Alternative MDA strategies for LF and Onchocerciasis elimination

Gary J. Weil
Washington University School of Medicine, St. Louis, USA

- Technical advances in diagnostics and treatment (plus drug donations) were key for initiating LF and Oncho elimination programs
- Additional technical advances will be needed to complete these programs
Outline of the talk

- Recent developments in LF diagnostics
- Current status and highlights from DOLF field studies of MDA regimens
DOLF Field Comparisons of the Binax Filariasis Card Test and the Alere LF Test Strip
Circulating filarial antigen (CFA) tests detect an adult worm antigen in human blood.

CFA rates in endemic areas are much higher than Mf rates.

Recent studies in DRC and Cameroon have detected false positive CFA tests in people with heavy loiasis.

Loa MF counts are often very high in night blood.

These facts complicate LF mapping and monitoring in Central Africa.

D Bakajika et al, PLoS NTD 2014
The new Alere Filariasis Test Strip is an improved version of the old Binax Filariasis card test.

*The Test Strip is 2 to 4-fold more sensitive than the Card Test (analytical sensitivity)*

This photo shows Test Strip (2+) and Card Test (1+) results obtained with the same blood sample. Photo @ 10 minutes.

Weil et al, AJTMH 2013
### Summary of DOLF Card Test and Test Strip comparisons

<table>
<thead>
<tr>
<th>Country</th>
<th>District</th>
<th>Age</th>
<th>No. tested</th>
<th>Card Test pos. (%)</th>
<th>Test Strip pos. (%)</th>
<th>% Agree</th>
<th>Discrepancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberia Pre-MDA</td>
<td>Foya 2012</td>
<td>&gt;5</td>
<td>519</td>
<td>100 (19.3)</td>
<td>124 (24.7)</td>
<td>95.4</td>
<td>24 of 124 pos Strips/neg Card 26% more positives</td>
</tr>
<tr>
<td>Côte d'Ivoire Pre-MDA</td>
<td>Akoupe</td>
<td>&gt;5</td>
<td>837</td>
<td>227 (27.1)</td>
<td>244 (29.2)</td>
<td>97.7</td>
<td>18 of 244 pos Strip/neg Card 7.5% more positives 1 pos Card /Neg Strip</td>
</tr>
<tr>
<td>DRC Pre-MDA</td>
<td>Bandundu province</td>
<td>&gt;5</td>
<td>187</td>
<td>29 (15.5)</td>
<td>42 (22.5)</td>
<td>93.0</td>
<td>13 pos Strip/neg Card 45% more positives</td>
</tr>
<tr>
<td>Indonesia Post-MDA</td>
<td>Pekalongan Java</td>
<td>7-15</td>
<td>512</td>
<td>14 (2.7)</td>
<td>18 (3.5)</td>
<td>99.0</td>
<td>Kids: 5 pos Strip/Neg Card 28% more positive Adults:16 pos Strip/Neg Card. 67% more pos.</td>
</tr>
<tr>
<td>Sri Lanka Post-MDA</td>
<td>Galle and Matara</td>
<td>&gt;5</td>
<td>852</td>
<td>18 (2.1)</td>
<td>43 (5.0)</td>
<td>97</td>
<td>25 pos Strip/neg Card 140% more positives</td>
</tr>
</tbody>
</table>

Co-investigators: Liberia: L Gankpala, F Bolay, K Curtis, K Fischer; Côte d’Ivoire: A Meite, P Fischer; DRC: M Boussinesq, N Awacha; Indonesia: T Supali; Sri Lanka: TC Yahathugoda
LF Card Test / Test Strip Summary

- These results suggest that a switch to the Test Strip will raise the bar for elimination.
- Some areas that would have passed TAS by Card Test may fail with the Test Strip.
- All things considered (sensitivity, cost, shelf life), the Test Strip appears to be a significant upgrade and an acceptable replacement for the Card Test.
Optimization of chemotherapy for control and elimination of onchocerciasis and lymphatic filariasis

A global health project supported by the Bill and Melinda Gates Foundation
Death to Onchocerciasis & Lymphatic Filariasis (DOLF)

- **Objective 1**: Large scale testing of alternative MDA strategies with modeling and cost analysis
- **Objective 2**: Randomized clinical trials with current drugs, new combinations/schedules
- **Objective 3**: Population-based studies of the Impact of MDA for LF/Oncho on soil-transmitted helminth infections
DOLF Questions

**Lymphatic Filariasis**
- Is semiannual MDA superior to annual MDA?
- Can MDA with Albendazole alone eliminate LF in Loa-coendemic areas? (Community and RCT)
- Test a 3-drug regimen (DEC+Iver+Alb) for LF: the “Knock-out punch” trial (RCT, 2 sites)

**Onchocerciasis**
- Is Alb+Iver more effective than Ivermectin alone? (2 sites)
- Also comparing annual vs semiannual MDA
- Huge potential importance for oncho elimination
DOLF Study Sites for MDA and Clinical Trials
A community study of mass drug administration with albendazole alone on lymphatic filariasis in the Republic of Congo

S. Pion, C. Chesnais, J. Bopda, F. Louya, P. Fischer, A. Majewski, G. Weil, M. Boussinesq, F. Missamou
*Loa loa*: a major challenge for LF and Oncho elimination in Central Africa

Areas in Central Africa have been excluded from MDA because of the risk of SAEs after ivermectin

**DOLF project:**
Alb (400 mg) 2x/yr for LF
Seke Pembe, Congo BZV
Seke Pembe: Semi-annual ALB 400 mg (all ≥ 2 y.o.)
Annual assessment (all ≥ 5 y.o.)

Sept '12  Sept '13
M0  M6  M12

W. bancrofti prevalence (%)

Sept '12  Sept '13
2 Rounds
Seke Pembe: Semi-annual ALB 400 mg (all ≥ 2 y.o.)
Annual assessment (all ≥ 5 y.o.)

- Sept ‘12
- Sept ‘13
- Oct ‘14

M0  M6  M12  M18  M24

W. bancrofti prevalence (%)

- Sept ‘12:
  - 2 Rounds

- Sept ‘13:
  - 2 Rounds

- Oct ‘14:
  - 4 Rounds
## Community impact of semi-annual ALB on *W. bancrofti*

<table>
<thead>
<tr>
<th></th>
<th>2012 (N=773)</th>
<th>2013 (N=741)</th>
<th>2014 (N=693)</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFA prevalence (%)</td>
<td>17.3</td>
<td>16.6</td>
<td>4.3</td>
<td>75.1 %</td>
</tr>
<tr>
<td>MF Prevalence (%)</td>
<td>5.3</td>
<td>4.2</td>
<td>1.4</td>
<td>73.6 %</td>
</tr>
<tr>
<td>Geo Mean Mf density in Mf+</td>
<td>202.2 mf/ml</td>
<td>80.9 mf/ml</td>
<td>27.7 mf/ml</td>
<td>86.3 %</td>
</tr>
<tr>
<td>Community Mf load</td>
<td>0.32 mf/ml</td>
<td>0.20 mf/ml</td>
<td>0.05 mf/ml</td>
<td>84.4%</td>
</tr>
</tbody>
</table>

$R_0 < 1$ ?
Longitudinal results for 498 people tested in 2012 and 2014

<table>
<thead>
<tr>
<th></th>
<th>2012</th>
<th>2014</th>
<th>% Complete Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFA positive</td>
<td>95</td>
<td>38</td>
<td>60%</td>
</tr>
<tr>
<td>MF positive</td>
<td>24</td>
<td>7</td>
<td>71%</td>
</tr>
</tbody>
</table>
Discussion

- These *preliminary* results suggest that semi-annual ALB can be used to eliminate LF in Central Africa

- This approach could open up that region for LF elimination by 2020

- Seke Pembe endpoint in Sept 2015

- We have started a second study in an area with higher baseline LF rates (DRC)
A pilot study of *triple therapy* for bancroftian filariasis in Papua New Guinea

Lead investigator, **Christopher L. King, MD, PhD**

Center for Global Health and Diseases
Case Western Reserve University
Veterans Affairs Medical Center, Cleveland, OH, USA
Hypothesis

Triple therapy IVM+DEC+ALB is superior to the standard MDA regimen (DEC+ALB)

Preliminary Results from a pilot study

- PK studies (? drug interactions)
- Efficacy
- Safety
Baseline Characteristics of the Treatment Groups

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>N</th>
<th>M/F</th>
<th>Geometric Mean microfilaremia (mf/mL) ± 95% CI</th>
<th>Geometric Mean Filarial Antigen (Unit/ml) ± 95% CI</th>
<th>Median age (yrs)</th>
<th>Mean weight (kg) ± SD</th>
<th>Mean hemoglobin (g/dL) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 drugs</td>
<td>12</td>
<td>6/6</td>
<td>1,558±2067 (209-13,776)</td>
<td>3,881±1227 (19-59)</td>
<td>30</td>
<td>53±9</td>
<td>11.2±1.3</td>
</tr>
<tr>
<td>2 drugs</td>
<td>12</td>
<td>6/6</td>
<td>1,857±2,037 (133-13,333)</td>
<td>3,347±1,018 (19-50)</td>
<td>28</td>
<td>49±8</td>
<td>11.0±1.2</td>
</tr>
</tbody>
</table>

Heavy infections, comparable groups
IVM had no effect on DEC or ALB levels

M Schmidt and L Fleckenstein, unpublished observations
Better Mf Clearance with DEC+ALB+IVM Compared to DEC+ALB
DEC/ALB/Iver reduced CFA levels more than DEC+ALB (12 months)
## Microfilaremia 1 & 2 Years Following a Single Drug Treatment

### Mf per ml

<table>
<thead>
<tr>
<th>Rx</th>
<th>Pre Rx</th>
<th>36h</th>
<th>7d</th>
<th>1 yr</th>
<th>2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEC + ALB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3235</td>
<td>4</td>
<td>9</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1599</td>
<td>10</td>
<td>8</td>
<td>11</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>1562</td>
<td>1</td>
<td>627</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1095</td>
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<td>4</td>
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</tr>
<tr>
<td>1107</td>
<td>13</td>
<td>1</td>
<td>27</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>1747</td>
<td>87</td>
<td>947</td>
<td>29</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td><strong>DEC+ALB+IVM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>689</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>677</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>1034</td>
<td>6</td>
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<tr>
<td>1476</td>
<td>1</td>
<td>4</td>
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<td>0</td>
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<tr>
<td>1857</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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</tr>
<tr>
<td>2509</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Adverse Events (AE)

- No SAEs
- Frequency of 1 or more AEs
  - 3-drug: 10 of 12 (83%)
  - 2-drug: 5 of 12 (50%)
- AEs resolved by 48 to 72h after treatment
Summary

• Triple drug LF therapy appears to be safe and more effective for clearing Mf than DEC/ALB

• This regimen could be an important tool for accelerating LF elimination (especially useful in areas that are difficult to access or in areas that have started late, including some areas in Africa)

• Enrollment for the full study in PNG is almost finished, no SAEs

• We will conduct a parallel study in Côte d’Ivoire (in an area with no Loa or onchocerciasis)
# Status of DOLF Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncho</strong> Iver/Alb vs. Iver alone (Ghana – Central)</td>
<td>Now at 25 months, endpoint (nodulectomies) in September 2015</td>
</tr>
<tr>
<td><strong>Oncho</strong>, same as above (Ghana – Volta Region). Heavier infections, less prior Ivermectin</td>
<td>IRB approved; screening and enrollment are starting now</td>
</tr>
<tr>
<td><strong>LF</strong>: Triple drug regimen (PNG)</td>
<td>Enrollment completed. Endpoint in late 2017</td>
</tr>
<tr>
<td><strong>LF</strong>: ALB monotherapy for LF. Will also include a triple drug arm. Côte d’Ivoire</td>
<td>IRB approvals in place. Now screening to identify participants</td>
</tr>
</tbody>
</table>