

Clinical RM

Advance. Accelerate. Achieve.

Clinical Trials of Convalescent Plasma in West Africa

IPFA/BCA Symposium
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About ClinicalRM

- Full-service Contract Research Organizaiton (CRO) founded in 1994 by Vicki Tifft (CEO), as a clinical trials center for the US Army Medical Research and Materiel Command.
- Bench-to-bedside research and support of product development for biologics, drugs, and devices.
- Wide array of research, regulatory, and sponsor services.

ClinicalRM's Global Network for Support of Large Studies & Programs



ClinicalRM's Global Network

- 475+ Full-Time Employees
- Access to 200+ Contractors Globally
- Staffed Full-Time Thought Leaders and Medical Expert Office
- Government Network Access

ClinicalRM Africa

- Leading African Consortium (Gov / MOH)
- GCP / ICH Trained Physician Oversight in East & West Africa

*Affiliate Offices

ClinicalRM's Strategic Partnerships

- Academic Partnership with Johns Hopkins University Hospitals, The University of North Carolina, and Duke University
- Ohio Clinical Trials Collaborative (OCTC) OCTC has a Network of 14+ Clinical Sites / Hospitals, including:
  - *University Hospitals Case Medical Center*
  - *Cleveland Clinic Foundation*
  - *Ohio State University Medical Center*
  - *University of Cincinnati Medical Center*

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Questions August 2014

- Is Ebola Convalescent Plasma (ECP) safe and effective?
- If so, how can we make it available to patients in the severely Ebola-affected countries?

Prevailing Dogma August 2014

- Antibody alone ineffective for treatment or immunization
- Human ECP data anecdotal, uncontrolled, unconvincing
- More refined and elegant approaches preferable

Countercurrents August 2014

- Dye, et al. (PNAS, 2012): high-dose treatment with immune globulin effective in severe NHP challenge model
- MAb cocktails efficacious in NHP, no human data
- Universal treatment of expats in US with ECP
- WHO interest in emergency use

Operational Principles

- Partner with local investigators/clinicians
- Improve local research and clinical care capability
- Work within culturally accepted views of transfusion efficacy
- Conduct trial according to ICH/GCP as far as possible

Operational Goals

- Design and execute clinical trial in Liberia and support other trials in West Africa
- Enable local production of ECP in Ebola-affected countries as a stopgap measure
- Provide scientific and technological basis for future, more refined products (immune globulin)

Implementation

- Designed and launched clinical trial and ECP collection protocols in Liberia (Jerry Brown, PI)
- Supplied apheresis/INTERCEPT-equipped bloodmobiles to Liberia, Guinea and Nigeria
- Provided ECP/INTERCEPT capability and trial management for U of Liverpool trial in Sierra Leone
- Introduced handheld point-of-care blood diagnostics (iSTAT) to improve management
- Trained local staff in Liberia and Sierra Leone
  - ECP collection
  - Clinical trial conduct

Collaborations

- Philanthropists
- Plasma and Transfusion Community
- NGO and Governmental Organizations
- Research Organizations and Sites

Philanthropists

Bill and Melinda Gates Foundation
Jim Greenbaum Foundation
Paul Allen Foundation
World Food Programme

Finished Bloodmobiles



Plasma and Transfusion Community

American Red Cross
Cerus Corporation
Blood Centers of America
Haemonetics
BBCS
Safe Blood for Africa
University of Minnesota

Hopemobile ("The Bus") at ELWA



Research Organizations

ClinicalRM
U.S. Army Medical Research Institute for Infectious Disease (USAMRIID)
Liberian Institute for Biomedical Research (LIBR)
Serving in Mission (SIM)
Eternal Love Winning Africa (ELWA)
University of Liverpool
Military Hospital 34 Freetown
Sierra Leone National Safe Blood Transfusion Service
University of North Carolina
Duke University

ELWA Triage


ELWA CLINIC
ELWA CLINIC
ELWA CLINIC
ELWA CLINIC
E.L.W.A HOSPITAL

Health Workers ELWA-2



ELWA Bleach Sprayer



Delivering Hopemobiles



Delivering Hopemobiles



Governmental and Non-Governmental Organizations

Centers for Disease Control
Food and Drug Administration
Department of Defense
World Health Organization

Trial Considerations

ECP production

- Survivor donor numbers uncertain
- Single unit WB-derived vs. apheresis
- Product safety and quality

Trial Design

- Therapeutic misconception
- Controls/treatment assignment
- Dose (volume and Ab quality/quantity)
- Clinical management
- Endpoints
- Power

Logistics

EVD-001 Objectives

Correlate anti-EBOV IgG and neutralization titers in ECP with viral load in treated subjects

Compare survival of subjects treated with and without ECP

Assess safety of treatment with ECP

EVD-001 Design

Eligibility: adults hospitalized less than 48 hours previously with EVD

Treatment assignment strictly based on availability of compatible ECP

Up to 3 ECP treatments 48 hr apart

- **100 mL ABO-compatible ECP from each of 2 donors (200 mL per treatment)**
- **All 3 treatments use ECP from same 2 donors**

Aggressive IV fluid management guided by iSTAT handheld point of care assay

- **Electrolytes, BUN, creatinine, calcium, prothrombin time/INR, hemoglobin**
- **Creative solutions for environmental challenges**

Endpoints

- **Sampling at consent, immediately prior and 4 hours after treatment, and daily until discharge**
  - EBOV viral load by RT-PCR
  - Anti-EBOV by ELISA, neutralization
- **Survival**
- **Adverse Events**

EVD-001 Status

6 Subjects enrolled

- 4 Subjects O pos (received ECP)
- 2 Subjects A pos (no ECP available, managed with IV standard of care)

Clinical Observations

- High levels BUN/creatinine, low CO2
- ECP well tolerated, no related AEs

Progress

- Enrollment stopped due to decline in cases
- Serial blood specimens sent for analysis

EVD-002 Design

Recruit EVD survivors

- EVD within last 2 years
- At least 60 days since disease onset
- At least 28 days since discharge
- 2 negative EBOV tests by RT-PCR

Qualification

- Adult, at least 50 Kg, with negative risk history
- Hemoglobin $\geq$ 12.0 g/dL, negative pregnancy
- Negative tests for HIV, HBV, HCV, syphilis, malaria
- Repeat donation possible every 14 days

Donor Recruitment

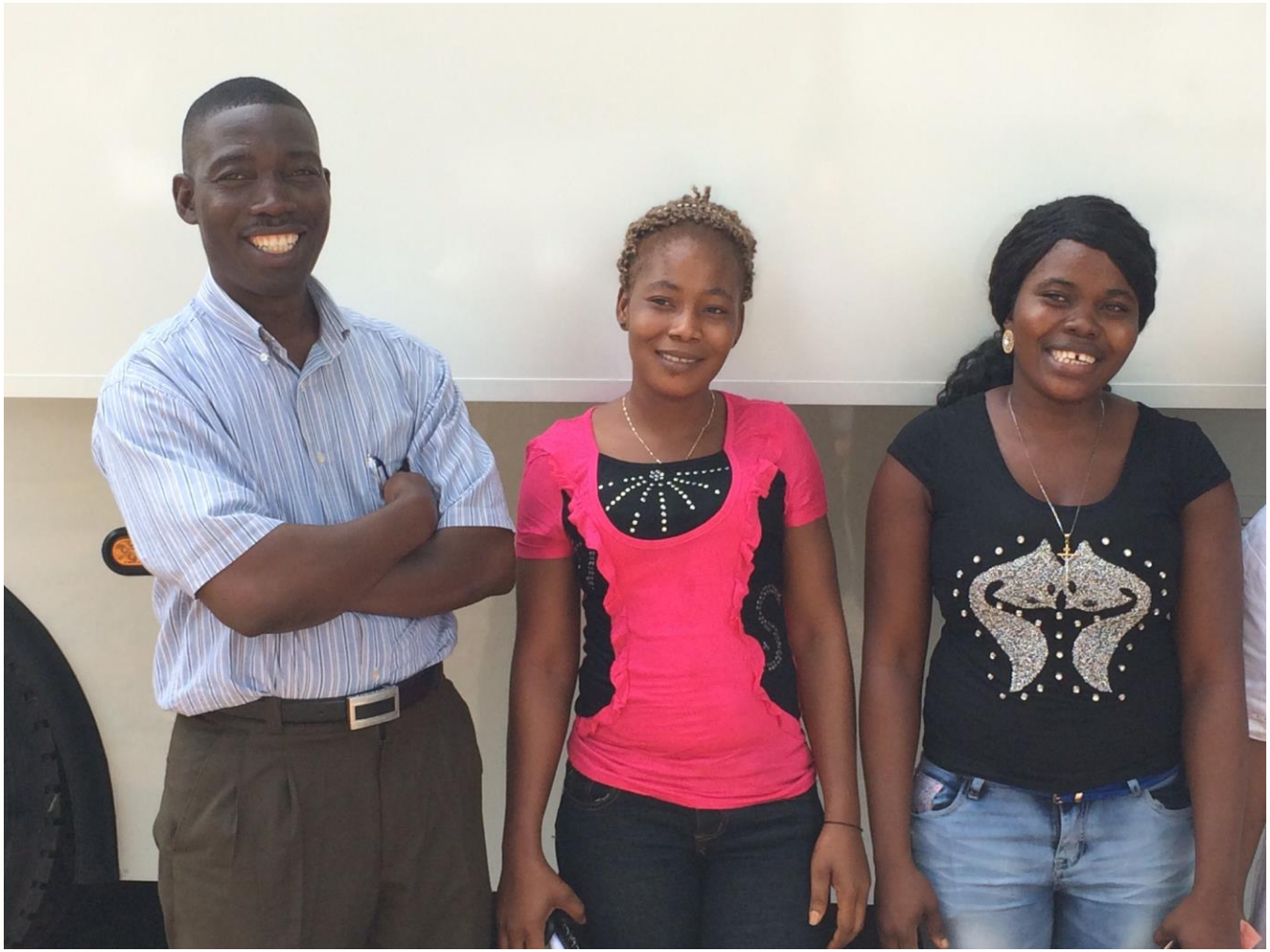
Survivor Encounters

- Survivor lists from ELWA-2
- Survivor fairs and workshops

Donor Assistance

- Transportation
- Compensation for time and travel

Dr. Jerry Brown with Survivors



ECP Collection

Recruitment, consent, initial interview and health/blood screening at ELWA

- PCR testing at LIBR by USAMRIID team
- Blood grouping and TTI testing at ELWA
- Blood Donor Management System from BBCS

Qualified donors returned to Hopemobile

- Interview and blood tests repeated
- 650 mL collection target
- Haemonetics PCS2
- Plasma treated with Cerus INTERCEPT
- Preparation of 6 X 100 mL treatment units per donation

ECP transferred to ELWA for freezing and storage as FFP

EVD-002 Donors

97 participants

85 full-volume ECP units collected

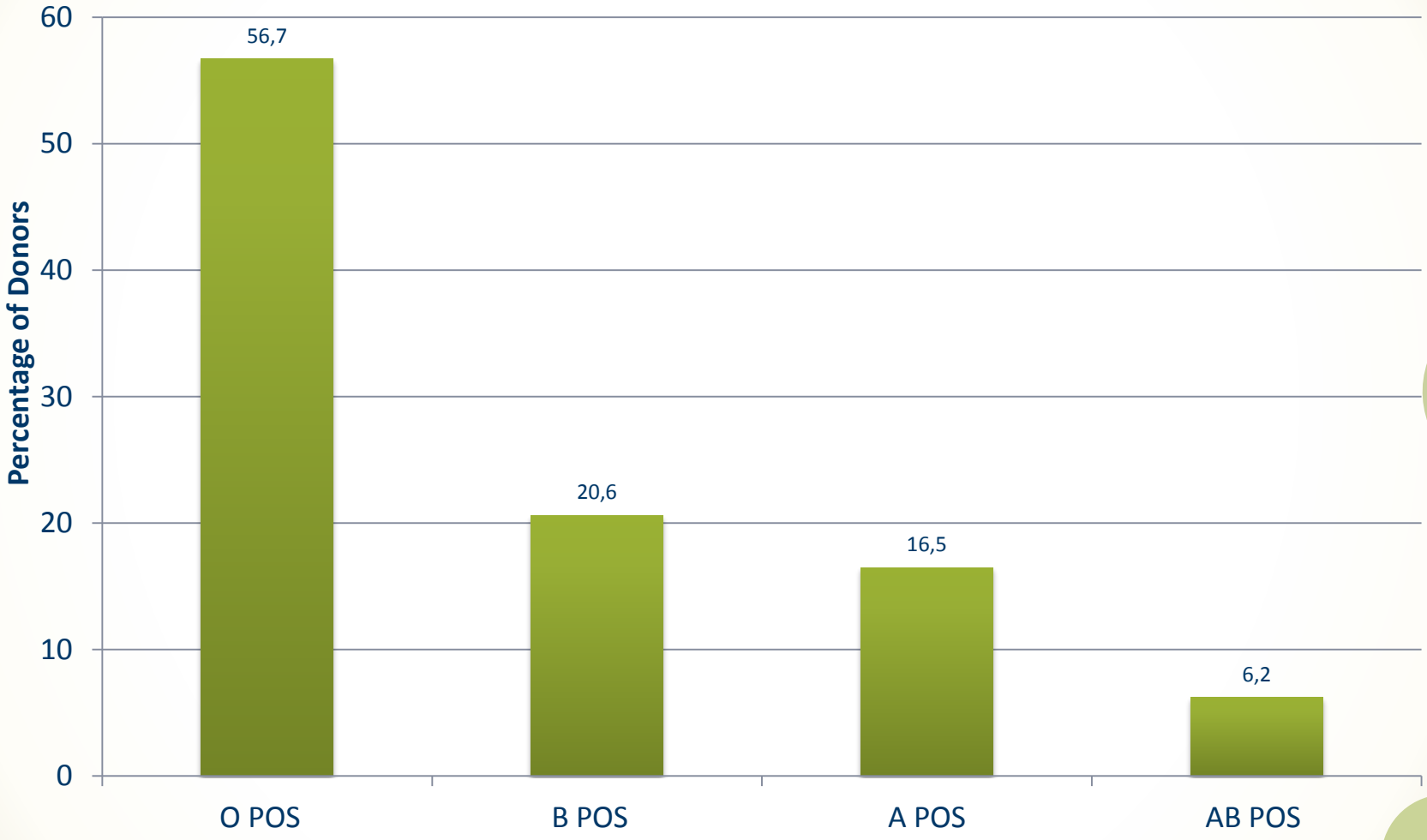
- 90.4% successful collection rate
- 39 units from repeat donors

Age 33.8 ± 8.6 years (19 to 67)

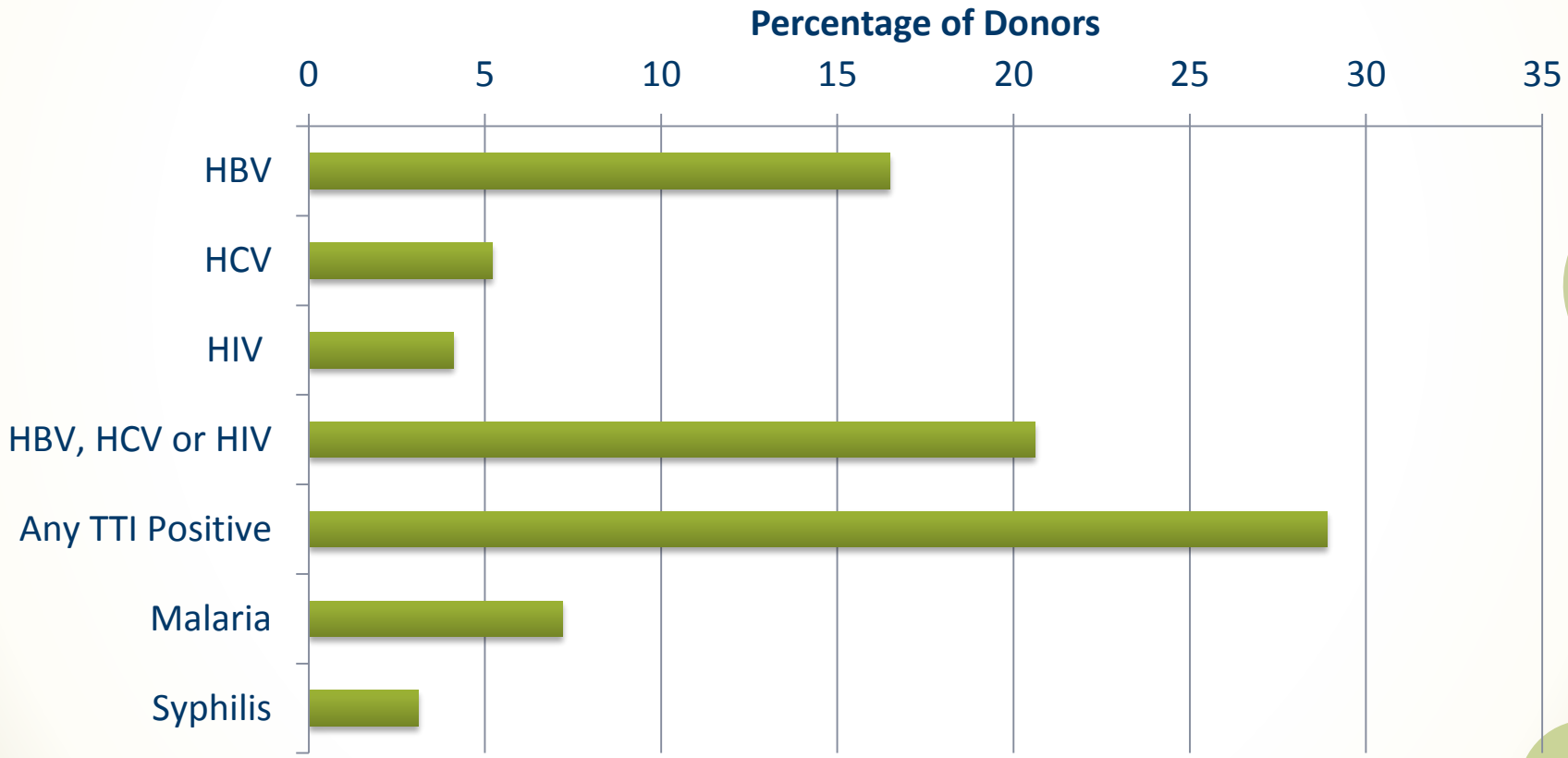
Weight 69.3 ± 11.4 Kg (50 to 112)

Hemoglobin 13.83 ± 1.26 g/dL (11.6 to 17.1)

ABO Groups

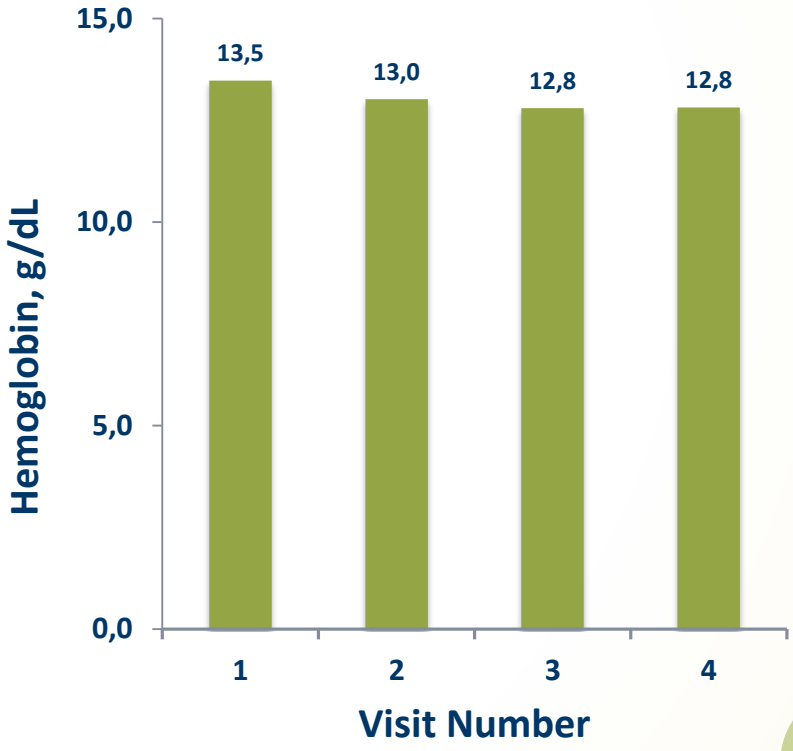

60
50
40
30
20
10
0
Percentage of Donors
56,7
20,6
16,5
6,2
O POS
B POS
A POS
AB POS

TTI Deferrals



Weight and Hemoglobin at Repeat Donations (N = 10)





EVD-002 Future Directions

Observational longitudinal survivor study Led by University of North Carolina collaborators

- Psychosocial, symptomatic data
- Urogenital fluid collection for PCR and virus isolation
- EBOV antibody levels
- Markers of immune activation and inflammation

Other ECP Trials

Guinea: Ebola-TX

- Institute of Tropical Medicine, Antwerp
- Donka Hospital, Conakry
- survival vs. historical controls
- 103 subjects enrolled as of July 2015

Sierra Leone: Ebola-CP

- University of Liverpool
- Military Hospital 34, Freetown
- 4 subjects enrolled to date (3 treated)
- 50 ECP units collected to date

Thank you!