

Safety Issues in HIV Prevention Research

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Notes: Prevention trials in biomedical, structural, and behavioral interventions bring up concerns of safety.

Particularly in communities not familiar to the medical model and especially keeping in mind the legacy of Tuskegee.

It's important to follow safety mechanisms and build trials to support safety.

Addressing Safety in Clinical Trials

- ❖ Involve community from the beginning
- ❖ Define a prevention "standard of care"
- ❖ Identify safety issues: biomedical and behavioral
- ❖ Design trials that will answer the questions
- ❖ Provide adequate informed consent
- ❖ Plan interim analyses with a DSMB
- ❖ Anticipate interpretation of trial results
- ❖ Plan for management of emergent safety issues

Notes: There's nothing more important than having community support. I believe in activism, the treatments that we have now are the result of activists chaining themselves to the desks at the NIH. We need to continue to build prevention advocacy.

Involve Community!

- ❖ Community input is vital during all aspects of trial design
- ❖ Community members raise real-life issues
- ❖ Community should have a clear understanding of potential risks (and benefits) and be able to explain to others
- ❖ Community members should review informed consent documents
- ❖ Include community on DSMB

Notes: Community input is really vital in ALL parts of the clinical trial design, they need to be at the table at the beginning.

Community brings perspective of real issues researchers may not be aware of. Tools to measure adherence were not practical for use, and was pointed out by the community. Community should CLEARLY understand the risks and benefits and be able to communicate that to others. Community members can act as translators and can push researchers to make information more understandable and build communication structures.

Community members should review the informed consent documents. MUST be understandable to trial participants

We must include community on Data Safety Monitoring Boards - you will be surprised how many of these crucial safety mechanisms don't include community.

Define a Prevention "Standard of Care"

- ❖ Prevention trials must take place with "optimized background prevention"=OBP
- ❖ Condoms, risk-reduction counseling, education
- ❖ Needle-exchange in trials of IDU (if possible)
- ❖ ? Role of male circumcision ?

- ❖ Unlimited free HIV / STD testing
- ❖ Referrals to services and care
- ❖ An aggressive prevention standard of care will enhance safety of participants

Notes: We have to include a prevention standard of care. We need to talk about Optimized Background Prevention as well. These are the services that must be a part of the background standard of care.

Sexual Behavior: Ghana

	Screening	Follow-up
Number of partners (30 days)	21	14
Number of new partners (30 days)	11	6
Number of sex acts (7 days)	12	15
Condom use (last act)	52%	94%

Slide courtesy Leigh Peterson, FHI

Notes: This standard of care will effect the outcome of the trials.

Note condom use increase between screening and follow-up. This is the outcome of the provision of counseling and access to condoms in the trials.

Identify Key Safety Issues

Each intervention has its own safety issues

- ❖ Behavioral: effect on mental and emotional health, risks to confidentiality
- ❖ Microbicides: drug-specific toxicity, delivery-system adverse events
- ❖ PrEP: drug-specific toxicity
- ❖ Circumcision: surgical risks, infection
- ❖ Vaccines: injection site reactions, drug-specific adverse events, immunologic adverse events

Cross-cutting Safety Issues

- ❖ Risk of abandonment of condoms, increased risky behaviors
- ❖ Mental and emotional stress
- ❖ Risk of disclosure, breach of confidentiality
- ❖ Risk of partner violence, abandonment

Notes: We need to make sure things that work are not abandoned in prevention trials, and we need to guard against and plan for these additional safety issues that may come with participating in a trial.

Design Trials That Will Answer the Questions

Population-specific considerations

- ❖ Define the target population (women, MSM, IDU, African-Americans, couples, monolingual Hispanics, adolescents, residents of specific geographic areas)
- ❖ Limitations of generalization beyond target population
- ❖ Evaluate special features of population

Notes: We can't say a study only done in white man will provide the same results that will apply for black women. We need to include the same populations that will eventually use these interventions in the design of the trial.



Notes: This is a slide that use a face of the community for one of our trials, and was designed by the community advisory board.

Design Trials That Will Answer the Questions

Sample size issues

- ❖ Include "target" populations in adequate numbers to answer scientific questions
- ❖ Address enrollment challenges by increased numbers of sites, marketing using electronic media, lots of education
- ❖ Recognize challenges for retention with harder to reach populations
- ❖ Address measurement of adherence with novel approaches

Notes: We have to have enough people to give us the big enough sample size so that we can answer the questions. We have to take into account retention and people dropping out half way.

Outcome Measures for Safety

- ❖ Safety labs: chemistry, hematology, drug-specific markers
- ❖ Screening for STIs: syphilis, Chlamydia, gonorrhea
- ❖ Study-specific immunologic monitoring
- ❖ Behavioral risk assessment
- ❖ Adherence assessment
- ❖ Treatment emergent adverse events
- ❖ Seroconverters: CD4+, viral load, resistance testing, viral tropism analysis

Notes: Some people said that it's difficult to measure adherence, but we need to look at using new technologies, such as cell phones, texting, hair samples to measure drug levels, etc. You have to have the right outcome measures - so that screening for STIs should always be available.

Informed Consent

- ❖ Explain procedures, risks, benefits, rights, and responsibilities involved in trial participation
- ❖ Provides ethical protection for participants
- ❖ Language must be understandable, reviewed by lay persons and community members

- ❖ Prepares participants to deal with emergent safety issues
- ❖ Trials can be stopped if participants and community advocates do not believe that they were appropriately made aware of risks associated with trial participation

Notes: This is one of the key way that we provide safety guidelines in clinical trials. Spending time and do the proper informed consent with participants is critically important in terms of safety.

Community Engagement:

PrEP Example

Cambodian PrEP trial was stopped before it even started due to community opposition and unaddressed concerns

Informed Consent: PrEP Example

“AIDS activists in Cameroon and France have alleged that the women volunteers taking part in the clinical trial in Douala have not been sufficiently informed of the risks involved.”*

- ❖ Signed informed consent is a legal document protecting researchers as well as trial participants
- ❖ Underscores importance of local ethical review board review of informed consent
- ❖ Underscores importance of community review of informed consent

Informed Consent Tools

- ❖ Use of flip chart
 - Key issues are emphasized in simple language to supplement informed consent
 - Pictorial examples used when possible
- ❖ Comprehension Test
 - Key questions about trial are asked after informed consent
 - Participant must pass test to be included in trial; may re-take test once

Notes: If people don't understand what they are getting into, it's not safe. So they have to pass a test in order to participate in the trial.

DSMB and Interim Analyses

- ❖ DSMB = Data Safety Monitoring Board
- ❖ Interim Analysis = data analysis during progress of the trial
- ❖ An independent safety board will assure that trial stops if
 - Adverse outcomes are detected early
 - The trial is not capable of answering the question

Notes: They look at the data during the trial, and if they see something is not working out (one arm doing much better than the other), they can stop the trial. They are not part of the trial researchers.

Interpretation of Trial Results

- ❖ Off-label use in the community
- ❖ Implications of negative trial results (STEP Study)
- ❖ Implications of “positive” trial results

- ❖ Interpretation of underpowered trial results
- ❖ Partial efficacy + risk compensation = increased transmission risk
- ❖ Effect on study participants of results from similar trials (adherence, behavioral risk)

Notes: This is also a safety issue. You've heard about off-label use of tenofovir, that people might go out and use it without being monitored. What are the issue of safety for people not in the trials?



Notes: Meanwhile, there have been a number of media reports suggesting that some HIV-negative men may already be using PrEP, either on a daily basis or intermittently as an evening before pill. These reports suggest that this practice may be widespread in gay dance clubs, where it is being used along with recreational drugs.

Plan for Management of Emergent Safety Events

- ❖ Plan for handling HIV seroconversion
- ❖ Access to care, drugs
- ❖ Plan for follow-up of medical adverse events: access to care
- ❖ Plan for possible long term follow-up if longer term safety concerns are raised (unanticipated immunologic consequences of vaccines?)

Notes: Trials must have a plan for adverse events, and long term follow-up. An example is the STEP vaccine trial, people have to be followed and make sure there are no long term negative consequences.

Q & A:

Drug Adherence Issues - Adherence is difficult to measure, but has been successful with research into other chronic, long term diseases. How can we apply this to HIV prevention research? There are validation tools we can use: 1. asking folks about taking drugs in the last few days vs. the last few months 2. Bottle caps that record opening the bottle 3. Hair sample testing.

Community engagement in treatment research - Community Advisory Boards such as the ACTG (AIDS Clinical Trials Group) are very active on Government funded trials, but there are no community input in drug company trials. Since most drug trials are done by the pharmaceutical companies, so MOST therapeutic trials do not involve the community.

Even when treatment studies comes to an ACTG site, the study is already designed and packaged, leaving no room for community input.

We shouldn't throw the ACTG model out. The AIDS Treatment Activists Coalition (ATAC) is working on pushing industry to use this model.