>
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<tbody>
<tr>
<td>¹  German, et al CID, 2007</td>
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<tr>
<td>²  Gasasira, et al CID, 2008</td>
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<tr>
<td>³  German, et al JAIDS 2009</td>
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</tbody>
</table>
Risk of adverse events

AQ/AS was associated with increased risk of neutropenia, abdominal pain and Malaise

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Risk of event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2.11 (0.046)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.97 (0.029)</td>
</tr>
<tr>
<td>Malaise</td>
<td>2.69 (0.032)</td>
</tr>
</tbody>
</table>

AQ/AS vs. AL adjusted for repeated measures, age and ART use
Time course for abnormalities in liver-associated enzyme levels

ALT (alanine aminotransferase)
AST (aspartate aminotransferase)
ULN (upper limit of normal)

**Bars, duration of study drug administration**

AQ/AS (amodiaquine + artesunate)
EFV (efavirenz)
## Incidence of malaria NNRTI-based vs. PI-based ART

<table>
<thead>
<tr>
<th></th>
<th>NNRTI-based ART</th>
<th>LPV/r-based ART</th>
<th>IRR** (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>PYAR*</td>
<td>Incidence</td>
<td>Events</td>
</tr>
<tr>
<td>All malaria episodes</td>
<td>176</td>
<td>78.2</td>
<td>2.25</td>
<td>109</td>
</tr>
<tr>
<td>Complicated malaria</td>
<td>2</td>
<td>78.2</td>
<td>0.026</td>
<td>2</td>
</tr>
</tbody>
</table>

* Person years at risk   ** Incidence rate ratio

LPV/r based ART was associated with a 41% reduction in the incidence of malaria compared to NNRTI-based ART.
Risk of recurrent malaria following treatment with AL

- LPV/r based ART was associated with a 59% reduction in the hazard of recurrent malaria following treatment with AL (HR=0.41, 95% CI 0.22-0.76, p=0.004)

- Ritonavir is a known inhibitor of the CYP 3A4 pathway involved in lumefantrine metabolism

<table>
<thead>
<tr>
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<th>LPV/r–based ART</th>
<th>NNRTI-based ART</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Median day 7 lumefantrine level ng/ml (IQR)</td>
<td>926 (473-1910)</td>
<td>200 (108-510)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Conclusions

- Malaria and HIV epidemics synergistic and overlapping
- HIV-infected adults and children have higher rates of clinical malaria and in non-malaria endemic areas more severe disease
- Advanced immune suppression is associated with an increased incidence of malaria
- Malaria episodes are associated with short term increases in viral load and decreases in CD4 cell count
- HIV is associated with increased placental malaria and poor birth outcomes
Conclusions

- A synergistic effect is seen with a combination of interventions- CTX, ITNs and antiretroviral therapy (ART).
- LPV/r increases and extends lumefantrine exposure and thereby reduces rates of recurrent malaria after treatment.
- HIV protease inhibitors may offer a new opportunity to prevent malaria in HIV infection.
- ACT Treatment for malaria in the HIV-infected population should follow current guidelines for the non-HIV infected population.
Future Research

- Significance of the impact of malaria on HIV disease progression remains to be determined.
- There is a need to monitor resistance in malaria parasites to CTX and to assess the effect of resistance on protective efficacy.
- Ongoing surveillance and clinical studies are needed to evaluate for potential interactions and adverse events that result from co-administration of therapies for malaria and HIV infection.
- More data are needed to determine if CTX may be discontinued after prolonged ART.