PREVAIL VIII:

A **C**o**HO**rt Clinical, Viral, and Immu**NO**logic Monitoring Study of People Living with **R**etroviral Infection in Liberia (HONOR)

Liberian Co-PIs:

J. Soka Moses

Ian Wachekwa, MBChB

NIAID PI:

Stephen A. Migueles, MD

Background: HIV Prevalence and Risk Groups

- >25.6 million PLHIV in Sub-Saharan Africa (36.7 million worldwide)

AIDS-related deaths declining globally, but increased in Western/ Central Africa in 2013 to 36%

In 2016, 310,000 deaths in this region in 2016 (UNAIDS, 2017).

Background: HIV Prevalence and Risk Groups

- Little is known about the nature of the HIV epidemic in Liberia.

- HIV prevalence in Liberia increased from 1.5% in 2007 to 2.1% in 2013 in the general population aged 15-49 years despite increases in the numbers of centers providing ART (LISGIS, *LDHS 2013*, 2014).

  - 43,000 PLHIV
  - 2.6% urban, 0.8% rural
  - 2.4% women versus 1.9% men
  - Increased in almost all age groups

Background: HIV Prevalence and Risk Groups

- High risk/prevalence populations (IBBSS, 2013)
  - MSM 19.8%
  - FSW 9.8%
  - Uniform Service personnel 5%
  - Transport workers, traders 4.8%, 4.6%
  - IDU 3.9%
  - Lowest: youth in schools 1.1%

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2 Placebo-Controlled Trial of Two Vaccines to Prevent Ebola in Liberia

S.B. Kennedy, F. Bolay, M. Kieh, G. Grandits, M. Badio, R. Ballou, R. Eckes, M. Feinberg, D. Follmann, B. Grund, S. Gupta, L. Hensley, E. Higgs, K. Janosko, M. Johnson, F. Kateh, J. Logue, J. Marchand, T. Monath, M. Nason, T. Nyenswah, F. Roman, E. Stavale, J. Wolfson, J.D. Neaton, and H.C. Lane, for the PREVAIL I Study Group*

In PREVAIL I, HIV prevalence of 1,500 study participants in Monrovia was 5.2% and only 0.6% reported being aware that they were infected with HIV (Kennedy et al., *N Eng J Med*, 2017)

Background: ART

- 18.7% on ART (National AIDS Commission Liberia, 2017)
- 69% pregnant women annually prescribed ARVs

- Available ARV regimens
  - 1st line: Tenofovir, lamivudine, zidovudine, efavirenz, nevirapine
  - 2nd line/HIV-2: Abacavir, lopinavir/ritonavir
- 2014 Integrated Guidelines for Prevention, Testing, Care and Treatment of HIV/AIDS in Liberia
  - ART initiation recommended for patients with WHO stages III or IV or asymptomatic patients with CD4 counts $\leq$500 cells/mm^3
  - Goals: “reduce morbidity and mortality by aggressively suppressing viral load, and preventing and treating OIs…maximize the benefits of treatment by encouraging consistent adherence to ART”

Background: ART Resistance

- Transmitted ARV resistance mutations among newly diagnosed patients at JFK and Redemption (Loubet et al., 2014)
  - CRF02_AG 66%
  - N=116 (85 women): 5.9% (CI: 1.7-10.1)

- Acquired resistance in those failing 1st line defined by clinical or immunologic parameters (Loubet et al., 2015)
  - N=90; ART>1 year (median 42 months)
  - 27% were <50 copies/mL; median pVL=4.7 $\log_{10}$ copies/mL
  - RAMs: NRTI 63%, NNRTI 71%
  - Most prevalent → 3TC/FTC, NVP and EFV
  - Virologic monitoring is needed.

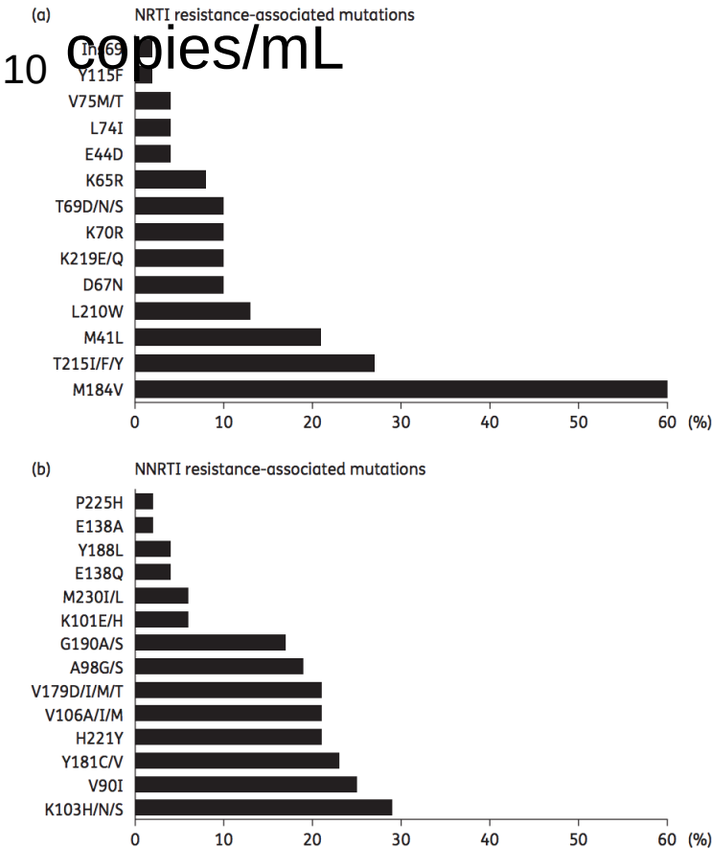

Figure 1. Proportion of patients whose viruses showed RAMs to NRTIs (a) and NNRTIs (b).

Background: Challenges

- Widespread norm of multiple and concurrent sexual relationships
- Increasing poverty leading to sex work
- Low condom use
  - 19.5% of MSM during anal intercourse (LHARPR, 2016)
- High incidence of STIs
- Widespread stigma, with some population particularly vulnerable, e.g., young girls, MSM and FSW
- Low comprehensive HIV/AIDS knowledge
- Limited access to HIV testing, measurements of CD4 counts and viral load, and ART
- Unclear actual burden/nature of the HIV/AIDS epidemic in Liberia
- Lack of awareness of HIV status
- Underutilization of services
- Low retention in care; higher for those on ART
- Fragile health system despite efforts to scale up
- Shortages of trained staff

Rationale for HIV Study

90–90–90

An ambitious treatment target to help end the AIDS epidemic

UNAIDS

- Knowledge gaps
- High quality scientific research is fill the knowledge gap

Importance of the Study

- Provide a clearer understanding of the HIV epidemic in Liberia

- Improve health and clinical follow-up of people living with HIV/AIDS

- Support policy and care through collaborative research

- Improve capabilities for independent research

HONOR Study Objectives

- Primary Objectives
  - Describe the major sociodemographic, clinical, immunologic and virologic characteristics of HIV disease in the study population at baseline.
  - Describe the course of HIV disease in the study population as a whole or by sub-group

- Secondary objectives
  - Prevalence and patter of HIV resistance at various time points during the study
  - Facilitate future research.

HONOR Study Objectives

Primary Objectives:

Objective	Characteristics/Outcome Measures
Describe major social/demographic, clinical, immunologic, and virologic characteristics of HIV disease in the study population at baseline.	☐ New or prior diagnosis of HIV-1/2 ☐ WHO HIV/AIDS clinical stage (I-IV)[a] ☐ Gender ☐ Age ☐ HIV risk factors[b] ☐ Prior Ebola virus infection ☐ Blood pressure ☐ Body mass index and pediatric age-for-length percentiles ☐ CD4 count ☐ Plasma HIV-1 RNA level ☐ ARV treatment status (duration, first- or second-line regimen, virally suppressed at enrollment) ☐ History of ARV toxicity/intolerance ☐ Prior or current trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis ☐ Prior or current opportunistic disease[c] ☐ Prior or current STIs[d] ☐ Prior or current other co-infections[e] ☐ Prior or current non-AIDS comorbidities[f] ☐ Pregnancies ☐ Highest education level ☐ Employment status ☐ Occupation ☐ Marital status ☐ Number of sexual partners ☐ Condom use ☐ Alcohol use ☐ Tobacco use ☐ Internalized AIDS-Related Stigma Scale
Describe the course of HIV disease in the study population as a whole or by sub-group.	Longitudinal measures include, but are not limited to: ☐ Alcohol use ☐ Tobacco use ☐ Number of sexual partners ☐ Blood pressure ☐ Body mass index and pediatric age-for-length percentiles ☐ CD4 counts ☐ HIV-1 RNA levels (including percent of time suppressed below the lower detection threshold, number of viral blips) ☐ ARV regimen modifications ☐ Hospitalizations ☐ Biomarker levels[g] Incidence of the following collected by self report, from medical record review or from testing in the current protocol: ☐ Opportunistic diseases[c] ☐ STIs[d,h] ☐ Other co-infections[e,i] ☐ Non-AIDS comorbidities[f,j] ☐ Death ☐ Pregnancy

[a] www.who.int/hiv/pub/guidelines/clinicalstaging.pdf.
[b] MSM, heterosexual, sex workers, intravenous drug use, blood transfusion, perinatal, unknown, other.
[c] We will collect the opportunistic diseases listed by the U.S. Centers for Disease Control and Prevention at https://www.cdc.gov/hiv/basics/livingwithhiv/opportunisticinfections.html.
[d] Syphilis, gonorrhea, chlamydia, Trichomonas vaginalis, herpes simplex virus, chancroid.
[e] Hepatitis B virus, hepatitis C virus, malaria, bacterial pneumonia, any infection requiring clinical evaluation/care.
[f] Cardiovascular, renal, hepatic, or serious non-AIDS malignancies.
[g] d-dimer, high-sensitivity C-reactive protein, interleukin-6.
[h] Gonorrhea, chlamydia and syphilis testing will be performed in this study at baseline, yearly and when clinically indicated.
[i] Hepatitis B surface antigen, core antibody, e antigen, surface antibody, and viral load testing will be performed at baseline and repeated yearly if not previously resulted as positive.
[j] The CKD-EPI creatinine equation will be used to estimate GFR and stage disease, if present.

Secondary Objectives:

Objective	Outcome Measures
Determine the prevalence and patterns of ARV resistance at various timepoints during the study period.	Determine ARV genotypic resistance mutations within 1 year of study initiation on stored samples from a subset of participants with HIV-1 RNA >1000 copies/mL at baseline (+/- ART) or at other early study time points.
Facilitate future research on stored specimens or additional measurements.	To further characterize HIV disease in the study population

Appendix C. Internalized AIDS-Related Stigma Scale

The 6 items included in the Internalized AIDS-Related Stigma Scale are as follows. Responses are dichotomous (Agree/Disagree).

1. It is difficult to tell people about my HIV infection.
2. Being HIV positive makes me feel dirty.
3. I feel guilty that I am HIV positive.
4. I am ashamed that I am HIV positive.
5. I sometimes feel worthless because I am HIV positive.
6. I hide my HIV status from others.

From Kalichmana, S.C., et al., *Measuring AIDS stigmas in people living with HIV/AIDS: the Internalized AIDS-Related Stigma Scale.* AIDS Care, 2009. **21**(1): p. 87-93.

Study Design:

- Study design
  - This is a natural history study of individuals currently receiving or initiating care for HIV infection.

- Study setting:
  - Montserrado and Margibi County
  - JFK IDC, CH Rennie, Duport Road, Redemption,

- Population:
  - People living with HIV initiating
  - N=3,500

HONOR Study Inclusion/Exclusion Criteria

- Inclusion Criteria
  - Adults and children with confirmed HIV infection
  - Ability and willingness to provide informed consent
  - Willingness to allow storage of biological samples for future research
  - Willingness to be referred for clinical care (if not already in care)

- Exclusion criteria:
  - Any condition that, in the opinion of the investigator, would compromise the safety of the study subject or staff, or would prevent proper conduct of the study.

Recruitment and Retention Plans

- Individuals will be enrolled at HIV clinics affiliated with PREVAIL sites, starting at JFK Hospital (2,300 PLHIV)
  - Enrollment will proceed sequentially at other PREVAIL sites in absence of unforeseen operational impediments to implementation.

- Recruitment from other networks and groups
  - Individuals enrolled at HIV clinics affiliated with PREVAIL
    - From within PREVAIL studies
    - National HIV counseling/testing and treatment centers
    - HIV support groups/other informal associations

- SMC
  - Study information will be disseminated through patient networks

Schedule of Procedures and Evaluations

Procedure/Evaluation	Screen (Day -21 to 0)	Day 0	Month 1 (±1 Week)	Month 3 (±1 Month)	Month 6 (±1 Month)	Month 12 (±2 Months)	Month 18 (±2 Months)	Month 24 (±2 Months)	Month 30 (±2 Months)	Month 36 (±2 Months)
Informed consent	X									
Eligibility assessment	X	X								
Physical exam (focused, symptom-directed)		X	X	X	X	X	X	X	X	X
Vital signs[a]	X	X	X	X	X	X	X	X	X	X
Height		X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Medical history		X	X	X	X	X	X	X	X	X
Medication history		X	X	X	X	X	X	X	X	X
Behavioral risk assessment[c]		X	X	X	X	X	X	X	X	X
ART counseling (subjects taking or beginning ART)			X	X	X	X	X	X	X	X
Internalized AIDS-Related Stigma Scale[d]		X			X	X		X		X
Complete CRFs	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Evaluations										
HIV-1/2 testing	X[e]									
Urine pregnancy test (women of childbearing potential)		X	X	X	X	X	X	X	X	X
Urinalysis[f]		X	X	X	X	X	X	X	X	X
Gonorrhea, chlamydia, urine NAT[c]		X				X		X		X
CBC with differential	X	X	X	X	X	X	X	X	X	X
PT/PTT, d-dimer		X	X	X	X	X	X	X	X	X
Chemistry[g]		X	X	X	X	X	X	X	X	X
WHBL (CD4, T cell, flow cytometry)		X	X	X	X	X	X	X	X	X
HIV-1 pVL		X	X	X	X	X	X	X	X	X
Syphilis[c]		X				X		X		X
HBV (antibody, antigen)[h]		X				X[i]		X[i]		X[i]
Interferon gamma release assay		X				X		X		X
Research Laboratory Evaluations										
IL6, serum		X				X		X		X
Plasma storage		X	X	X	X	X	X	X	X	X
Serum storage		X	X	X	X	X	X	X	X	X
PBL storage		X				X		X		X

Abbreviations: ART, antiretroviral therapy; CBC, complete blood count; CRF, case report form; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IL, interleukin; NAT, nucleic acid test; PBL, peripheral blood leukocyte; PT/PTT, prothrombin time/partial thromboplastin time; TB, tuberculin; VL, viral load; WHBL, whole blood.

[a] Subjects with a new HIV diagnosis only.

[b] Body temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight.

[c] Participants <18 years of age only.

[d] Participants ≥12 years of age only.

[e] Participants ≥18 years of age only.

[f] Chest x-ray will be performed in lieu of TB skin test for participants who received Bacillus Calmette–Guérin (BCG) vaccine in infancy and are ≤18 years of age at enrollment and for those who received BCG in adulthood ≤10 years prior to enrollment. Participants receiving the TB skin test will return to have the test read 48 to 72 hours after placement.

[g] By ELISA and Western blot or by HIV-1 RNA. Subjects will receive pre- and post-test counseling.

[h] Dip stick for qualitative glucose, protein, pH, specific gravity.

[i] Sodium, potassium, chloride, total carbon dioxide, creatinine, glucose, urea nitrogen, estimated glomerular filtration rate, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, alanine and aspartate transaminase, total and direct bilirubin, C-reactive protein, amylase, and lipid panel.

[j] Includes hepatitis B surface antigen, core antibody, e antigen, surface antibody, and viral load.

[k] Evaluations will not be repeated if previously resulted as positive.

HONOR: Informed Consent/Assent

- Information sessions facilitated by use of illustrated flip books to enhance individuals' understanding of the study requirements, risks, and benefits.

- Participants will sign/mark the informed consent document before any study procedures are performed.

- The participants may withdraw consent at any time throughout the course of the study.

- The rights and welfare of the participants will be protected by emphasizing that they will continue to receive medical care if they decline to participate.

- Informed consent of children less than 18 years of age:
  - Provided by parent or legal representative
  - Participants 8-17 years old will also provide assent in addition. Without assent the participant will not be enrolled.

Statistical Analysis Plan

- **Estimate the prevalence and incidence of various outcomes of HIV infection in the cohort and for various subgroups**.
  - Sample proportions and 95% confidence intervals [15]

- **Test if certain participant characteristics are risk factors for a collection of outcomes**
  - Chi-squared tests or Fisher's exact test
  - Logistic regression to control for potential confounders, such as age and CD4 levels.
  - Kaplan-Meier curves and the log rank test
  - Cox models and their modifications to conduct adjusted analyses that control for potential confounders.
  - All analyses will use a significance level of 0.05, but all results will be reported.

- **Power of the study design**: With 3,500 participants, the standard error associated with a sample proportion is less than 0.009, which gives a margin of error less than 0.017 so that 95% confidence intervals for prevalence and incidence estimates will have a maximal width less than 0.04. These constitute precise estimates.

Statistical Analysis Plan

- **Estimates for sub-groups** would have less precision depending on the size of the subgroup. Estimates for subgroups which comprise at least 20% of the study population will have precise estimates (i.e., the total width of a 95% confidence interval will be less than 0.1), whereas subgroups which comprise less than 5% of the study population will have wide confidence intervals (i.e., the total width of a 95% confidence interval will approach 0.15).

- **The power to find an association between a risk factor and an outcome depends on the frequency of the risk factor and outcome and the magnitude of the association between the risk factor and outcome.**
  - To detect associations as weak as a relative risk of 1.5, the outcome prevalence would need to exceed 10% for a risk factor which is found in half the sample to have acceptable (i.e., 80%) power.
  - For stronger associations, we will have acceptable power for less common outcomes and risk factors. While these results are stated in terms of a prevalence, similar reasoning holds for outcomes that are observed longitudinally and would better be described as an incidence. For example, if the outcome was progression to AIDS and the risk factor was a baseline risk factor (e.g., MSM) these same calculations apply.

Statistical Analysis Plan

- **Power of time to event analyses** (Table 2). We assume that a certain proportion have a risk factor and we observe a certain number of events.
  - We can use Freedman's formula to compute the power as it depends on the number of events (using the expected number of events given the sample size and outcome prevalence), the relative size of the at risk group (using the expected sizes using the risk factor prevalence and sample size), and the hazard ratio (using the inverse of the relative risk). Comparison of the Tables 1 and 2 indicates that there is more power associated with the time to event analysis, especially as the risk factor prevalence increases.

Clinical Referral

- Participants will continue to receive medical care and treatment, including ART provision and management, from local clinicians according to local care standards or be enrolled in care.

- Patients not already enrolled in care will be enrolled in care

- The study team will share results of all clinical tests and applicable research tests with the participant's PCP.

Overview of Operational Plan

- **Data Monitoring**
  - Conducted under the direction of a protocol team
  - Data collection plans may be modified; new sub-studies may be planned.

- **Risks of study participation will be minimal:**
  - Blood draw: transient pain, bleeding, bruising, light headedness, etc.
    - Blood: Adult: 10.5 mL/kg, max. 550 mL; Child: 5mL/kg/visit, max. 9.5 mL/kg over 8 visits.
    - PI discretion to limit these volumes in any participant whose clinical condition might be adversely affected.

  - Loss of confidentiality (staff and trackers will be trained)

Safety Assessment

- Research-related interventions include blood drawing and TB skin testing.
- Only AEs occurring within 48 hours of the research procedures and assessed by site investigator as possibly, probably or definitely related will be recorded on the CRF, reviewed by the PI, reported following NIAID IRB and NREB reporting requirements, and followed through resolution by the PI.
- No other medical occurrence will be considered an AE for this study.

Sample Storage, Use and Sharing

- **Storage and Tracking**
  - All samples and data will be stored in locked freezers in the PREVAIL Repository and rooms in Liberia.
  - All samples and data will be stored using ID codes.
  - Password-protected computers will be used plus limited access.

- **Disposition of and use of stored samples**
  - NIAID IRB and NREB approval will be sought before sharing any sample/data with new collaborators.
  - Some exemptions from the need for approval might apply.
  - At completion of study, samples will either be destroyed or banked/transferred to another protocol (this will require IRB/NREB approval).

Ethical Conduct and Compensation

- Local Review and approval of Protocol and Informed Consent by IRB/NIAID and NREB
- Ethical Conduct of the Study according to:
  - Declaration of Helsinki US regulations protecting of human subjects such as 45 CFR 46
  - Requirements of Good Clinical Practice (GCP)
  - US Office for Human Research Protections (OHRP)
  - Laws governing research and rights of human subjects in Liberia
- Confidentiality of study participants
  - The confidentiality of all study participants will be protected in accordance with GCP Guidelines and national regulations.
- Compensation
  - Participants will be compensated $10 at each research visit, when specimens are collected, for their time and inconvenience.

Challenges

- Stigma associated with the disease
- Fatality rate
- Confidentiality
- Enrolling children