

# **Lessons learned from FDA audits: The Partners PrEP Study experience**

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ASPIRE Protocol Team Meeting  
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# Audit

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- A **systematic and independent examination of trial-related activities and documents** to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).

ICH E6 1.6

# Why audits?

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- Assess knowledge of and adherence to laws and regulations governing clinical trials
  - 21 CFR 50 (IC), 54 (COI), 56 (IRB), 312 (IND)
  - ICH E6 (GCP)
- Ensure safety, rights and welfare of subjects
- Assess quality, integrity, validity/reliability and acceptability of study data
- Ensure trial conducted according to applicable protocol(s), SOPs and regulations/guidelines
- Review training documentation
- Assess monitoring of site

# Purpose of this talk

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- Not a comprehensive overview of how to undergo an FDA audit
  - Other opportunities, other (much better) trainers
- Instead, some practical lessons learned, from an investigator/site perspective, that might help us prepare now for the FDA audits that (hopefully!) ASPIRE will have someday

# Partners PrEP Study

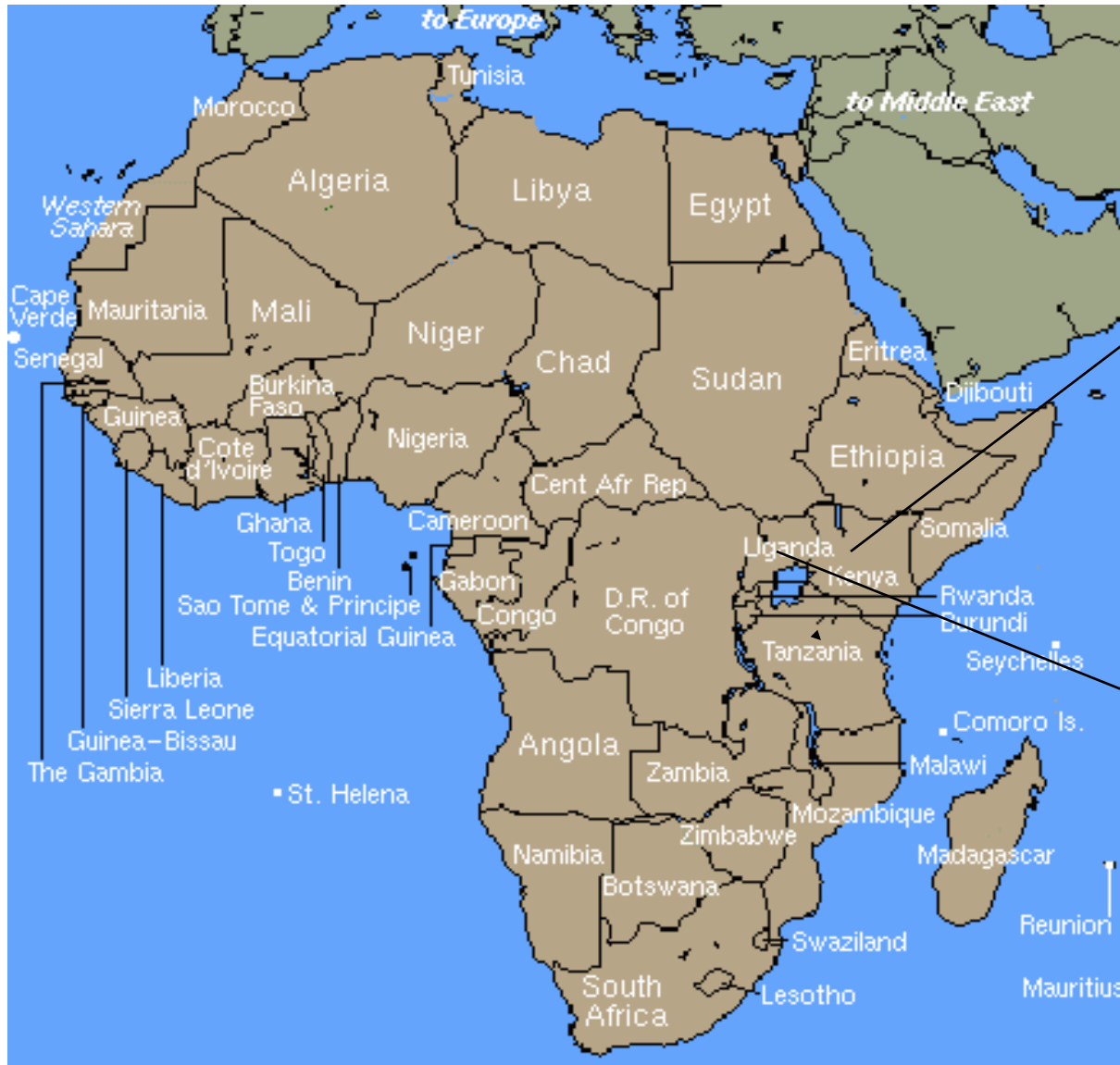
- The Partners PrEP Study is a *phase III, randomized, double-blind, placebo-controlled, three-arm* trial of daily oral tenofovir (TDF) and emtricitabine/tenofovir (FTC/TDF) PrEP for the prevention of HIV-1 acquisition by HIV-1 seronegative partners in heterosexual HIV-1 serodiscordant partnerships



Thika, Kenya Partners PrEP Study site



# Study Sites



Eldoret,  
**Kisumu,**  
Nairobi,  
Thika,  
**Kenya**

Jinja,  
Kabwohe,  
Kampala,  
Mbale,  
**Tororo,**  
**Uganda**



# Audited sites

- Kisumu, Kenya site
  - Urban site (3<sup>rd</sup> largest city in Kenya)
  - Collaboration between Kenya Medical Research Institute & UCSF
  - Established 2004
  - Enrollments = 629 couples
  
- Tororo, Uganda site
  - Urban/rural site (4h drive from Kampala)
  - Collaboration between TASO & CDC-Uganda
  - Site established for Partners PrEP
  - Enrollments = 638 couples



# Audits

- Two auditors
- 5 days per site
- Pre-announced





# Lesson #1: document, document, document

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- If it isn't documented it wasn't done. Also, document smartly = more is not better, useful is.
- Think about the cross-cutting interface of different systems (DoA, training files, start dates, SOP)
- FDA, above and beyond ICH, will look at the data and will step back to see if the process for getting those data is clear and apparent
- If you say you will use something routinely (checklists, sign off sheets, temperature monitoring, EQA), then be sure it is consistently used.



# Lesson #2: inspectors do not know the study

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- But they do know how to look out for study practices that are concerning, regardless of the topic of the research
- Practice at explaining the study, study processes, and the organizational relationships (CORE, site, DAIDS) involved.
  - Large, complex studies are red flags for audits
  - Organograms (within institution and across institutions) are helpful



# Lesson #3: communications are key source

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- Full review of communications done. Printed, filed emails of core communications between trial Coordinating Center and site were very useful (e.g., priority emails), for documenting sponsor oversight and for demonstrating follow-up and closure of problematic issues (follow-up of monitor reports, fixing of problems, etc.)



# Lesson #4: know your IRB requirements

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- Full review of all IRB documents (dates, content of letters, requirements of the IRB [stamped consents, review of CRFs, timing of reporting of AEs, etc.] was done.



# Lesson #5: human subjects protections

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- Inspectors are charged with determining whether human subjects protections were in place
- Know your informed consent process inside and out,
  - Who, where, when, how, evidence
  - Processes for consent of illiterate participants
  - Processes for assessing understanding of the study



# Lesson #6: fully review key files

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- All seroconverters
- Potentially all SAEs
- Potentially all pregnancies
- All protocol violations
- Participant #001 – entire binder, in full (demonstrating study done right from Day 1)
- Monitor reports (including logs of visits)



# Lesson #7: mistakes happen

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- Looked until they found mistakes (data that are too perfect are not believable)
- What processes were in place to recognize, fix, prevent errors? Reviewed CAPAs / notes to file in detail.



# Lesson #6: the burden is on the IoR

- The Investigator of Record, in signing the Form 1572, assumes responsibility for execution of the study at the site
  - Audits are largely out of the sponsor's/funder's control
  - And, within the Network, it is the IoR, not CTU leadership, who will be the focus
- Staff are qualified, trained, delegated, and supervised
  - Delegation of authority log was open and on the table throughout the entire audit
  - Training records were reviewed in detail





# Lesson #9: impressions matter

- Clinic is clean and organized
- Clinic is a controlled space (inspector greeted at the door, signed in, provided with accompanying person)
- Documents are accessible (relevant charts brought when requested, inspectors were timing how long it took)
- Filing approach is smart, consistent
- Teams were courteous, agreeable, and not argumentative



# Lesson #10: prepare now

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- Think about audits from the beginning
- Auditors will follow FDA inspectional checklists (which are available to the public) to the T



# FDA approval of FTC/TDF PrEP for HIV prevention



Consumer Health Information  
[www.fda.gov/consumer](http://www.fda.gov/consumer)

## FDA Approves First Medication to Reduce HIV Risk

*“It is still better to prevent HIV than to treat a life-long infection of HIV.”*

Deborah Birnkrant, director of the  
Division of Antiviral Products, US FDA,  
16 July 2012

# Conclusions

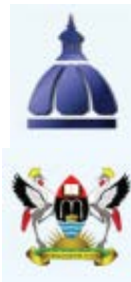
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- Be calm, attentive, methodical throughout the execution of the study – and that approach will be apparent in the records
- It is OK to be nervous about inspections (I was!)
- It is all worth it in the end – if we can be a part of developing a new HIV prevention item

# IT TAKES A TEAM



Malawi College of  
Medicine – JHU  
Research Project



UNC Project -  
Malawi



INTERNATIONAL  
PARTNERSHIP FOR  
MICROBICIDES



University of Zimbabwe,  
School of Medicine

