


CONTROLLING THE HIV EPIDEMIC WITH  
**ANTIRETROVIRALS**



From Consensus  
to Implementation

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# PrEP Trial Design

## *Navigating the Landscape*

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# 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



- Regulatory Pathway
- Benefit-Risk
- Manufacturing
- Pricing

Increase chances of success

↑ number of candidates

## Delivery

- Acceptability
- Epidemiologic impact
- Cost-effectiveness
- Affordability

Increase chances of success

↑ understanding of market

adapted from S Becker March 2013



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# 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

Donnell JAIDS 2013



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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



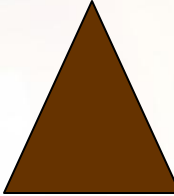
# Drug=API+Intended Use

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



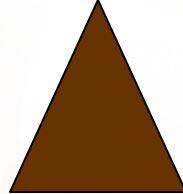
Efficacy

Safety



Benefit

Risk



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 112-144
- 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



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# 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



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# Adaptive Design in Vaccine Research

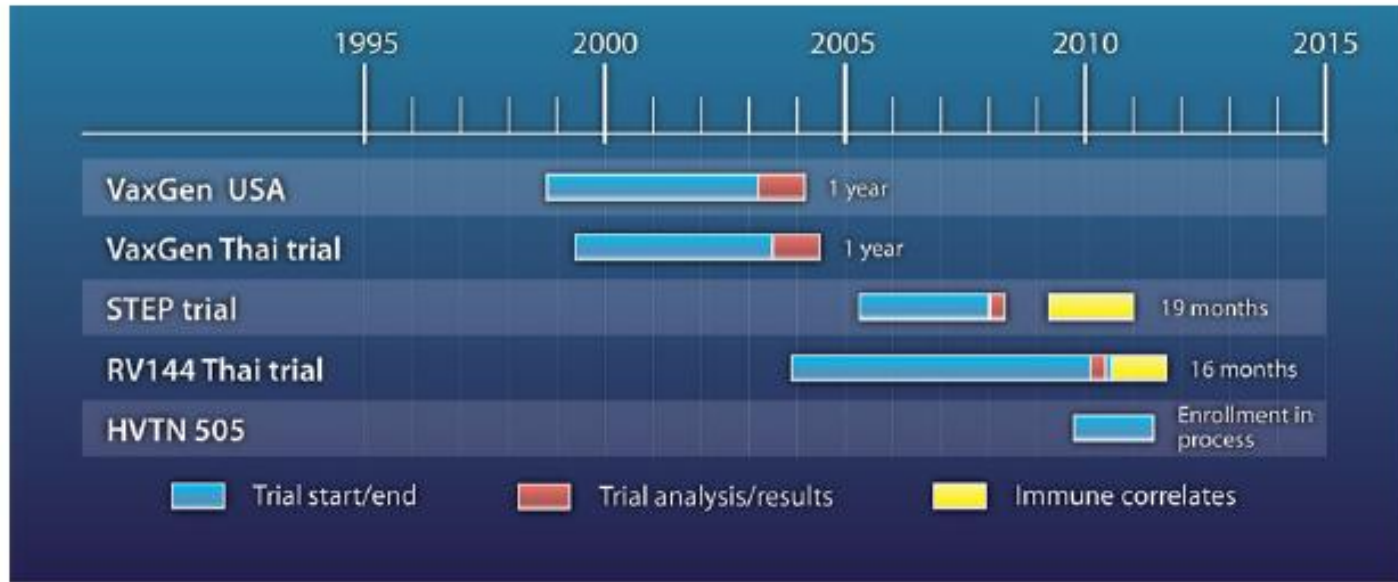
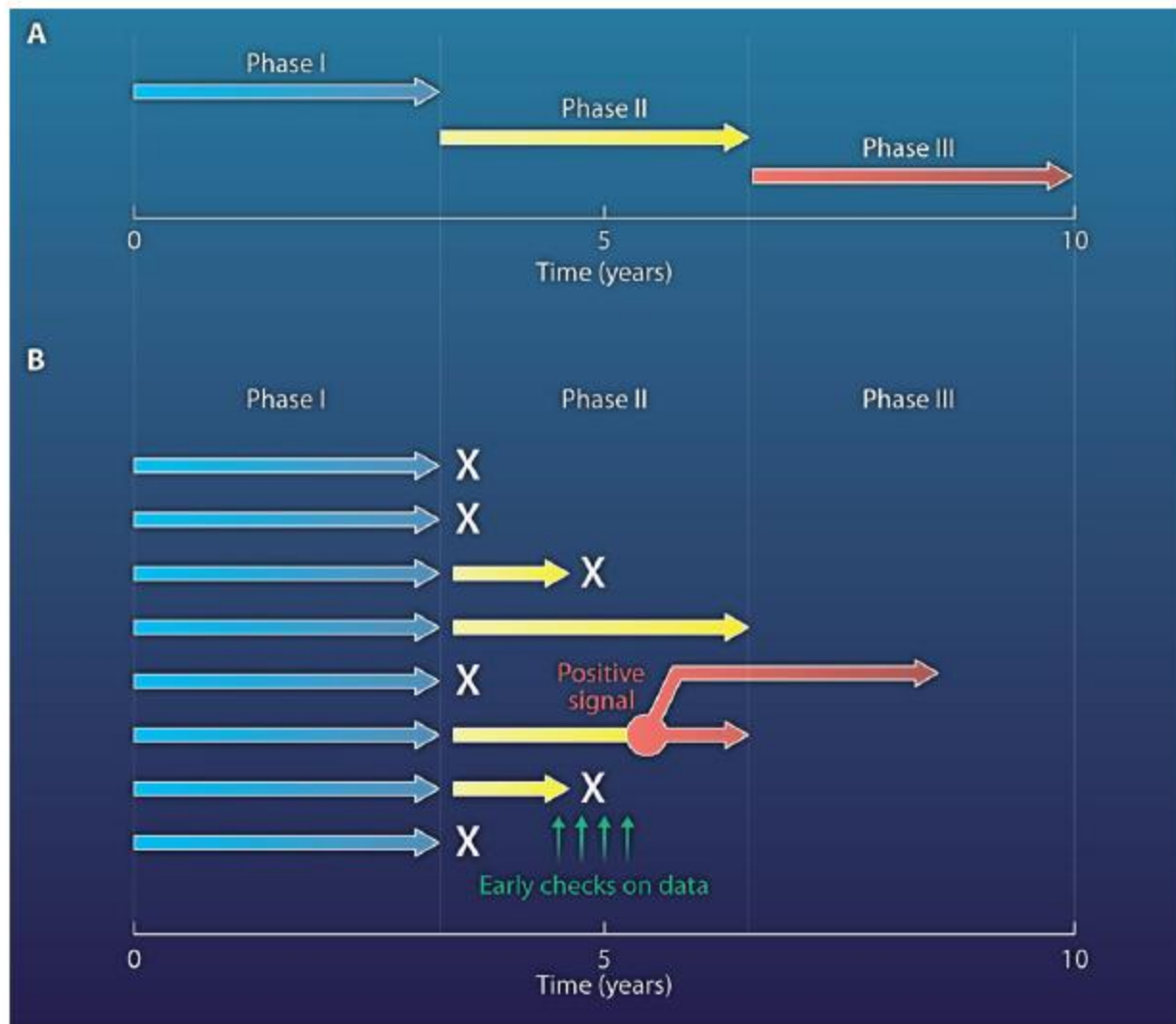


Figure 1. Timeline of HIV vaccine efficacy trials

Corey Sci Transl Med 2011



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**Figure 2. Adaptive trial designs accelerate vaccine development**

Corey Sci Transl Med 2011



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# Summary

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

