Landscape for developing a VL database

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WorldWide Antimalarial Resistance Network (WWARN)
A Database for Kala Azar?

- Why a clinical database for VL?
- Landscape of clinical data on VL?
Why a database?

Challenges

• **VL is underfunded** - few trials and small sample sizes

• **Few drugs** (~5) and **poorly stocked pipeline**

• Existing drugs **toxic/expensive/resistance threat**

• **Complications** - regional efficacy variation, HIV-VL

• Careful use and monitoring of drugs is required to **maximise efficacy, reduce toxicity** and **minimise resistance**

• Clinical trial data are ‘**buried**’ in publications or **not published** or **delayed**
Standardised Clinical Trials Database

• Provides comprehensive up-to-date **clinical trial landscape**

• Allows **meta-analysis**: improved statistics, highlight subpopulation variations and resistance

• Inform **treatment allocation** and future **clinical trial design**
WWARN Case Study

- 350 Clinical trials from 200 research institutions
- Raw data on 100,000 individuals (≈3M data points)
- WWARN Explorer
- Pooled analyses
A unique standardised database for VL?

Questions

• Are there enough trials? Are there enough data?
• Are the data from different trials comparable? Consistency in study parameters? (e.g., dose, regimen, diagnostic tests, follow-up time and assessments?)

Assessment

• Conduct systematic review of clinical trials landscape
• Gather key information from trials (e.g., # participants, study parameters)
• Explore the potential of a database of raw data to allow for meta-analyses
Clinical Trials Registries

Clinical trials.gov launched in 2000

ICTRP gathers trials from all major registries

- Australian New Zealand Clinical Trials Registry
- ClinicalTrials.gov.
- EU Clinical Trials Register (EU-CTR)
- ISRCTN
- Brazilian Clinical Trials Registry (ReBec)
- Chinese Clinical Trial Registry
- Clinical Research Information Service - Republic of Korea
- Cuban Public Registry of Clinical Trials
- German Clinical Trials Register
- Iranian Registry of Clinical Trials
- Japan Primary Registries Network
- Pan African Clinical Trial Registry
- Sri Lanka Clinical Trials Registry
- The Netherlands National Trial Register
- Thai Clinical Trials Register (TCTR)
Clinical Trials Registries

Search for ‘visceral leishmaniasis’ and ‘kala azar’

33 registered trials

Excludes duplicates and trials on vaccines, canine VL, vector control, nets, prevalence estimations, diagnostics, PK/PD, prophylaxis, and cutaneous leishmaniasis
Clinical Trials Publications

Search for ‘visceral leishmaniasis’ and ‘kala azar’

13 registered and published

- 11 Active
- 3 Terminated
- 6 Complete not published
- 13 Published

141 published

Published and registered

Published

Excludes duplicates and trials on vaccines, canine VL, vector control, nets, prevalence estimations, diagnostics, PK/PD, prophylaxis, and cutaneous leishmaniasis
Landscape of Clinical Trials

Find publications and extract data

Found 138/141 original publications

• Data extracted from abstracts for other 3 publications
• Some available at online journals
• Some available only in hard copy (from WHO Library)
• Some available only through contacting author
Create spreadsheet of key parameters

<table>
<thead>
<tr>
<th>Clinical trial ID</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication name</td>
<td>Study design (single arm, comparative, dose finding)</td>
</tr>
<tr>
<td>Authors</td>
<td>Allocation (randomised, consecutive cohorts)</td>
</tr>
<tr>
<td>Address for clinical trial</td>
<td>Study Sponsor</td>
</tr>
<tr>
<td>Journal of publication</td>
<td>HIV co-infection</td>
</tr>
<tr>
<td>Publication date</td>
<td>Inclusion and exclusion criteria</td>
</tr>
<tr>
<td>Trial start and end dates</td>
<td>Method of diagnosis</td>
</tr>
<tr>
<td>Drug(s) and dose</td>
<td>Test for cure method and time point</td>
</tr>
<tr>
<td>Enrollment</td>
<td>Length of follow-up</td>
</tr>
<tr>
<td>Sex</td>
<td>PubMed ID</td>
</tr>
</tbody>
</table>
Clinical Trials Landscape

- **141 clinical studies** on VL drugs
- **25,865 patients** (68% male)
- Most trials enrolled less than 200
- **1,379** patients in completed, unpublished trials
- **9,802** in active trials
  - **Total of 37,046 patients**
  - Earliest publication was 1983
  - Since 2000: 69 published/ 35 started
  - Delay to publication: average 26 months (range 8-78)
Where and When?

Most enrolment in Indian subcontinent or Africa
Gradually increasing enrolment each year

<table>
<thead>
<tr>
<th>Country</th>
<th>Patients</th>
<th>Trials*</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>18192</td>
<td>91</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>2250</td>
<td>3</td>
</tr>
<tr>
<td>Sudan</td>
<td>1675</td>
<td>10</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>1280</td>
<td>6</td>
</tr>
<tr>
<td>Nepal</td>
<td>755</td>
<td>5</td>
</tr>
<tr>
<td>Kenya</td>
<td>667</td>
<td>11</td>
</tr>
<tr>
<td>Italy</td>
<td>290</td>
<td>7</td>
</tr>
<tr>
<td>Uganda</td>
<td>234</td>
<td>2</td>
</tr>
<tr>
<td>Spain</td>
<td>208</td>
<td>4</td>
</tr>
<tr>
<td>Brazil</td>
<td>206</td>
<td>6</td>
</tr>
<tr>
<td>Others</td>
<td>119</td>
<td>7</td>
</tr>
</tbody>
</table>

*Trials in n countries split into n trials, 1 per country
Drugs

2000-6000 patients enrolled for each drug
• Mostly from India, Africa well represented for some drugs
• Suggests large scale comparisons are possible

Most enrollments for newer drugs are recent (5-10 years)
• Easier to obtain data
• Suggests more data to come
**Dose**

Good consistency in dose regimens used
1000’s of patients enrolled per dose

- Allows for pooling of data
- Allows for large scale comparisons of different dose regimens

![Dose graph showing various drugs and dosages](chart.png)

- **Pentavalent antimonials**
- **Amphotericin B deoxychlorate**
- **Miltefosine**
- **Paromomycin**

- **Other**
- **20mg/kg/day, 20 days**
- **20mg/kg/day, 30 days**
- **1 mg/kg/alternate days, 20 doses**
- **1 mg/kg/day, 15 doses**
- **1 mg/kg/alternate days for 15 doses**
- **1 mg/kg/day, 20 doses**
- **50 mg (<25 kg), 100 mg (>25kg), 2.5 mg/kg (Age <12), 28 days**
- **11 mg/kg/day, 21 days**
### Trial Design

Trials evenly split between single arm, dose-finding or comparative

- Usually randomized

**Patient follow:**

- 6 months (~25,000)
- 12 months (~5000)

Allows pooling of data since end points consistent

Allows comparison of 12 and 6 months follow up on the scale of 1000`s
Diagnoses

Diagnosis by observation of parasites in an aspirate (>76%)
- High confidence in correct diagnosis
- Do different diagnostic tests affect outcome?

End of treatment test is generally the same as for diagnosis
- 88% patients parasitologically tested for cure after treatment

End of follow up test is usually clinical (79%) or bone (10%)
- Is there a difference in relapse with clinical vs parasitological test
Summary

- Individual trials are small, but many trials (141) and participants (25,865, with potential for 37,046)
- Good consistency in study design and parameters
- Trial results are difficult to access, some raw data may already be lost
- A database would improve accessibility and longevity
- Develop a visualization tool for trial results
- Meta-analysis would allow comparisons on large cohorts (1000’s/arm) to improve treatment efficacy and design for future studies
- Compare outcomes based on drug, dose, country, length of follow-up, diagnosis, test for cure, etc.
**Vision:** Effective and safe malaria treatment for all

**Mission:** To implement a collaborative platform to assess the evolution, epidemiology and public health impact of antimalarial drug resistance, and to generate the reliable evidence necessary to inform malaria control and elimination

**Goal:** To inform optimal use of available and future antimalarials for malaria control and elimination

**Established:** 2009 as a programme of the University of Oxford Centre for Tropical Medicine and Global Health
Linking Scientific Disciplines

- Pharmacological assessment
- Phenotypic assessment of drug sensitivity
- Clinical drug efficacy
- Molecular markers for resistance
- Drug Quality
Data Standardisation Process

Data submission

- Access
- Stata
- SAS
- Excel

Heterogeneous data

Cleaning

Transform

Standardize

Analyse

Data sharing

Processing

Outputs

Standardized data sets

Data Repository

Automated Reports

http://www.wwarn.org/resistance/explorer

WWARN Explorer

Research applications
Data Visualisation

Mapping summary data from antimalarial drug studies

Data types
- Clinical
- Molecular
- In vitro
- Pharmacology

Select treatment
Anti malarial:
- Group: All Artemisinins
- Component:
  - Artemether (AM)
  - Armodafidine (AQ)
  - Artemutin (AS)
  - Atovaquone (AV)
  - Chloroquine (CQ)
  - Chloroquine (CQ)
  - Chloroquine (CQ)
  - Chloroquine (CQ)
  - Dexamethasone (DAP)
  - Dihydroartemisinin (DHA)
  - Halofantrine (HL)
  - Lumefantrine (LUM)
  - Mefloquine (MQ)
  - Naphthoquinone (NQ)
  - Pyrimethamine (PPQ)
  - Quinine (QIN)
  - Sulfadoxine-pyrimethamine (SP)
  - Sulindione (S)
  - Tetrahydrocannabinol (THC)

Limit to studies of:
- All studies of treatment

Reset filters

Active filters
- Treatment type: All studies of treat
- Data range: 1977-
- Data type:
- Species: P. falciparum
- Regions:

Map showing All Artemisinins data between 1977-2014

Legend
- Clinical
- Molecular
- In vitro
- Pharmacology

Study data by country

Explanation
- Clinical:
  - Clinical data based on average day 2/3 efficacy data for a study location.
- Molecular:
  - Molecular data based on prevalence of known resistance markers in each study location.
- Marker indicator:
  - In vitro:
    - In vitro data based on percentage of samples with an IC50 higher than the indicating resistance. When a specific study location is unknown, map markers

D28 success rate indicators:
- <50
- 50-95
- >95

Study these studies are filtered by the set of filters applied to the map above.
- Clinical: Hide details...
- AL (AL): See details...
- AL-SUP (AL-SUP): See details...
- AL4 (AL4): See details...
- AL48 (AL48): See details...
- AL60 (AL60): See details...
- AL60 (AL60): See details...
- AL95 (AL95): See details...
- ALD18 (ALD18): See details...
- AM (AM): See details...
Pooling Data for more Powerful Analyses

DHA-Piperiquine mg/kg Dosing Study Group

• **26 studies**  (74% of 35 studies)
• **7,072 patients** between 2003–2011  (70% of 10,168)
Literature review of all published clinical trials
1,115 studies

49 published studies with DHA-PIP
(N=11,935)

1066 studies not including DHA-PIP

14 studies not targeted for pooled analysis
(N=1,767)
6 studies with <3-day dose regimen (712)
3 studies with only P. Vivax (N=552)
3 studies with no PCR results (N=299)
1 study with pregnant women (N=50)
1 Study is a subset of another study (N=154)

35 studies targeted for pooled analysis
(N=10,168)

8 targeted studies not available (N=2,100)
170 patients missing from available studies

27 studies in WWARN repository
(N=7,898)
77.7% of targeted sample size captured

2 unpublished studies (N=183)

3 studies excluded (N=375)
2 studies were subset of larger studies (n=303)
1 study was a retreatment study (n=72)

26 studies included in the analysis
(24 published and 2 unpublished)
(N = 7,706)

634 Patients excluded for protocol violations
200 Patients with no P. falciparum at enrolment
12 patient with missing species at enrolment
111 Patients missing body weight or dosing variable
54 Patients with incomplete treatment
107 Indeterminate or unknown PCR results
150 Duplicate patients

7,072 patients included in the analysis
6,977 patients with P. falciparum mono-infections
95 patients with mixed infections (P. falciparum + P. vivax)
Tools for Characterizing Drug Resistance

WWARN Parasite Clearance Estimator (PCE Tool)
Smart Surveillance

Where should we plan the next studies?

• To optimise resources
• To minimise time for recruitment
• To target the correct populations
Smart Surveillance

Model prediction

Uncertainty

Population density

Endemicity
WWARN EQA Programme

Reference Material Programme
• Distribute certified antimalarial drug standards
• Pharmacology/PK labs
• In vitro/drug sensitivity testing
• Drug quality

Proficiency Testing Programme
• Assess performance and provide assistance
• Pharmacology labs
• Molecular labs
Challenges to Data Sharing

Data unavailable

27 relevant published studies identified
Authors invited by email to participate

6 studies contributed
All published after 2005

21 studies not contributed
81% published before 2005

9
No response
Invalid emails, researcher no longer at site

4
Data destroyed
Study > 10 years old, funder or institution rule

4
Data lost
Laptops stolen, hard drives crashed

4
Data irretrievable
Data stored on floppy disc, other unsuitable archive

3
Positive response, data not uploaded
Busy researchers, worried about data quality?
WWARN Data Repository

- 350 clinical trials
- 200 research institutions
- Raw data on 100,000 individuals (≈3M data points)
- 2/3 of all published data since 2000
Building a VL Data Repository

- WWARN platform exists – do not need to start from scratch
  - Data repository structure
  - Data upload systems
  - Data curation and harmonisation processes
  - Template data-sharing terms and agreements
  - Ethical considerations
  - Lessons learned from malaria
  - Reduces cost for establishing database
Successful Data Sharing requires...

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