CONTROLLING THE HIV EPIDEMIC WITH ANTIRETROVIRALS

From Consensus to Implementation

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PrEP Trial Design

Navigating the Landscape

Veronica Miller, PhD
Forum for Collaborative HIV Research
UC Berkeley

Definition

- PrEP= Pre-exposure prophylaxis (ARVs)
  - Oral
  - Topical
  - Long-acting release formulations
  - Vaginal ring

Will it work?

- Efficacy-Effectiveness
- What populations?
- What dosing regimen?
- Duplication of effort?
- Public Health approach
- Placebo control

Yes it does (sometimes)

FTC/TDF
(oral)

July 2012/FDA

----------INDICATIONS AND USAGE----------

TRUVADA is a combination of EMTRIVA and VIREAD, both nucleoside analog HIV-1 reverse transcriptase inhibitors.

TRUVADA is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. (1)

TRUVADA is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. (1)

Now what??

- Active control arm
- Number/type of diff regimen
- Demonstrating efficacy in
- context of heterogeneous effect
- Diverse regulatory perspectives
- Ethical challenges
- Placebo control?

PrEP Research Challenges

Resources/Landscape

- Large # participants
- Trial sites
  - Selection
  - Maintenance
- Incidence rate
- Community
  - Engagement/Buy-in
  - Support

Trial Design /Conduct

- Efficacy/Effectiveness
- Adherence
- Non-inferiority/superiority
- Control arms
- Biology/behavior
- Populations
- Long-term safety

Efficacy – Effectiveness Continuum

Efficacy

- True biologic efficacy
  - 100% adherent group
- Can we build it?
- Development

Effectiveness

- In the "real world"
  - ??% adherent group
- (If we) Will they come?
- Delivery

PrEP Research – Moving Forward

Development ⟷ **Delivery**

- Regulatory Pathway
- Benefit-Risk
- Manufacturing
- Pricing

- Acceptability
- Epidemiologic impact
- Cost-effectiveness
- Affordability

<u>Increase chances of success</u>
↑ number of candidates

<u>Increase chances of success</u>
↑ understanding of market

adapted from S Becker March 2013

No chance for effectiveness absent efficacy

- To demonstrate efficacy
  - Randomized trials
    - experimental vs. active control/placebo
  - Optimal conditions
  - Continue quest for surrogate markers
- To demonstrate effectiveness
  - Randomized trials (prioritized products)
    - Experimental vs. active control
    - Strategy A vs. Strategy B
  - Demonstration projects
  - Implementation research methodologies

Experience: HIV treatment

- Efficacy (IND) trials
  - Drug sponsor
  - Drug label/indication
- Strategy trials
  - Drug sponsor, trial networks, clinical investigators
  - Compare different ART regimen
    - Different patient populations (e.g. pre-treatment)
    - Different co-morbidities
  - Potential to expand label/indication

Adherence: Efficacy Trials

Optimal Conditions for daily oral or topical products

- Provide effective adherence support
- Enrich for adherent participants
- Establish best practices for documenting adherence
  - Drug levels
    - When, how often, and where
    - Real time
  - Taggants and other new technologies
- Assess adherence in placebo/control group

Adherence: Efficacy Trials

- Sidestep adherence issues
  - Long-acting products
  - Vaginal rings
- Still need to measure adherence in control group

Adherence: Effectiveness Studies

- Best practices for increasing and measuring adherence in different populations
  - Discordant couples
  - Young women, young men
  - MSM
  - IDU
- Appropriate market research

Superiority *vs.* Non-Inferiority

Superiority

- Head-to-head comparison
- Experimental is better (or not) than active control/placebo
- Settings where FTC/TDF had little/no effect

Non-Inferiority

- Rule out unacceptable increase in risk of HIV infection for experimental vs. active control
- Dependent on previously randomized study of (now) active control

  Requires:

  – Effect of active control large

  – Precise estimation of effect

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Active Control Arms

FTC/TDF: Active Control Arm

- Experimental
  - Other oral agents
  - Other modalities

FTC/TDF: Prevention Package

- Experimental
  - Other modalities
    - Topical gel
    - Vaginal ring

Control Arm: Placebo

- May be appropriate*:
  - in settings/populations not accepting FTC/TDF
  - in settings where adherence to FTC/TDF is not achievable
    - not willing or not able to adhere

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Biology- Behavior

- So you have a product that "works"
- What are the behavioral pitfalls?
  - Adherence behavior for daily/coital oral/topical products
    - See above
  - Transmission risk behavior (risk compensation)

Dealing with Risk Compensation

- Efficacy trials (*always maintain optimal conditions*)
  - Minimize risk compensation
    - Best practices for combination prevention practice in optimal setting
  - Establish best practices for assessing risk compensation
  - Understand contribution of risk compensation to efficacy results
- Effectiveness studies
  - Understand contribution of risk compensation to PrEP effectiveness in larger setting
  - Establish best practices for decreasing compensation in "real world"

Populations

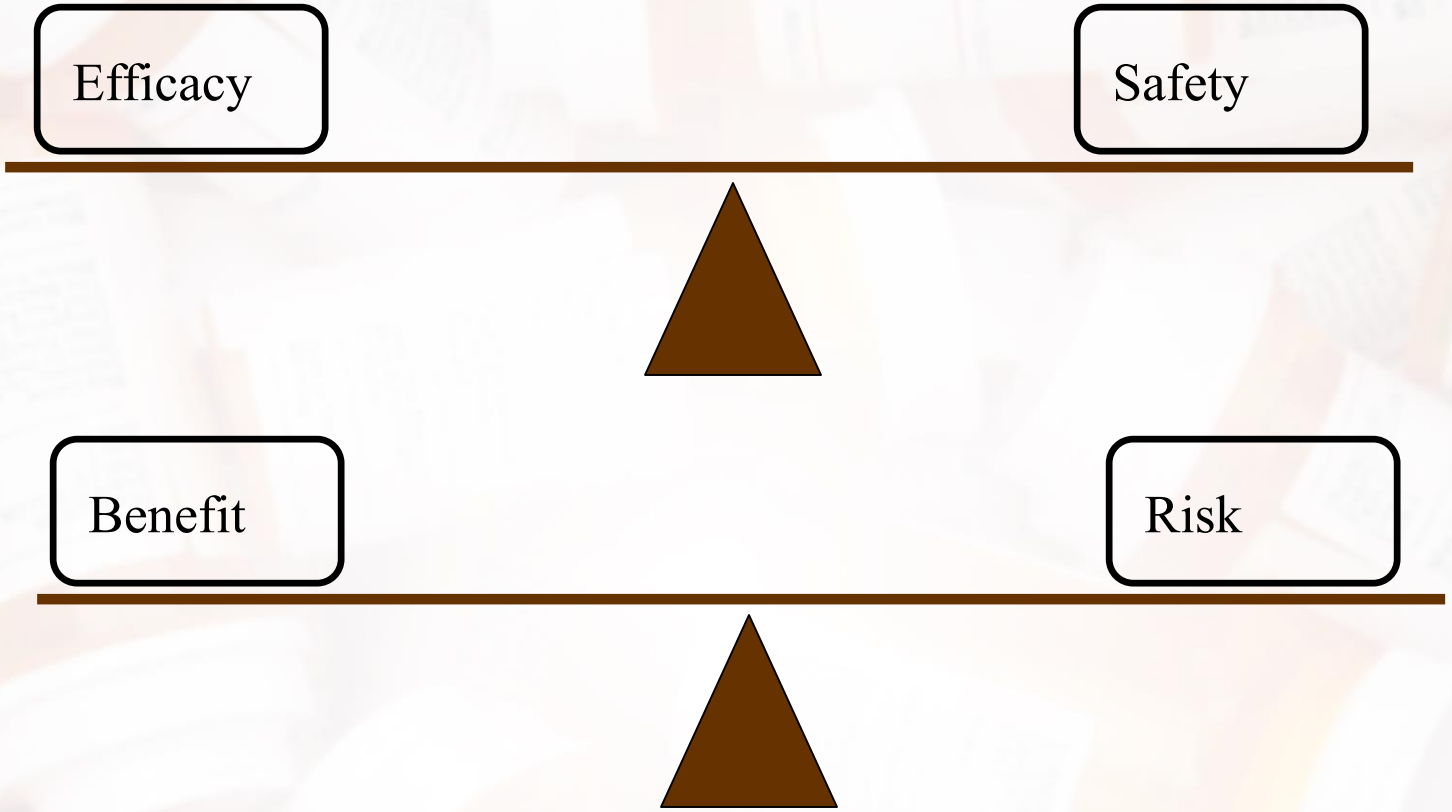
- When can we be confident that:
  - PrEP MSM = PrEP IDU = PrEP heterosexual
    - Repeat/confirm for each new regimen?
    - Extrapolation from FTC-TDF to other ARV based approaches?
- Translation from optimal conditions of efficacy studies to real world populations
  - Demonstration studies
  - Implementation research

Long-term safety

- Pharmacological
  - Drug toxicity for PrEP client
  - Special situations, e.g. pregnancy
- Virological
  - Drug resistance
- Behavioral
  - Risk compensation

Drug=API+Intended Use

- Efficacy
  - Rationale for a drug
- Safety
  - Drug is conditional on
- The two are irrevocably intertwined



Benefit-risk assessment: basis for FDA's decisions in pre-market and post-market review process

FDASIA

- Food and Drug Administration Safety and Innovation Act
  - Public Law 122-144
- Section 905 amends Section 505(d) of FD&C Act
  - "*implement a structured risk-benefit assessment framework……*"

PrEP Safety Assessment

- Pre-marketing
  - History of drug in treatment context (if applicable)
  - Efficacy and effectiveness studies
- Post-marketing commitments
- REMS
  - Risk Evaluation Mitigation Strategy

OTHER APPROACHES

Adaptive Trial Design

Summary Box

a. Adaptive design clinical trials move away from the normal phase I, II and III as they have a built-in process of responding to new data and so trials change as they progress.
b. Adaptive design clinical trials save money, time and can be more ethical as they can avoid participants being un-necessarily exposed to side effects or ineffective treatment
c. Adaptive design clinical trials have been championed by the pharmaceutical industry yet could also be highly advantageous in academic led disease management studies.
d. Adaptive design clinical trial could be exploited in the field of global health however the sharing of methods, resources and best practice may be needed to fill the capacity gap

FIGURE 1. Summary box.

Lang Am J Trop Med Hyg 2011

Adaptive Design in Vaccine Research

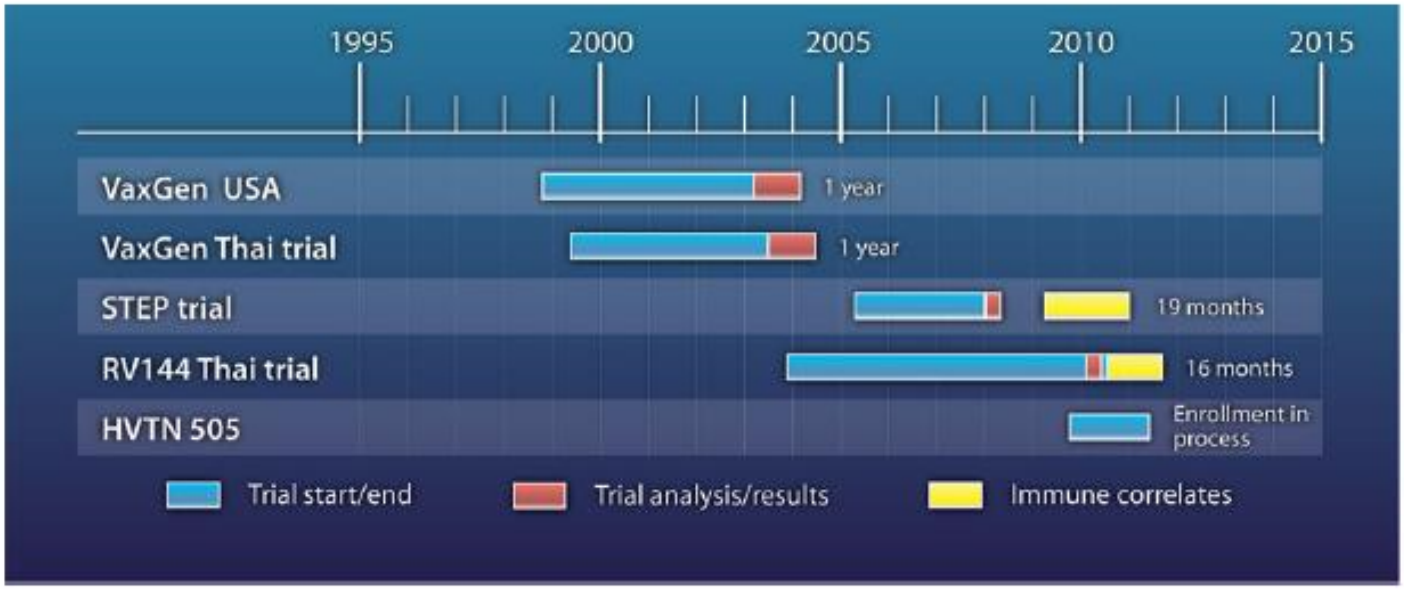


Figure 1. Timeline of HIV vaccine efficacy trials

Corey Sci Transl Med 2011

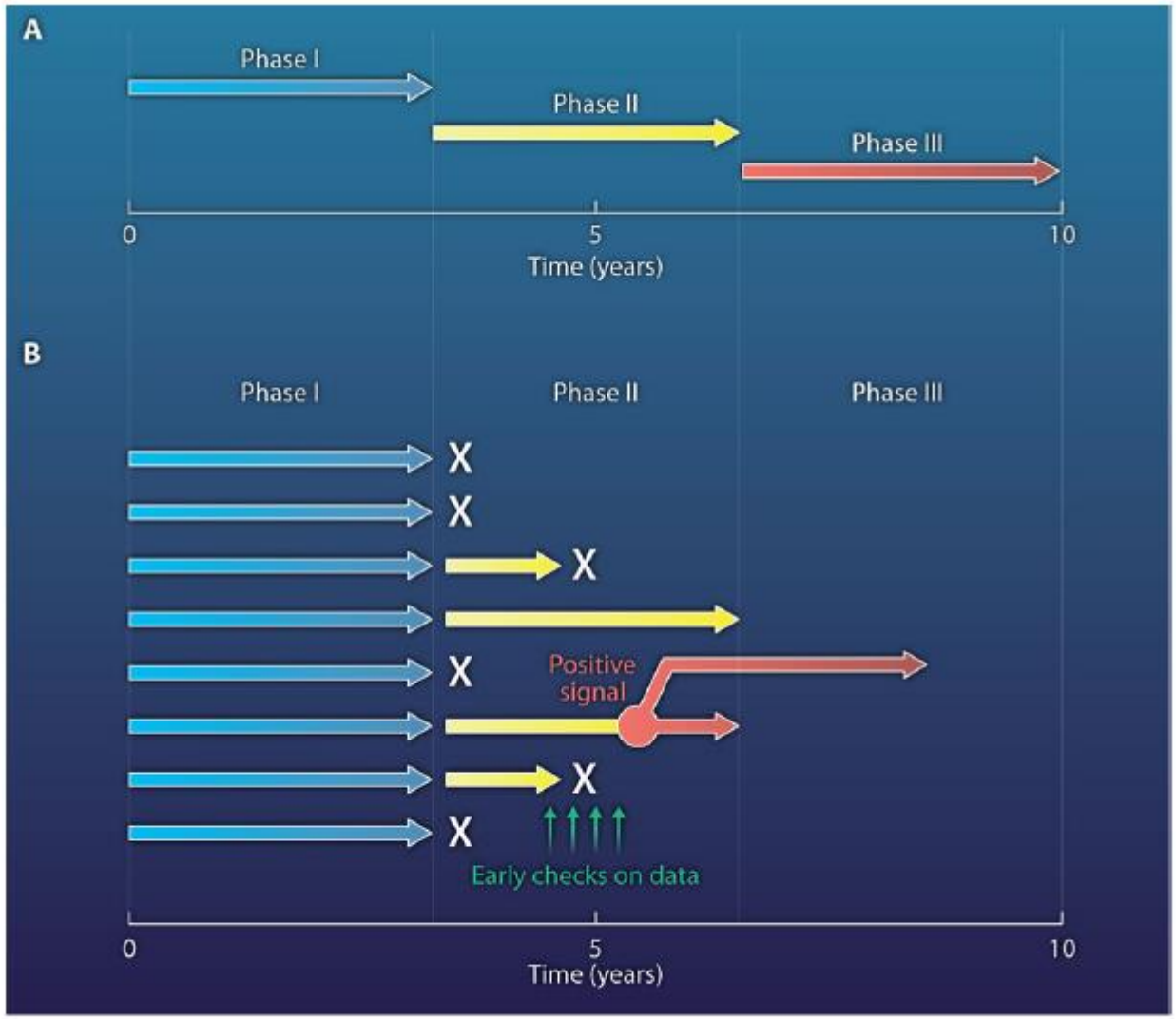


Figure 2. Adaptive trial designs accelerate vaccine development

Corey Sci Transl Med 2011

Summary

- It's complicated
- It's not insurmountable
- Statisticians, pharmacologists, behavioral scientists, implementation researchers, clinicians, community, regulators, ethicists, policy experts, pharma, UNITE!