Chronic HIV Infection Impairs the Non-Opsonic Phagocytosis of Malaria Parasites

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HIV and Malaria - Yes I should care!

• Major overlap in sub-Saharan Africa
• 30% of all HIV cases occur outside of sub-Saharan Africa – minimal adaptive immunity to malaria
• Up to 80 million international travellers are at risk for malaria (Canadians are avid travellers!!)

Malaria

HIV
Malaria is more severe in HIV+ individuals

- HIV+ individuals (especially those with no immunity to malaria) are more likely:
  - to get infected with malaria
  - to have higher parasitemia
  - to experience more clinical and severe malaria ➔ more likely to die

- Mechanisms responsible for these pathological interactions remain unclear.
HIV impairs monocyte and macrophage function

- Impaired mono/mac effector functions have been reported in HIV infection including impaired phagocytosis of bacteria, fungi, and parasites
- These defects contribute to the morbidity and mortality associated with opportunistic infections in HIV+ individuals
Monocytes and macrophages are the first line of defence against malaria parasites

- Innate phagocytic clearance of parasites provides an early control of parasitemia
- CD36 is a major innate, non-opsonic phagocytic receptor for malaria parasites
Question – Why higher parasitemia?

- Does HIV infection alter phagocytic capacity for malaria parasites?
- Does ARV therapy have an impact on this phagocytic capacity?
Methods: Phagocytosis Assay

Monocytes from chronic HIV+ or HIV- donors

Incubate 3hrs.
Lyse non-internalised parasites.
Fix and stain.
Quantify microscopically.

P. falciparum parasitised erythrocytes

Assay performed pre-treatment, at 3 months and at 6 months post-treatment.
<table>
<thead>
<tr>
<th>Donor</th>
<th>CD4</th>
<th>Viral load</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
<td>Month 3</td>
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<tr>
<td>Donor 1</td>
<td>351.</td>
<td>378.</td>
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<tr>
<td>Donor 2</td>
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<td>355.</td>
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<td>Donor 15</td>
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<td>218.</td>
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<td>Donor 17</td>
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<td>Donor 18</td>
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<td>474.</td>
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<td>541.</td>
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<td>Donor 20</td>
<td>132.</td>
<td>139.</td>
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<tr>
<td>Donor 21</td>
<td>277.</td>
<td>529.</td>
</tr>
<tr>
<td>Donor 22</td>
<td>329.</td>
<td>751.</td>
</tr>
</tbody>
</table>

Donor CD4 and viral load data

|        | Median |        | 403.5 | 445.5 | 100050 | <50 | <50 |
Non-opsonic phagocytosis of malaria parasites is impaired in chronic HIV+ donors but improves with ARV treatment.
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Parasite phagocytosis in HIV+ donors normalised to controls.

Level of phagocytosis in the HIV-controls.

Median 80% 81% 91% of control
Opsonic phagocytosis is also impaired but recovers quicker with treatment.

Opsonised RBC phagocytosis in HIV+ donors normalised to controls

Level of phagocytosis in the HIV-controls
Monocyte CD36 levels: similar between HIV+ and controls

CD36 MFI Ratio

Pre-treatment

3 months post-treatment

6 months post-treatment

P=0.13

P=0.41

P=0.96
Summary

• Monocytes from HIV+ donors show a defect in their ability to phagocytose non-opsonised malaria parasites
• This impairment is corrected following 6 months of treatment
Conclusions

• These data may partially explain the higher parasitemia levels observed in HIV+ malaria infected patients

• Support the use of antiretroviral therapy to improve malaria outcome
Acknowledgements

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- Roberta Halpenny
- All our donors

Thank you!

The CTN
Malaria life cycle in humans

- Sporozoite
- Hepatic
- Merozoite
- Sexual intraerythrocytic
- Asexual intraerythrocytic
- Ring
- Trophozoite
- Schizont
- Gametocyte stage I and II
- Gametocyte stage V

Stage causing clinical disease
Monocyte CD40 levels: trend for lower in HIV+
Monocyte CD86 levels: trend for lower in HIV+}

**Pre-treatment**

**3 months post-treatment**

**6 months post-treatment**

CD86 MFI Ratio

Control HIV(+)

P=0.05

P=0.19

P=0.07

Monocyte CD86 levels: trend for lower in HIV+
Monocyte HLA-DR levels: similar between HIV+ and controls

- **Pre-treatment**: MFI Ratio of HLA-DR for both control and HIV+ groups.
  - Control: 0, 500, 1000, 1500, 4000
  - HIV+: 0, 500, 1000, 1500, 4000
  - P=0.30

- **3 months post-treatment**: MFI Ratio for both groups.
  - Control: 0, 500, 1000, 1500, 4000
  - HIV+: 0, 500, 1000, 1500, 4000
  - P=0.41

- **6 months post-treatment**: MFI Ratio for both groups.
  - Control: 0, 500, 1000, 1500, 4000
  - HIV+: 0, 500, 1000, 1500, 4000
  - P=0.31