An alternative design: immediate vs deferred PrEP

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David Dunn and Angela Crook

on behalf of PROUD and MDP study teams

PROUD

MRC Clinical Trials Unit

MDP Microbicides Development Programme

Overview

- Context for selecting the wait-listed design
- Pilot study to determine feasibility
  - Clinical considerations
- Current thinking regarding the trial design
  - Statistical considerations

Background

- FDA approve Truvada as PrEP July 2012

- Proven biological efficacy of PrEP, but 'real world' effectiveness unknown, and specific uncertainties about adherence and risk compensation in the UK

The British HIV Association/British Association for Sexual Health and HIV Position Statement on pre-exposure prophylaxis in the UK

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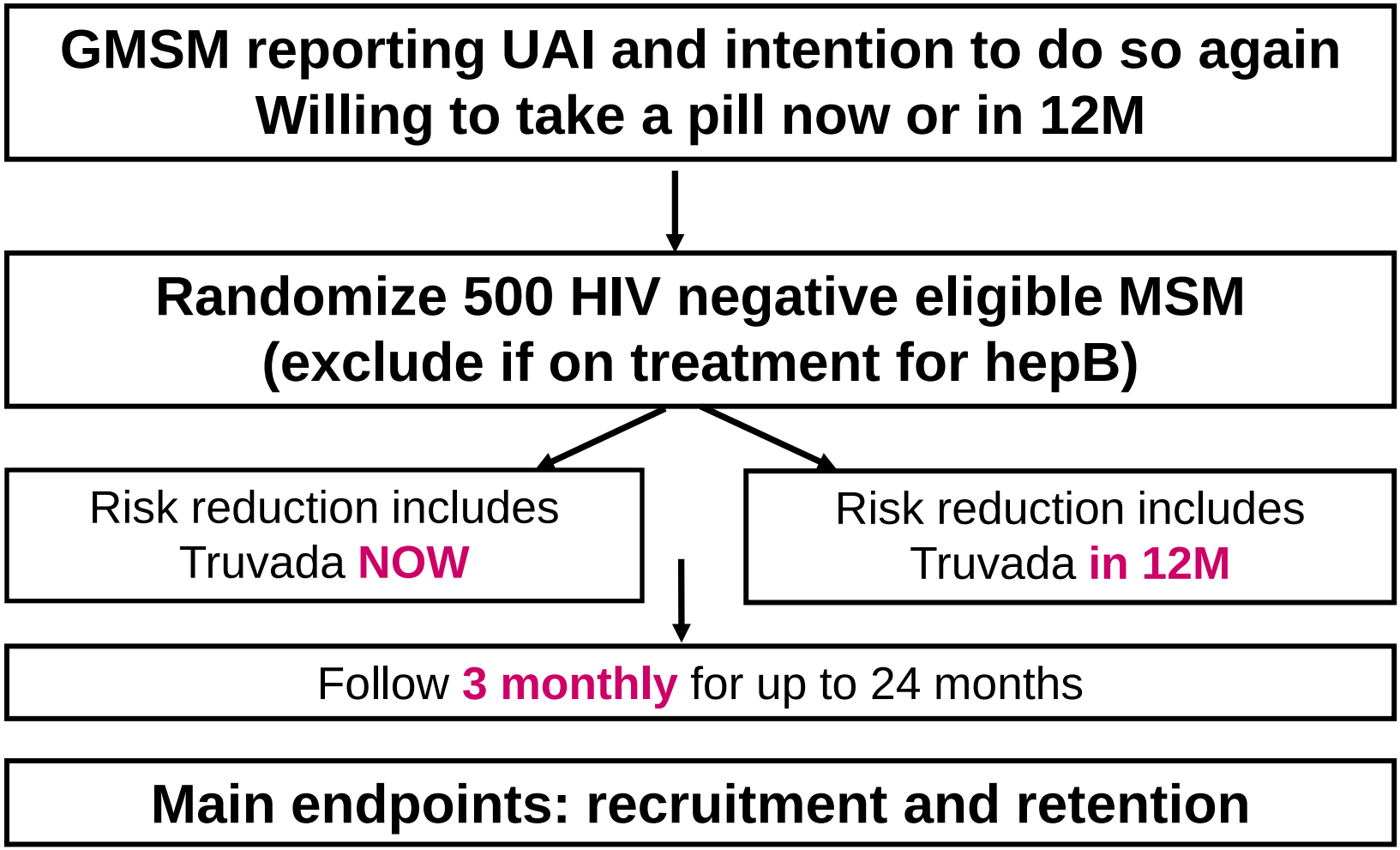
- PrEP only available in UK through PROUD pilot study

PROUD Pilot Study

PRe-exposure Option for reducing HIV in the UK: an open-label randomisation to immediate or Deferred daily Truvada for HIV negative gay men

Wait-listed Design



Fully enrolled 30th April 2014 (n=545)

Who is enrolling?

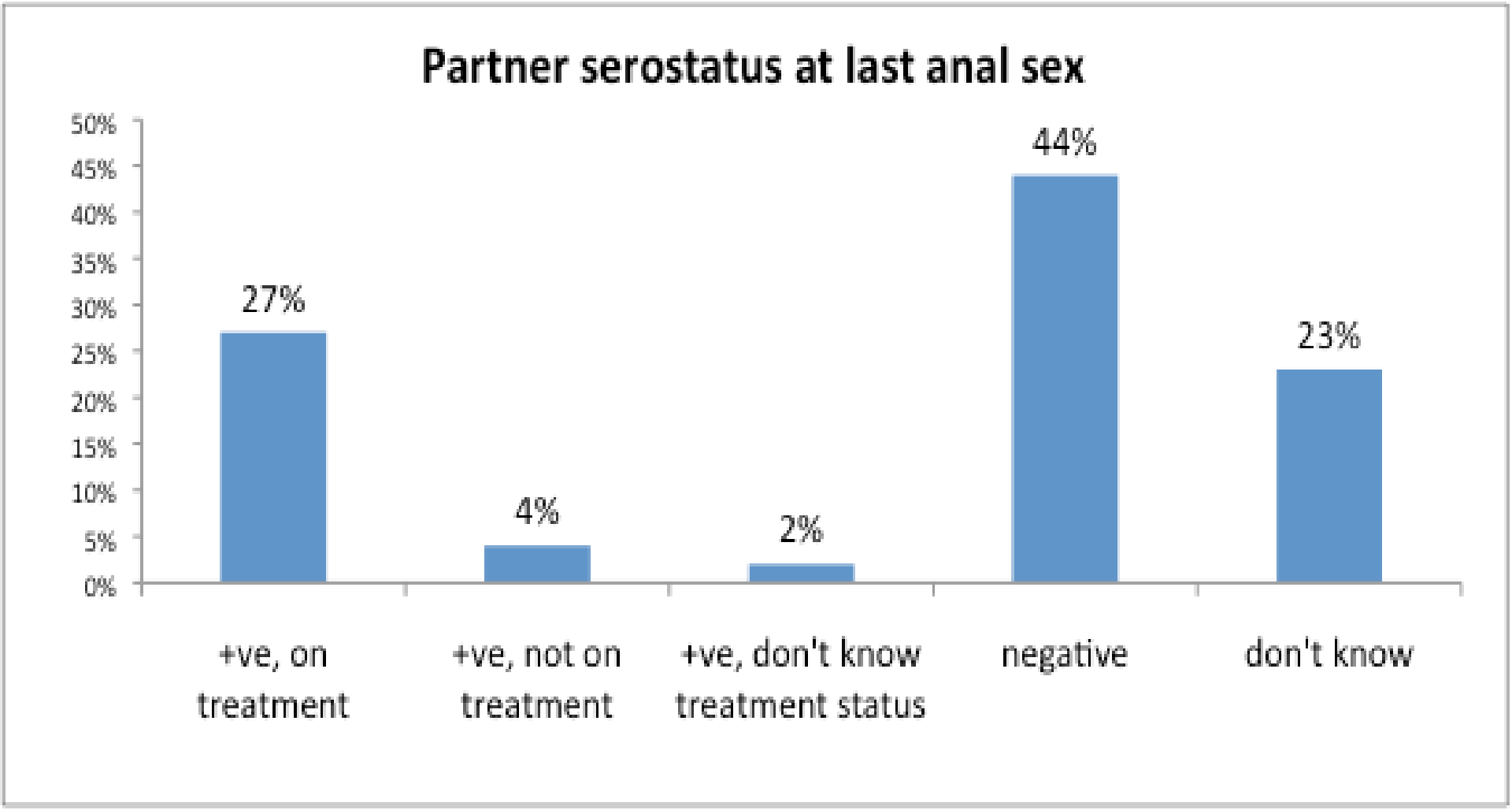
Data based on 494 enrolled, 443 baseline CRFs

		Number (N=439-443)	Percentage (%)
Age	Median	35.5	IQR: 29.4-42.3
Ethnicity	White	349	80%
	Black	14	4%
	S Asian	27	6%
	Other	48	10%
Maximum education	University degree or above	258	59%
	A-levels/equivalent	73	17%
	No qualifications	11	3%
	Other	97	23%
Enrolled as partners		17 (+1 triplet)	

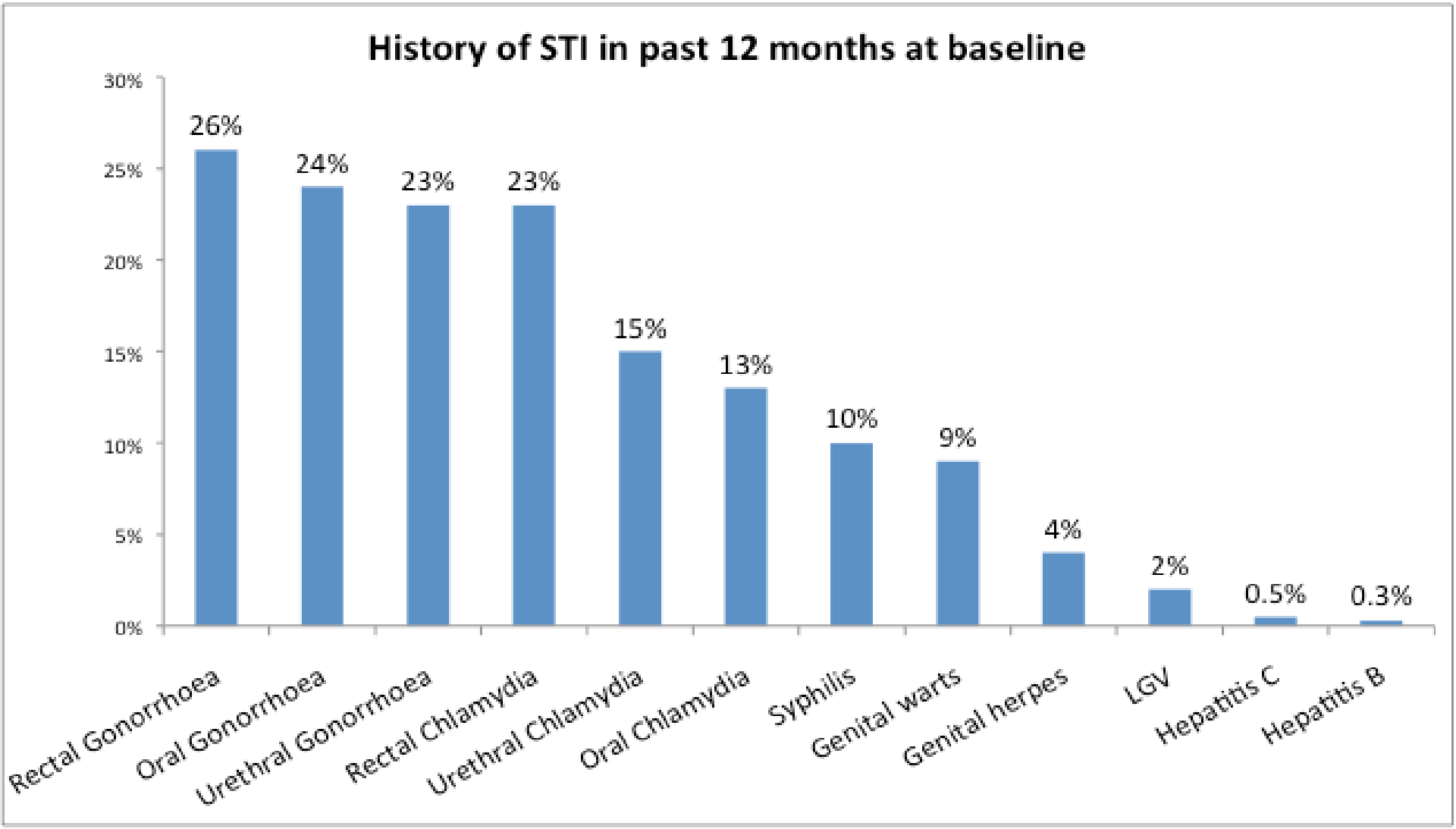
Sexual risk at baseline

	Median	IQR
Sexual partners		
Total	10	4-20
Condomless receptive anal sex	2	1-5
Condomless insertive anal sex	3	1-6
	Number (N=440)	**Percentage (%)**
Partnerships		
In ongoing partnership	206	47%
Living with partner	138	31%

Partner serostatus at last anal sex



Sexually transmitted infections



Comparison data: 1. Public Health England: STI data tables for England 2012; 2. Centers for Disease Control 2010 STDs in Men who have sex with men http://www.cdc.gov/std/stats10/msm.htm

Recreational drug use

- 322/434 (74%) report use of recreational drugs in past 12 months

Drug	Frequency of reports (N=957)	Percentage of participants
Poppers (amyl nitrate)	213	49%
Viagra	182	42%
Mephedrone*	158	36%
GHB (liquid ecstacy)*	136	31%
Cannabis	102	24%
Cocaine (coke)	113	26%
Ecstacy	84	19%
Crystal meth* (methamphetamine)	78	18%

Comparison data: 1. National Gay Men's Sex Survey 2007 2. UK British Crime Survey 2012

Current thinking

- Baseline data and new hepatitis C infections to date suggest the HIV incidence will be higher than national estimate

- If we answer the effectiveness, what next?

- Previously developed a proposal to assess 1% tenofovir vaginal gel compared to no gel, and include a non-inferiority comparison of single versus BAT24 regimens

Sample size considerations

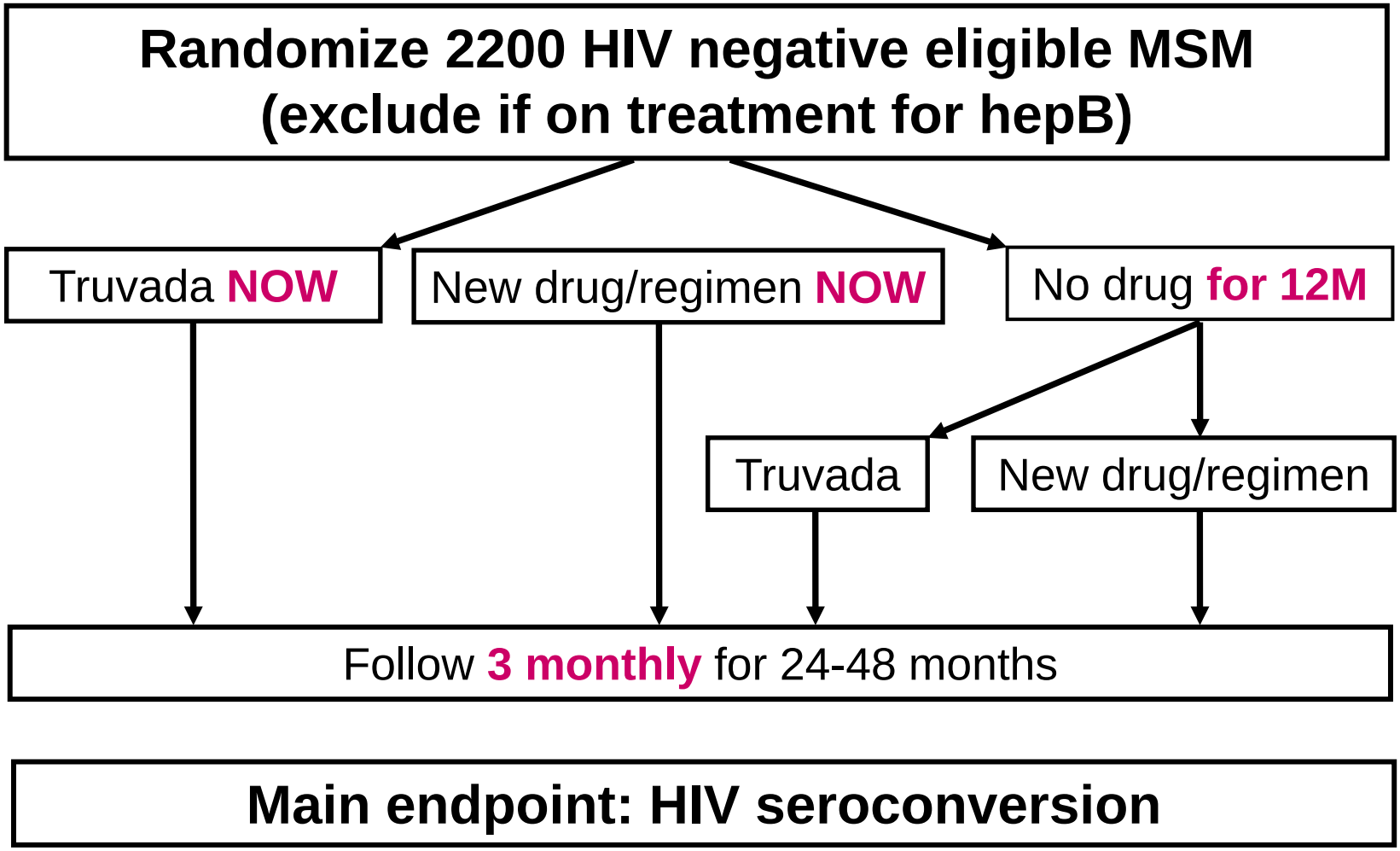
80% power, two-sided alpha 0.05, assuming 15% loss to follow-up

Incidence	Effectiveness	Sample size (total)
2.5	50	4430
	70	1960
	90	1000
5.0	50	2200
	70	980
	90	500
7.5	50	1480
	70	650
	90	330

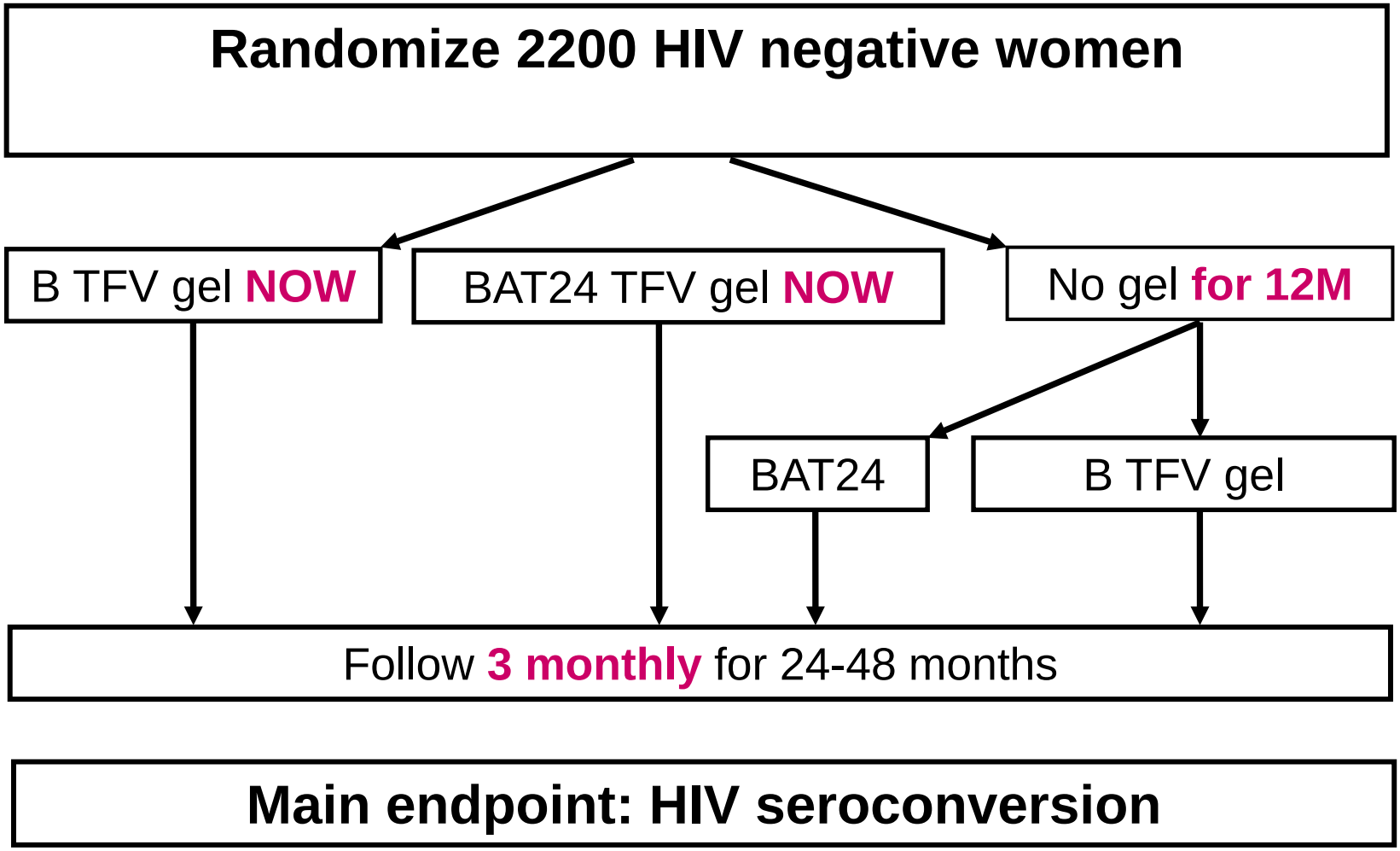
Assumptions

- Incidence 5/100 pyrs; effect size 50%; LTFU 15% pyrs
- 2200 to be enrolled over 24 months; the duration of trial will be 48 months; participants continue in follow-up
- Randomised evidence for the main question is generated during the first 12 months of follow-up

PROUD


Randomize 2200 HIV negative eligible MSM
(exclude if on treatment for hepB)
Truvada NOW
New drug/regimen NOW
No drug for 12M
Truvada
New drug/regimen
Follow 3 monthly for 24-48 months
Main endpoint: HIV seroconversion

Proposal (MDP401)



Statistical approach to comparisons

- The traditional metric for PrEP compared to no PrEP is rate ratio
- Precision is a function of the number of events (e_1, e_2)
- $\mathrm{Var}(\log(RR)) = 1/e_1 + 1/e_2$

Statistical approach to comparisons

- Arguably, key metric for public health when comparing two treatments is the rate difference
- Precision is primarily a function of total follow-up (F_1,F_2)
- $Var(RD) = e_1/(F_1)^2 + e_2/(F_2)^2$

Hypothetical outcomes

- Anticipate ~1900 person-years follow-up per arm

Incidence per 100 person-years*	Expected events per arm	Typical 95% CI for rate ratio	Typical 95% CI for rate difference
2.0	38	0.62,1.61	-0.90,0.90
1.5	28.5	0.57,1.75	-0.77,0.77
1.0	19	0.50,2.00	-0.63,0.63
0.5	9.5	0.35,2.84	-0.44,0.44

* assumed equal in two arms

Advantages of design

- Use data efficiently by including the secondary analysis
- Deferred period provides critical benchmark when there is uncertainty
- Trial can continue if deferred randomisation needs to be terminated early
- Second dosing regimen may be superior

Risks

- The second dosing strategy may be less efficacious/more vulnerable to missed doses
  - Loss of power for the primary analysis

Summary

- Wait-listed design is feasible for PrEP and likely microbicides – although a pilot is essential
- Assesses real world effectiveness and provides critical benchmark where there is uncertainty
- Second randomisation to one of two drugs/regimens uses follow-up data efficiently
- Main risk is the loss of power for the primary analysis if second strategy proven inferior
  - BUT it is critically important to know this!

Adaptive Enrichment Trial Design for Microbicide Gel HIV Prevention Efficacy Trials

Benoît R. Mâsse, PhD

Washington DC, June 23, 2014

WORKSHOP ON ADAPTIVE ENRICHMENT TRIAL DESIGN FOR MICROBICIDES

CONRAD

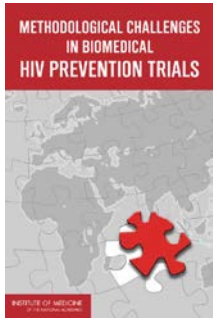
CRCHUM
CENTRE DE RECHERCHE

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant
Pour l'amour des enfants
Université de Montréal

Université de Montréal — Statistical Center for HIV/AIDS Research & Prevention SCHARP — FRED HUTCHINSON CANCER RESEARCH CENTER VACCINE AND INFECTIOUS DISEASE INSTITUTE — MTN microbicide trials network

What are we trying to achieve?

- Or what we should have been trying to achieve?
  - IOM report in 2008

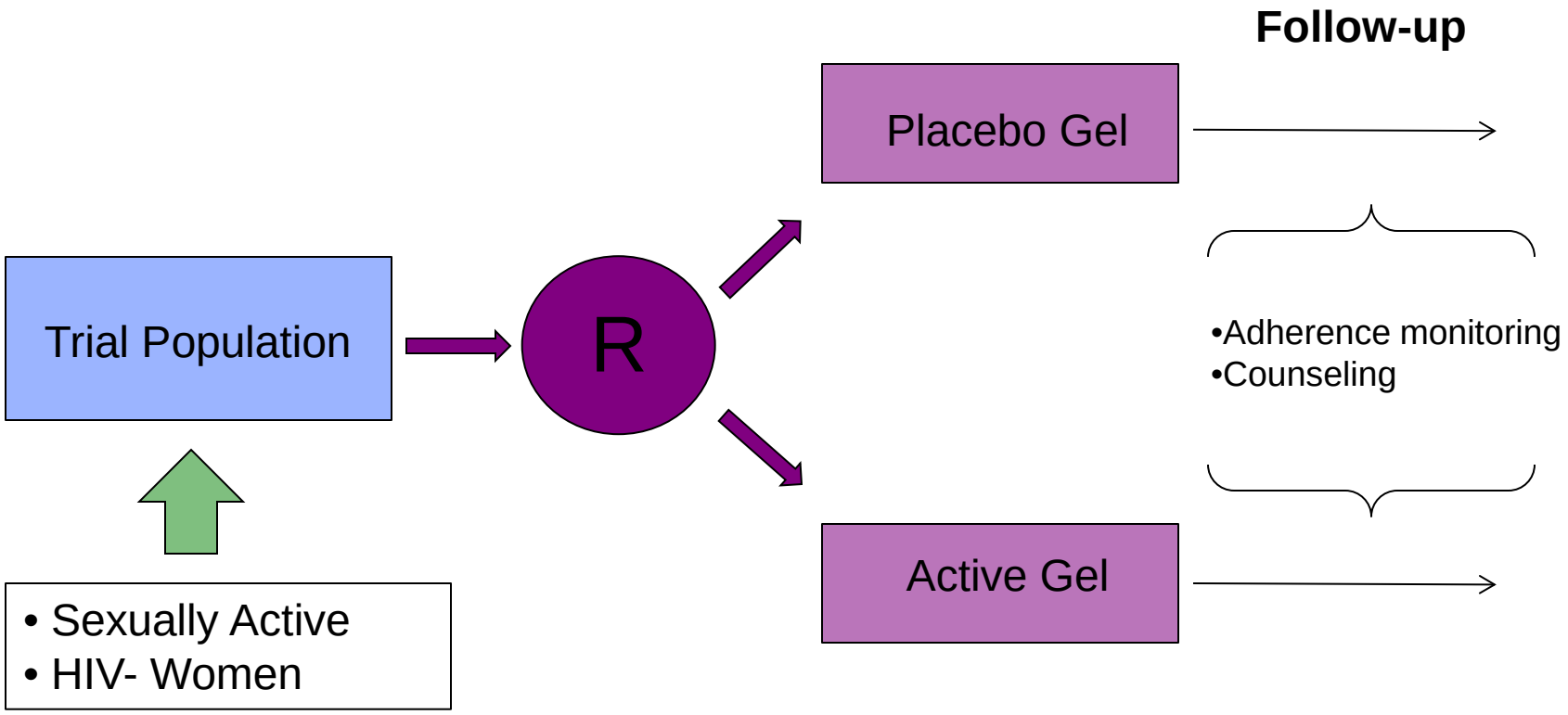


- The goal :
  - To obtain another efficacy estimate of the gel?
  - To add evidence upon the existing strength of evidence? If so, how much is needed?
  - Expand the external validity?
  - Enhance safety profile?
  - Others?

Trial & Design Goals

- First and foremost : *avoid bias*
  - Controlling the type-I error, sample size and power are secondary
- For licensure, need to focus on efficacy and not on effectiveness
- Low adherence leads to efficacy dilution if gel is efficacious
  - Goal: minimize efficacy dilution by maximizing adherence
- Adherence is not the only dilution factor in a trial to prevent HIV acquisition via vaginal intercourse
  - Unprotected anal sex is a potential dilution factor

Trial Design : *The usual*



Main issue: Potential dilution of efficacy by non-adherent women

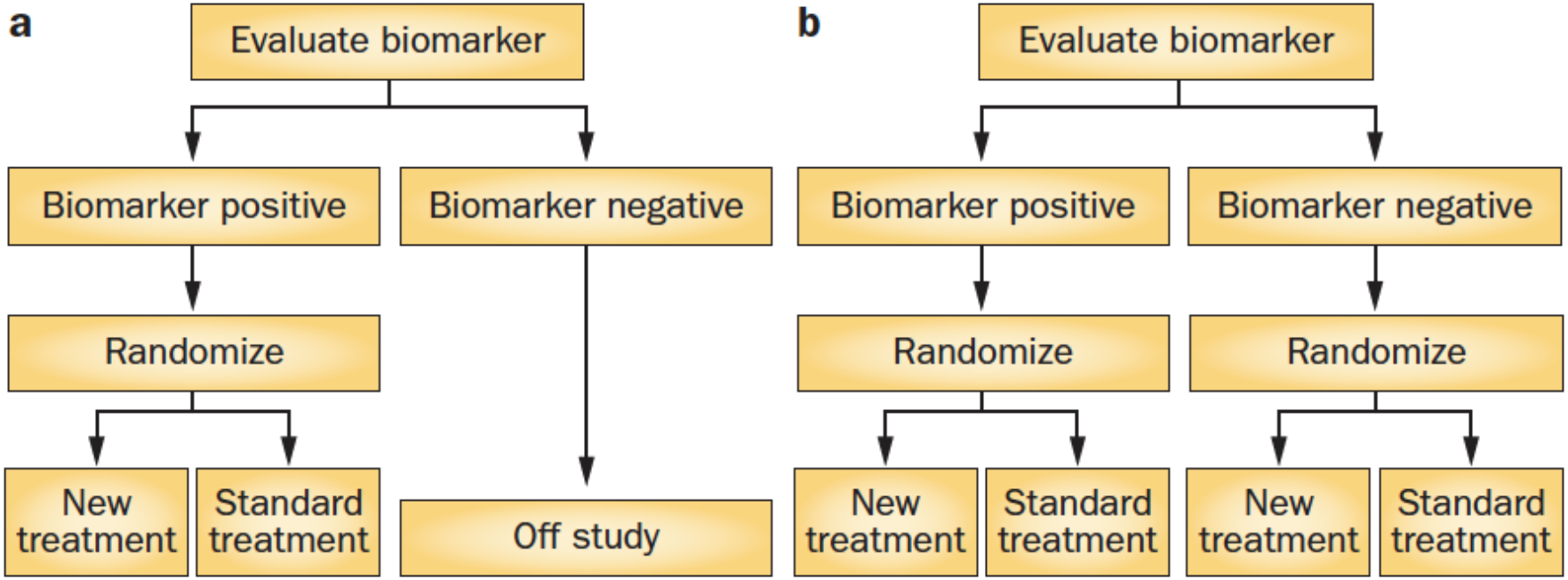
Enrichment Strategies

- Selection of a trial subpopulation of participants in which the efficacy of the gel is most likely to be demonstrated
  - Simple strategy that can lead to gain in efficiency
  - Decrease in external validity

- Non-adaptive: Selection of the trial subpopulation done prior to randomization
  - Selection can be based on participant/patient criteria : clinical and none-clinical
  - Selection can be based on predictive or prognostic biomarkers of treatment response

Enrichment Strategies

- Non-adaptive with a biomarker for adherence

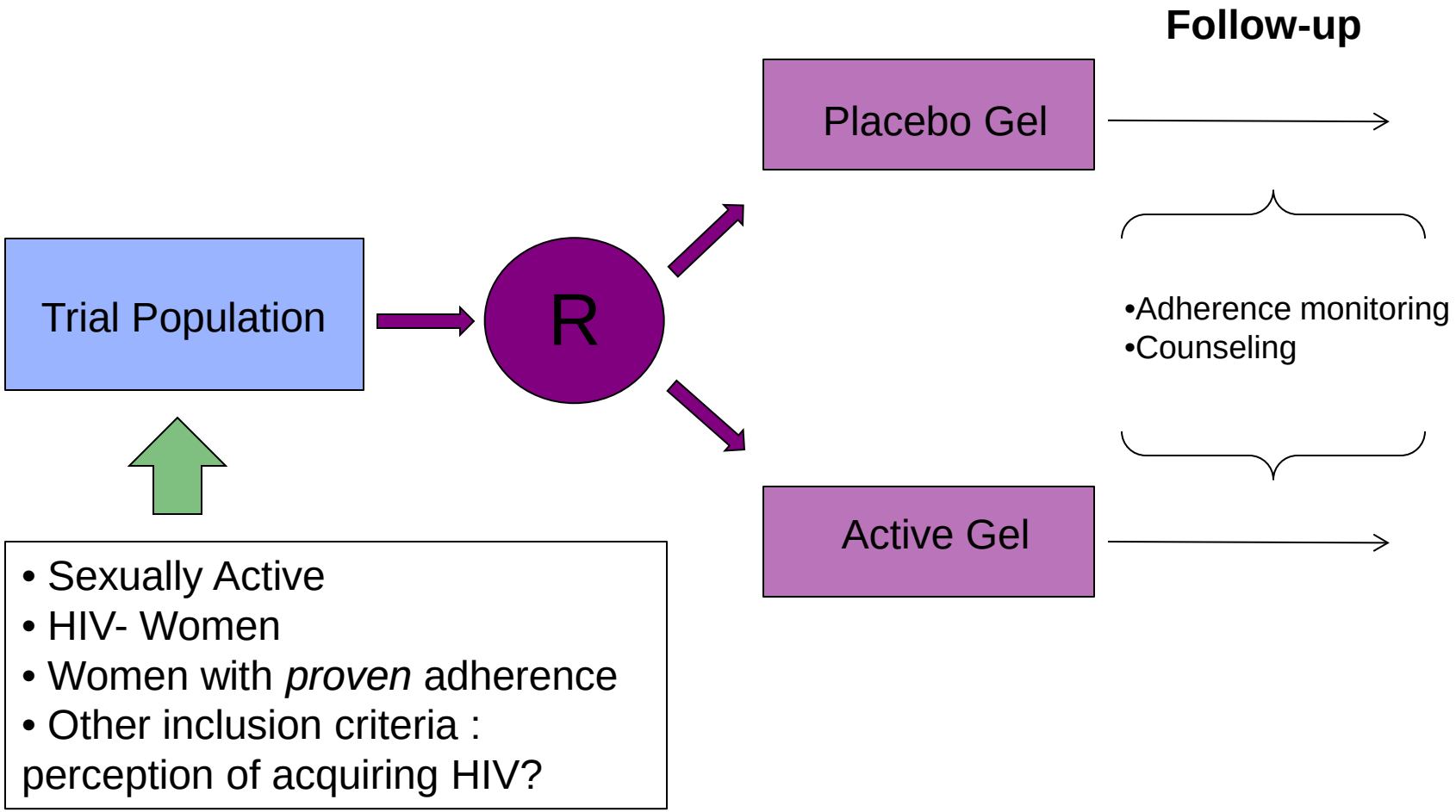


Freidlin, B. & Korn, E. L. *Nat. Rev. Clin. Oncol.* **11**, 81–90 (2014)

Enrichment Strategies

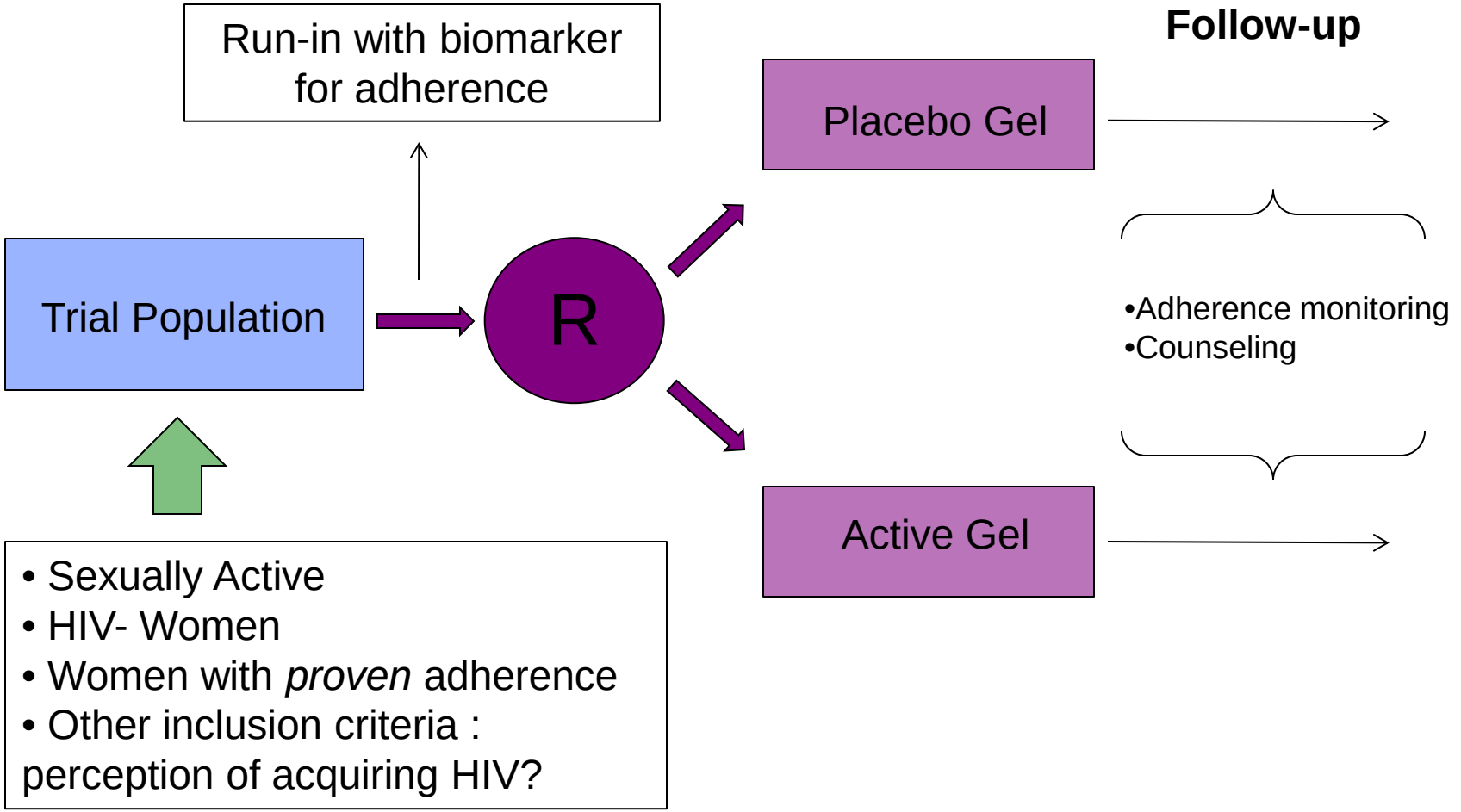
- Adaptive: Selection criteria are identified during the trial and can be used to guide future recruitment into the trial
  - Can be used when the ‘cut-off’ for the biomarker is not well-established
  - May be extremely hard to achieve with a time-to-event primary endpoint with relatively low incidence like HIV infection
- Somewhat related … stopping recruitment at sites with low adherence

Trial Design : *The usual 2.0*

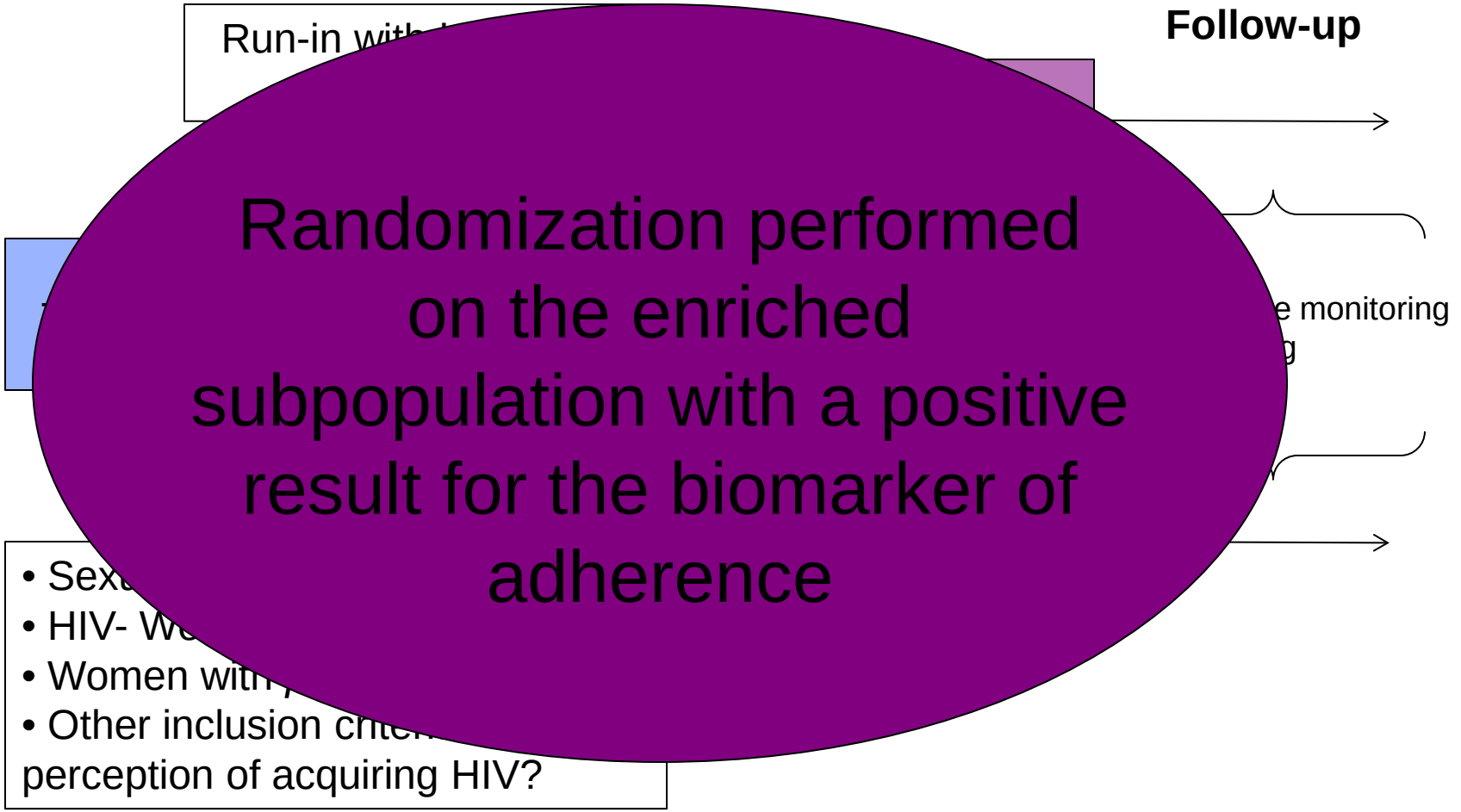


Main issue: Past adherence may not lead to future adherence

Trial Design : *Run-in* + *The usual*



Trial Design : *Run-in* + *The usual*



Run-in and biomarker

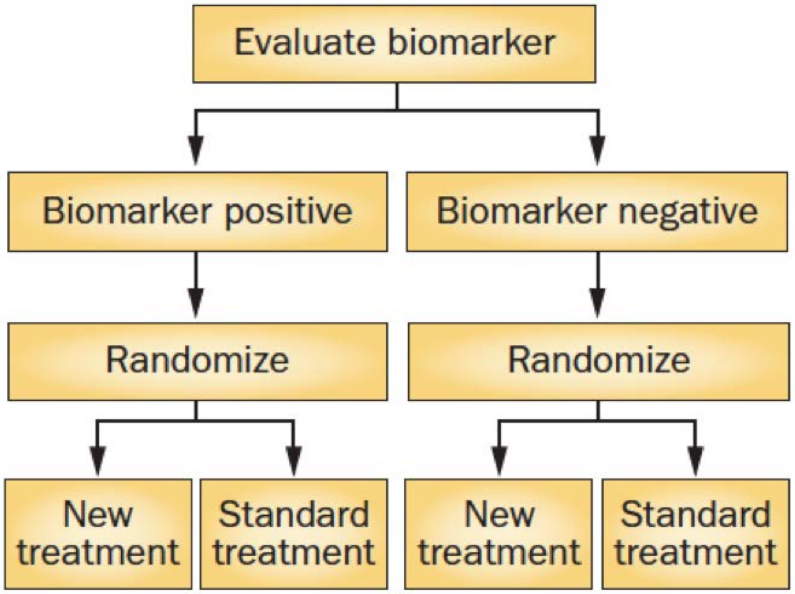
- Run-in: How long and with what?
  - With placebo gel?
  - How long? Length of run-in might be more of an issue for the BAT24 regimen
- Biomarker of adherence:
  - Need one with very good ‘credentials’
  - What should be the cut-off for inclusion or exclusion?
    - Too stringent : need to screen and run-in a lot of participants
    - Too liberal : leaning back to square one

Further notes on the biomarker

- Literature on enhancement strategies using (predictive or prognostic) biomarkers of treatment response describe biomarkers that are not under the control of the participants
  - In our context, a woman can chose to be adherent during the run-in and not after randomization
  - A concern : strong willingness of women to participate in gel trials at many sites … some women might be adherent only for the run-in so to be included in the larger trial

Inclusion of low adherers?

- Might be necessary unless it is well established that low adherers do not benefit and there are no safety issues
- Might need to demonstrate the validity of the biomarker of adherence and its cut-off prior to the trial
- Selecting only the highest of the adherers or excluding the lowest of the low adherers … not the same



Dropping-off women with low adherence

- Design Strategy: After randomization, women found to be non-adherent are dropped from the trial
  - No more study gel is provided to these women
  - FUP of these women continues so to assess the primary HIV endpoint

- Primary Analysis Strategy: excluding the drop-outs
  - No different from excluding ‘low adherers’ in a trial which women are not dropped-off
  - Depending on the % of drop-outs, the potential for bias is quite substantial
    - Positive ITT analysis results will be needed
  - One can increase the sample size for the potential efficacy dilution induced by the drop-outs but bias is the most critical issue

Dropping-off sites with low adherence

- Design Strategy: After randomization, recruitment is stopped at sites where women are non-adherent
  - FUP of enrolled women would continue
  - Site adherence: average adherence up to the stopping point?
  - Cut-off point for stopping recruitment?
  - Need to define those a-priori
- Primary Analysis Strategy: ITT analysis
  - Include all randomized women
  - No major bias concerns
- Obviously, cannot stop recruitment at all the sites

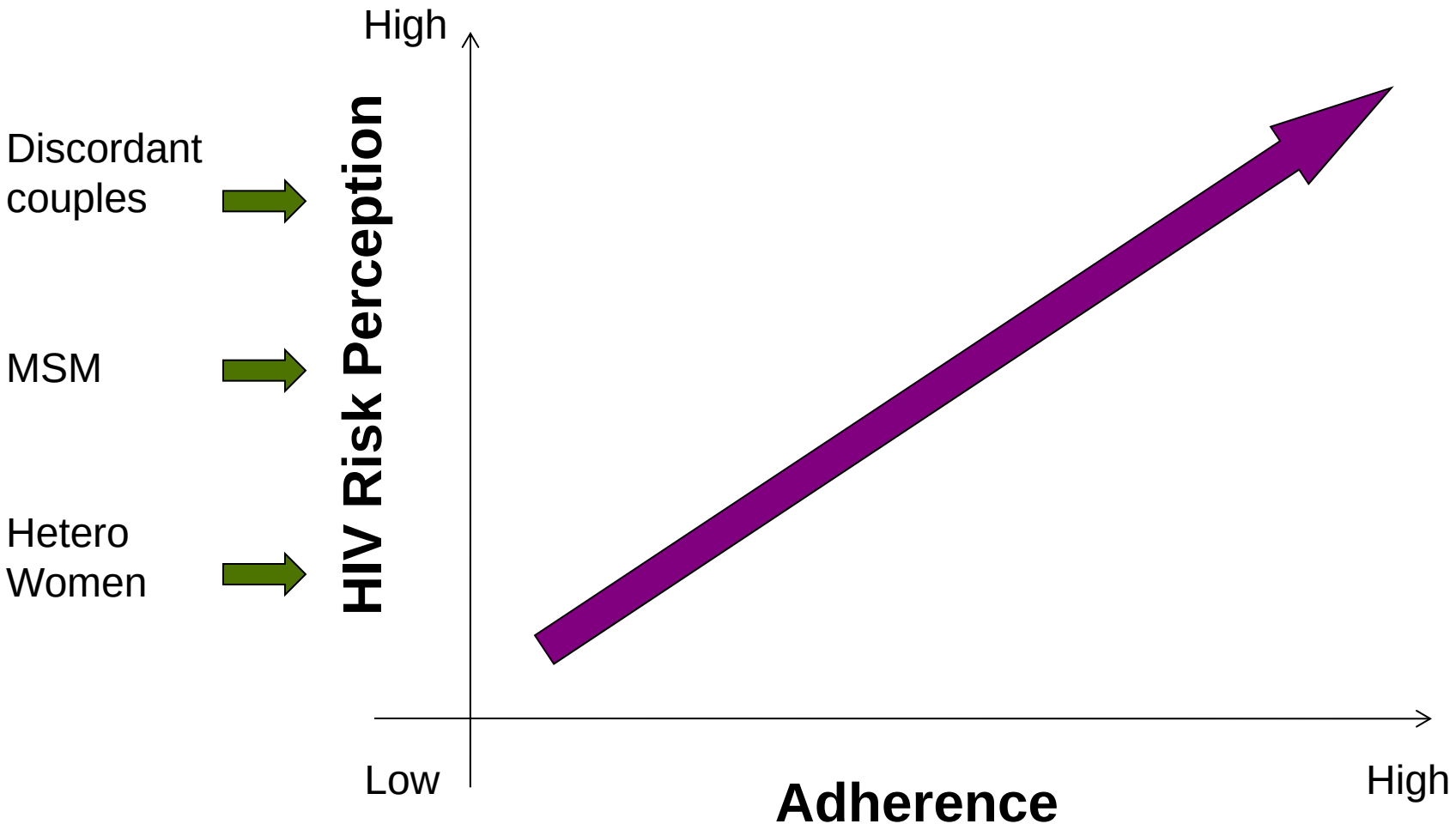
Key points

- Control of bias … first and foremost
  - Gain in efficiency is secondary
- Non-adaptive enhancement strategy:
  - Critical to establish the credentials of the biomarker of adherence (and its cut-off)
  - Might need to include low adherers in the trial
- Dropping-out low adherent women during trial?
  - Not much different from excluding low adherers in past trials
  - Strong potential for bias if excluded from the analysis
- Stopping recruitment at sites with low adherers
  - Less concerns for bias
  - Might be hard to define the ‘stopping’ point

Perception of risk

- From oral PrEP, it appears that adherence/product use is associated with the type of trial population
  - Discordant couples, MSM, & hetero women
- Reasonable to assume that ‘Perception of risk of acquiring HIV’ is associated with adherence

An hypothesis …

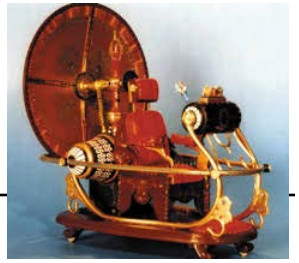


Questions?

- Are they '*reliable*' tools for assessing a person perception of acquiring HIV in the near future
  - Perceived risk of HIV infection scale (Napper et al, 2012)
    - Scale based on 8 likert-questions
  - Literature rather thin in the context of prevention …
- Can HIV risk perception be a good predictor of adherence in HIV prevention trials?
  - Counter-intuitively such a predictor may have a negative association with HIV acquisition:

    Women feeling more at risk of acquiring HIV may do more in terms of protecting themselves … leading to a lower incidence in this group (eg 2% HIV incidence observed in Partners PrEP)

If I could go back in time …



- Investigate measures of HIV risk perception and its association with adherence
  - Early in the microbicide preparedness studies
- Add in/ex-clusion criteria based on HIV risk perception so to optimize adherence in efficacy trials

RTI INTERNATIONAL | turning knowledge into practice

WOMEN'S GLOBAL HEALTH IMPERATIVE

Factors that correlate with adherence in HIV prevention studies

Ariane van der Straten, PhD, MPH

WORKSHOP ON ADAPTIVE ENRICHMENT TRIAL DESIGN FOR MICROBICIDES

Washington DC; 23 June 2014

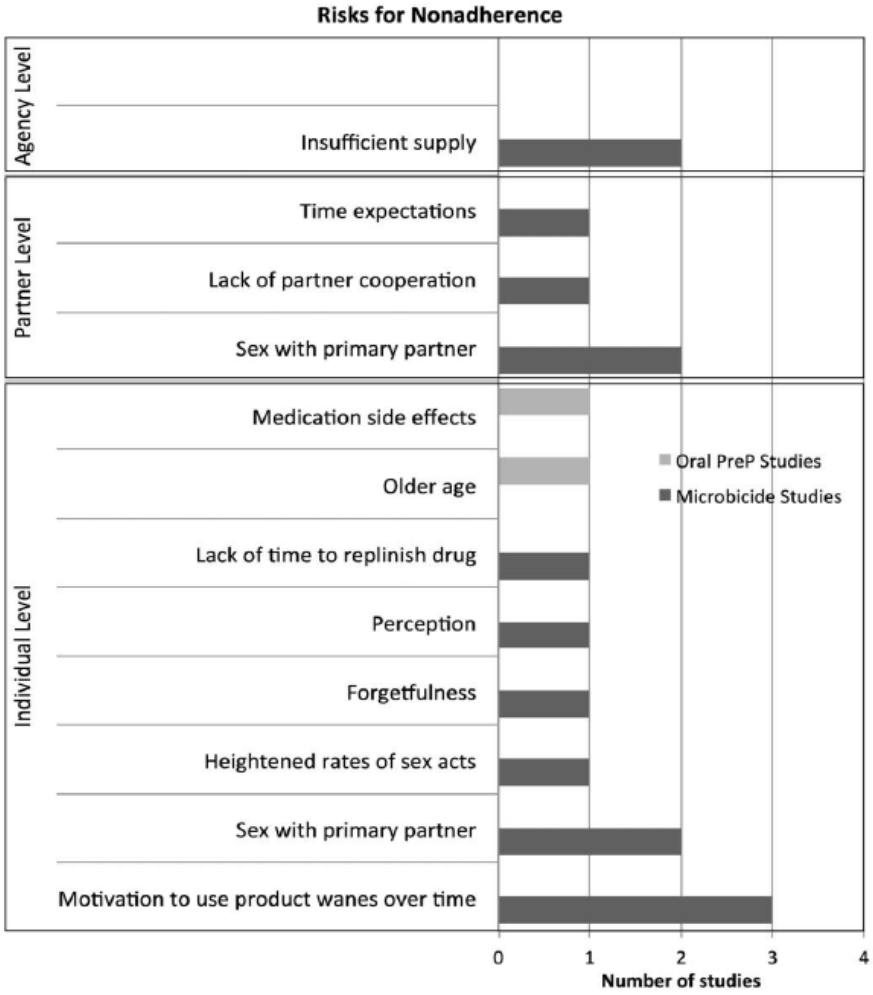
UCSF University of California San Francisco

MTN microbicide trials network

Presentation Outline

- Reviews of PrEP trials and Rx studies
- Correlates of adherence in selected PrEP trials
  - iPrEx
  - Bangkok Tenofovir Study
  - Partners PrEP
  - FEM-PrEP
  - MTN-001
  - MTN-003, the VOICE study
- Adherence fatigue
- Fixed vs modifiable factors and summary remarks

State of the Science of Adherence (2012)



- 19 trials (published 1987-2012)
- Microbicides: 7 products
- Oral PrEP: TDF and Truvada
- Common risks for *reported* microbicide non-adherence:
  - **decreased motivation over time**
  - Sexual activity with I^{ary} partner
  - insufficient product supply
- Common risks for oral PrEP non-adherence (preliminary data)
  - Older age
  - medication side effects

Muchomba et al, JAIDS, 2012

Lessons learned from PrEP trials & Rx studies (2013)

Higher efficacy with demonstrated adherence

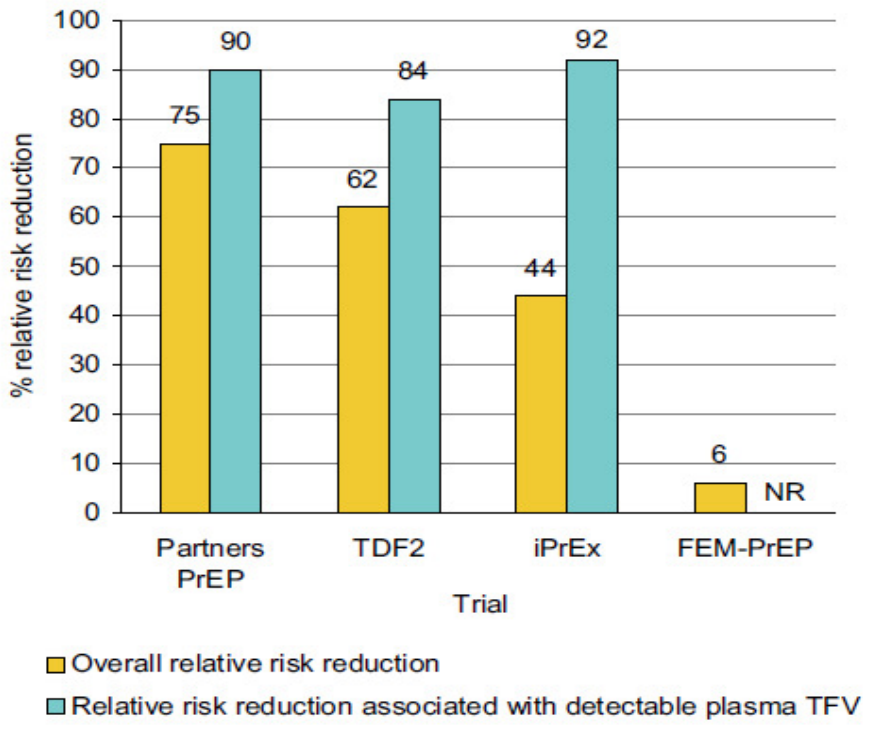


Figure 1. Relative risk reduction in acquiring HIV infection (compared to placebo) in PrEP trials

Note: Overall and by adherence measured as detectable plasma TFV
NR, not reported; TFV, tenofovir

Correlates of adherence

- Partners PrEP unique features:
  - **Partners** aware/engaged & enrolled
  - Long term relationships
  - PrEP preserves the relationship
- **Perception of risk**:
  - Known personal risk: HIV+ partner (PP)
  - 70% perceive low risk in next 4 wks (FP)
  - ↗ use with risk behavior: uRAI (iPrEX)

Correlates of poor adherence

- **Younger ager** (multiple trials)
- Heavy alcohol (multiple trials)
- **Sex** with outside partners (PP)
- Being at a **non US site** (iPrEX)

Koenig et al, Am J Prev Med, 2013

Lessons from Rx studies: ART non-adherence

- Clinical factors e.g. number and types of **adverse events**
- Comorbidities e.g **substance use**, depression
- Rx competency e.g. **optimism**, mis/**understand Rx benefit**
- Regimen dosing e.g. **burden**, **complexity**

- Demographic factors: women, younger, ethnic minorities have poorer adherence & lower persistence → **markers of underlying sociocultural inequalities, Rx experience or other underlying factors**

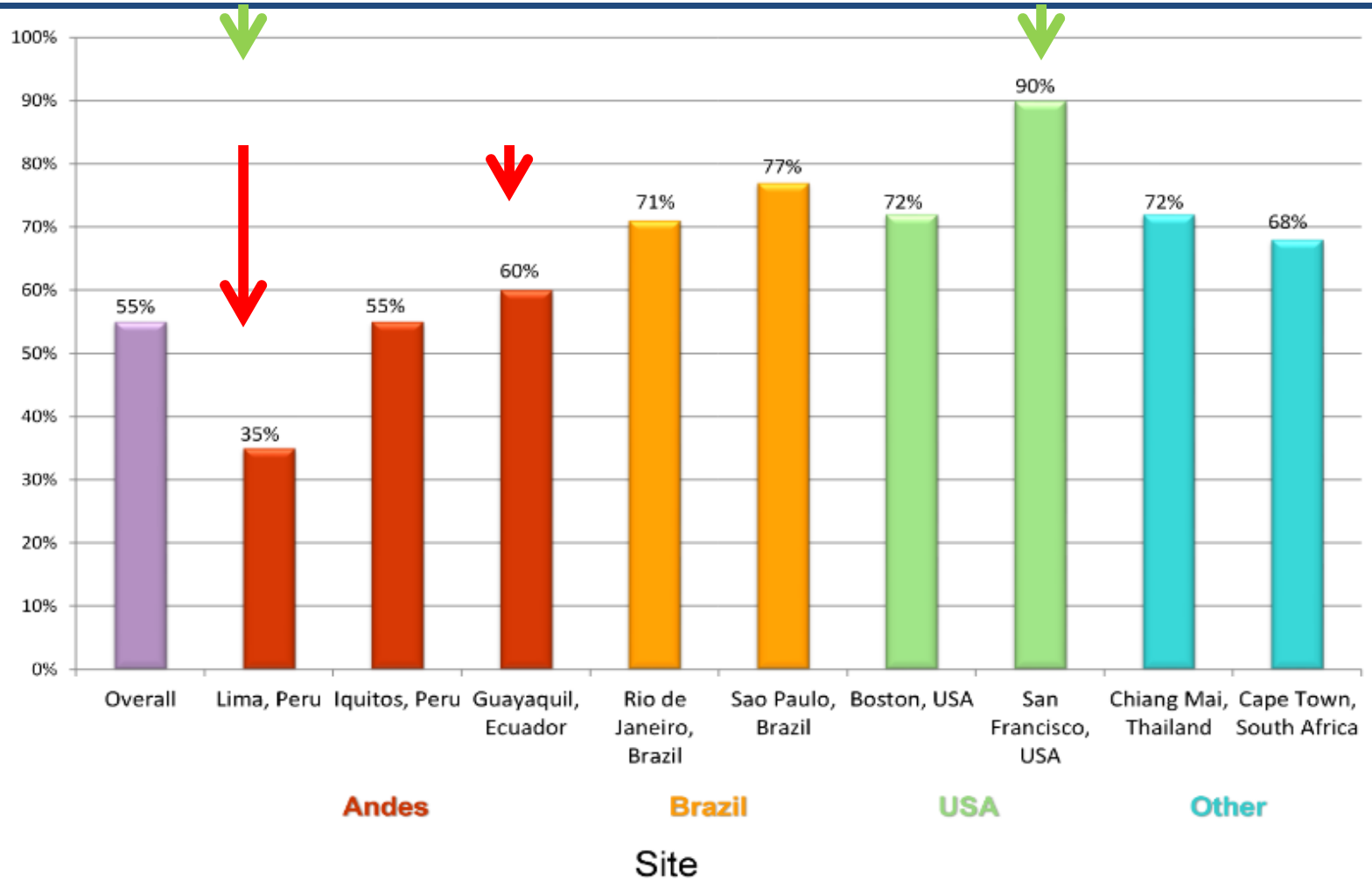
Koenig et al, Am J Prev Med, 2013

Adherence to PrEP in 7 blinded RCTs (2014)

- Demographic: **older age**, ♀, marriage, ↗ SES & education
- Behavioral: no alcohol abuse, **sex**: activity & type
- Psychosocial: HIV risk & risk perception; beliefs in product efficacy, relationship: context and dynamics
- RCT setting:
  - **Clinic**: selective non-engagement with products despite engagement with study procedures (e.g. retention, testing)
  - **Socio cultural disconnect**: community and biomedical research
- Regional differences & preferences for drug delivery form?
- **Research engagement beliefs >>> individual health promotion beliefs**

Amico & Stirratt CID 2014

iPrEx: Week 8 Plasma Drug Detection, by Site



Important variations **across** regions but also within regions (across sites)

iPrEx: Correlates of Drug Detection XS and longitudinal

- **Longitudinal analysis:** Distinct patterns of study product use identified
  - ~ 1/3 had no evidence of starting study product (or early discontinuation)
  - ~ 1/3 consistently used study product

- **Factors associated with drug detection**
  - **US sites**
  - **Older age** (8 weeks: >30 and longitudinal analyses : >20)
  - Perception of PrEP efficacy "**don't know**" (longitudinal)

  - Non-condom RAI (longitudinal)
  - >1 – 5 partners ((longitudinal)

"Research" literacy?

Higher risk sexual practices

- Perceived risk: ↗perceived likelihood of HIV infection in lifetime: trend but not significant

- **Factors not associated with drug detection @ 8 weeks**
  - Education, substance use, being transgender, living situation, concern about having a job or place to live

  - **Side effects**: Reporting GI symptoms (nausea, vomiting, diarrhea, flatulence, or abdominal pain) or headache at week 4 or 8 was *not associated* (@week 8 or week 24)

Bangkok Tenofovir Study: Daily Tenofovir in Injecting Drug Users

- Adherence
  - Drug diaries: mean 84% of days (median 94%)
  - Plasma drug levels: 66% of subset (N=151)
  - Plasma drug levels detected in 39% of HIV(+) participants (N=13) and 67% of HIV(-) participants (N=138)

- Correlates of **non-adherence** (DOT and drug diaries)
  - **Younger age**: <40 vs. ≥40
  - **Male gender**, controlling for age

Choopanya et al, Lancet 2013

Partners PrEP: Daily Tenofovir or Truvada in African Women and Men - Adherence Substudy

- Adherence: (UPC and MEMS)
  - UPC median 99%, MEMS median 97%
  - <80% adherence for ≥ 1 quarter: 7% (UPC) & 26% (MEMS)

- Factors associated with lower (<80%) adherence
  - Abstinence (**no sex**)
  - **Sex** with both study partner & other partner within last month
  - **Younger age** (continuous, by decade)
  - Not being in a polygamous marriage
  - **UPC only**: heavy alcohol use
  - **MEMS only**: **longer time taking PrEP** (>24 mo vs. 1-6 mo)

- Factors associated with higher (≥80%) adherence
  - **MEMS only**: **Sex** only with a partner other than study partner

- Barriers identified during adherence intervention:
  - travel and forgetting

Haberer et al, PLOS Medicine 2013; Psaros JIADS 2014

Partners PrEP: Correlates of plasma PK

- Adherence case-control study (Plasma PK): Non-seroconverters were adherent at 71% of visits, (& had consistent patterns of PrEP concentrations during follow-up) vs 21% at seroconversion visit for cases.
- Factors associated with non-adherence (TFV ≤40ng/ml):
  - **Younger age**
  - **Longer time** on study
  - Reporting **no sex** with their HIV-infected partner

Donnell et al, JAIDS 2014

Fem-PrEP: Daily Truvada in African Women

- Factors associated with good adherence: (plasma TFV >10 ng/mL & intracellular TFV-DP concentration in ULPCs > 10^5 fmol/mL)
  - -Having **some perceived HIV risk** (time dependent analysis)
  - -From the Bloemfontein **site** (vs. Pretoria and Bondo, Kenya),
  - -Liking the pill color

- Oral contraceptive pills at enrollment associated with < good adherence

Corneli et al., IAS 2013; Corneli et al., JAIDS, in press

Fem-PrEP: ACASI and SSIs follow-up study

Sampling of good to low adherers (6pt scale based on TFV levels):

- **ACASI** (N=224): factors influencing non-adherence, selected by ≥ 25% women

Research literacy?	Pill investigational (47%)	Perceived on placebo (27%)
Side effects	**Feared** side effects (26%)	Had side effects (14%)
Low motivation?	Forgot (29%)	Feeling at low risk of HIV (28%)
Product/regimen	Daily pill burdensome (32%)	Pill too big (27%)

- **Main underlying reasons for non-adherence**: concerns about investigational drug, apprehension surrounding side-effects, belief that pill may cause harm/sickness.
  These concerns directly affected women, and indirectly by discouragement from others participants, partners and community members.

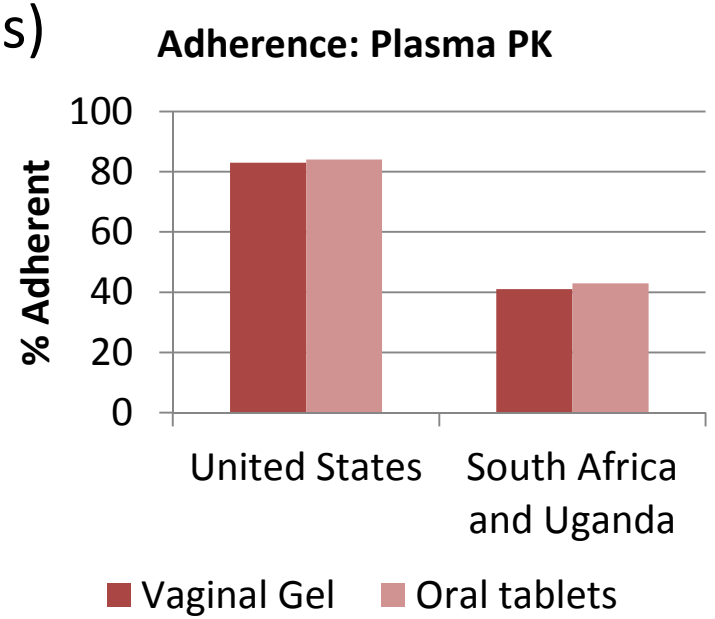
- **Motivating factors for taking pills***: Partner awareness/support, support for the research/altruism, perceived HIV risk, established routine/tools, motivation: post-enrollment or from counseling.

(*) among good/moderate adherers

Corneli, CROI 2014 & IAPAC 2014

MTN 001: Daily Oral TDF & Vaginal TFV Gel in US and African Women

- Adherence (6 weeks period)
  - Self-report: 99% of days in past week
  - Plasma PK: ~80% in U.S., ~40% in Africa
  - Adherence similar for gel vs tablet within same locations (despite different stated preferences)
- Correlates of non-adherence:
  - **US**: Unmarried, male condom use, current injectable contraception
  - **Africa**: **younger age** (18-25)



Minnis, et al., AIBE 2013, & under review

VOICE: Daily Oral & Vaginal Tenofovir in Sub-saharan African Women

- Baseline characteristics associated with TFV <u>detection</u> (adjusted for sites)
  - **Older age** (> 25 years)
  - **Married**
  - Independent income
  - Multiparity

- All these factors are also associated with **<u>lower risk</u>** of HIV

VOICE
VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

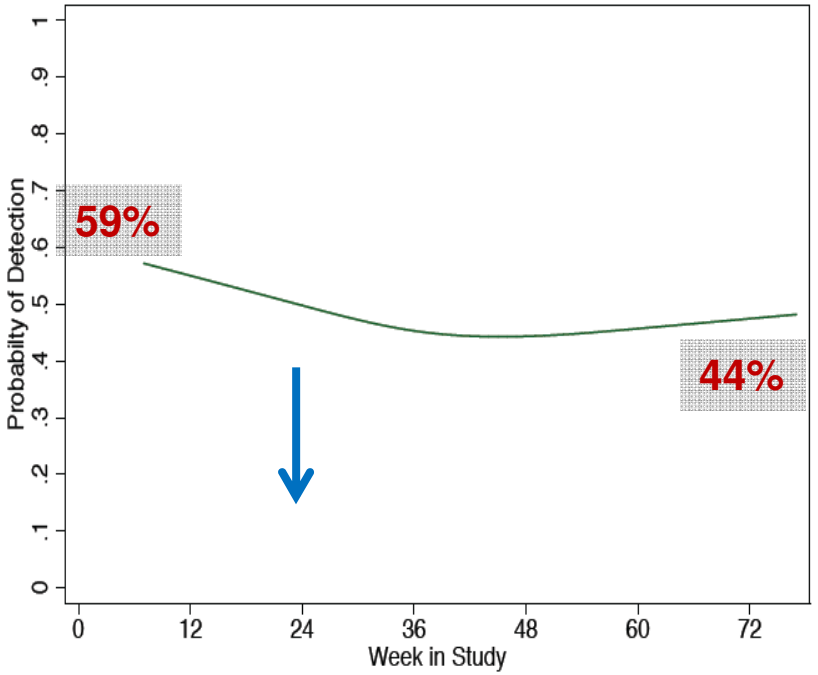
MTN
microbicide trials network

VOICE-D: Adherence Challenge Themes

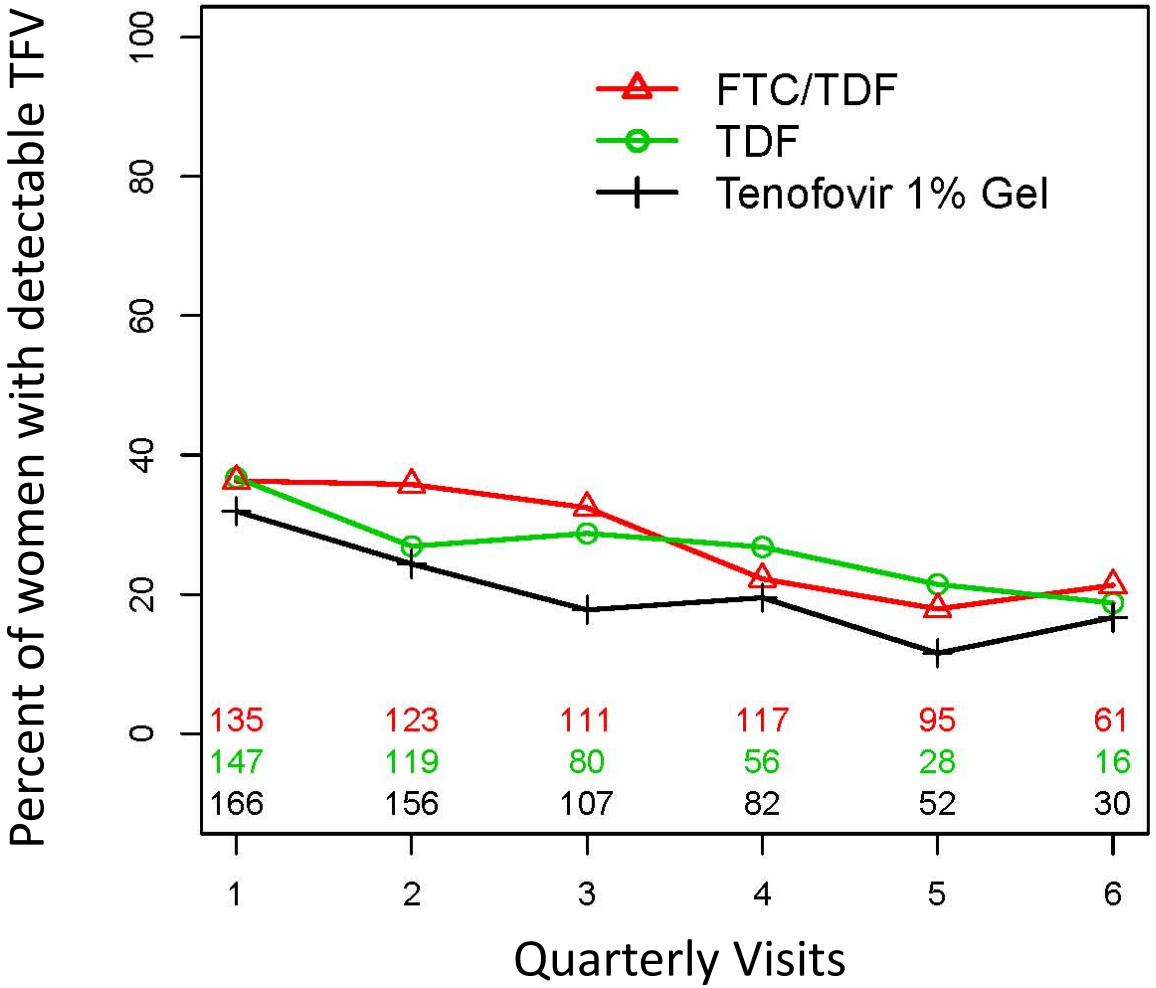
Themes Ranked as Top Adherence Challenge	N=68
I experienced or was worried about **side effects**	10
joined the study for **health** services at the clinic	9
Change in routine/schedule, including travel*	7
My **partner** disliked the products/ VOICE	5
Forgot*	5
The products cannot prevent HIV	3
I wasn't at risk of getting HIV	3
I didn't have enough support from others	3
I was too busy to take products every day	3
My family or friends disliked the products/ VOICE	2
Others would think I have HIV if I took the products	2
It was boring to take the products daily	2
I had to hide when taking my products	2
other participants were not taking their products	2
Pregnancy*	2
Someone told me to not take the products	1
The products may be harmful	1
I was not interested in using the products	1
I didn't need to take the products	1
Challenge to swallow big tablets/insert a gel in my vagina	1
Fell sick*	1
Alcohol related*	1

Adherence fatigue:

- iPrex
  - Probability of drug detection: decreased from 59% at Week 8 to 44% at Week 72 (end of study)
  - Median time to discontinuation: 24 weeks.
  - Other PrEP trials: longer time in study correlates with lower use



VOICE: Plasma Tenofovir Detection in Random Cohort Sample



Level of TFV detection

≥ 0.3 ng / ml

Addressing "fatigue": using bias (decision-making errors) as entry points for intervention

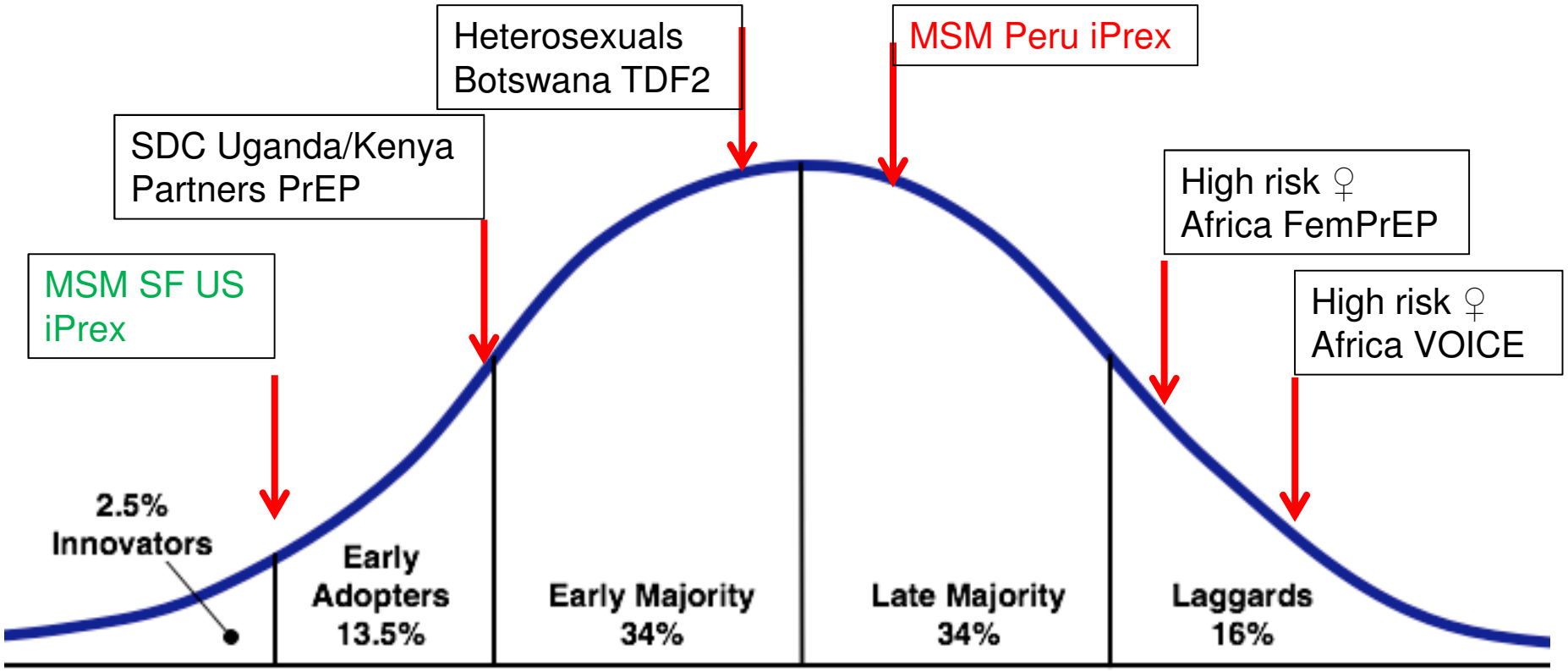
- Intervention using behavioral economics (BE) principles for patients with "treatment fatigue": *Reward Adherence Program, Uganda*
- Baseline BE questions associated with poor adherence:
  - **Myopia**: giving in to short-term temptation rather than long-term benefit- Cost is immediate and benefit happens later.
  - **Overconfidence**: thinking you do better than average person.
- ***RAP***: lottery system & small prices incentives to target myopia & add "fun" element to adherence

- *?BE questions: perhaps not directly associated w/ lower HIV risk?*
- *? Can BE questions be used as screening tool to enrich for more adherent participants in prevention trials ?*
- *Will PrEP participants change adherence with a BE intervention?*

Linnemayr, IAPAC 2014

Diffusion of Innovations

- ARV-based prevention is an innovation, including in RCT settings
- Key factors for adoption: ideation and social network
- Are different trial populations at different adoption stages?
- Are there key characteristics to identify innovators/early adopters?



Rogers, E.M 1995 Diffusion of Innovation, 1995 4th ed ; Kincaid, D.L.,2000; SSM

Fixed factors

- **DEM**: **age**, **marriage**, parity, education, SES, **region/site**
  → Markers: identify underlying factors
  → Tailor study product messaging
  → enrich w/ *"good"* participants
- **Behavioral & cognitive bias**:
  → further characterize for PrEP RCT
  → leverage in adherence intervention
- **Partners/significant others**
  → engage or enroll them in RCTs
  → target messages & intervention
- **RCT/investigational products**
  → Educate volunteers & communities
  → Change clinic site culture: ppt focus
  → Emulate altruism & **research engagement** prior and during trial

Modifiable factors

- **Sexual risk, risk perception and beliefs**
  → increase saliency of HIV risk
- **Perceived product efficacy /SE concerns**
  → Educate volunteers & communities
  → Manage product expectations
- **Perceptions about research**
  → Emulate activism, **research literacy**
  → Manage rumors, negative stories
  → Focus on **Research engagement** beliefs
- **Motivations: internal & external**
  → simplify study procedures
  → Test BE adherence interventions
  → Minimize negative social influences
- **Participant burden and fatigue**
  → simplify study procedures & drug regimen
  → Keep time on study shorter
  → Change site culture/add fun element
  increase product appeal

What to focus on to enrich a trial in adherent participants?

- **Demographic factors and geographic location**:
  - Simple to select; likely markers of underlying developmental & sociocultural factors TBD
  - Challenge: selecting for low incidence population if DEM factors negatively associated w/ HIV
- **Motivations: target internal and external motivators**
  - **Risk behaviors & perceptions**: need to standardize measurement; vary over time
  - Easier to focus on fixed risk: individual level (e.g. serodiscordant partner) or group risk: challenge: issue of stigma, sexual risk conflates with relationship and partners' acceptance
  - Leverage positive social influences to maintain motivation (peer motivators)
- **Visit retention and early drug detection (associated with persistence)**
  - Consider incentives to maintain motivation to honor study visits, and to use product
  - High intensity of intervention at start of study to optimize proportion who initiate/adopt
  - Address proactively negative social influences that discourage use
- **Sexual partners and partnerships :**
  - Recruit via male partners; engage and educate them early-on, or enroll couples?
- **Find new factors associated with ↗adherence and not lower HIV incidence :**
  - Identify characteristics linked with "BE bias": to screen out ppts or to leverage in intervention
  - Characterize and identify participants who may be the innovators and /or early adopters

THANK YOU!
& Acknowledgements

- Ellen Luecke (RTI/WGHI)
- MTN-001 (Ali Minnis, Craig Hendrix)
- VOICE, VOICE-C and D teams
- Microbicides Trials Network (MTN)
- A. Liu (SFDPH/UCSF)
- A. Corneli (Fem PrEP; FHI360)
- S. Linnemayr (Rand)
- MTN is funded by NIAID (5UM1AI068633), NICHD and NIMH, all of the U.S. National Institutes of Health

CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

UNAIDS

CAPRISA IS A UNAIDS COLLABORATING CENTRE FOR HIV RESEARCH AND POLICY

Enriching for adherence

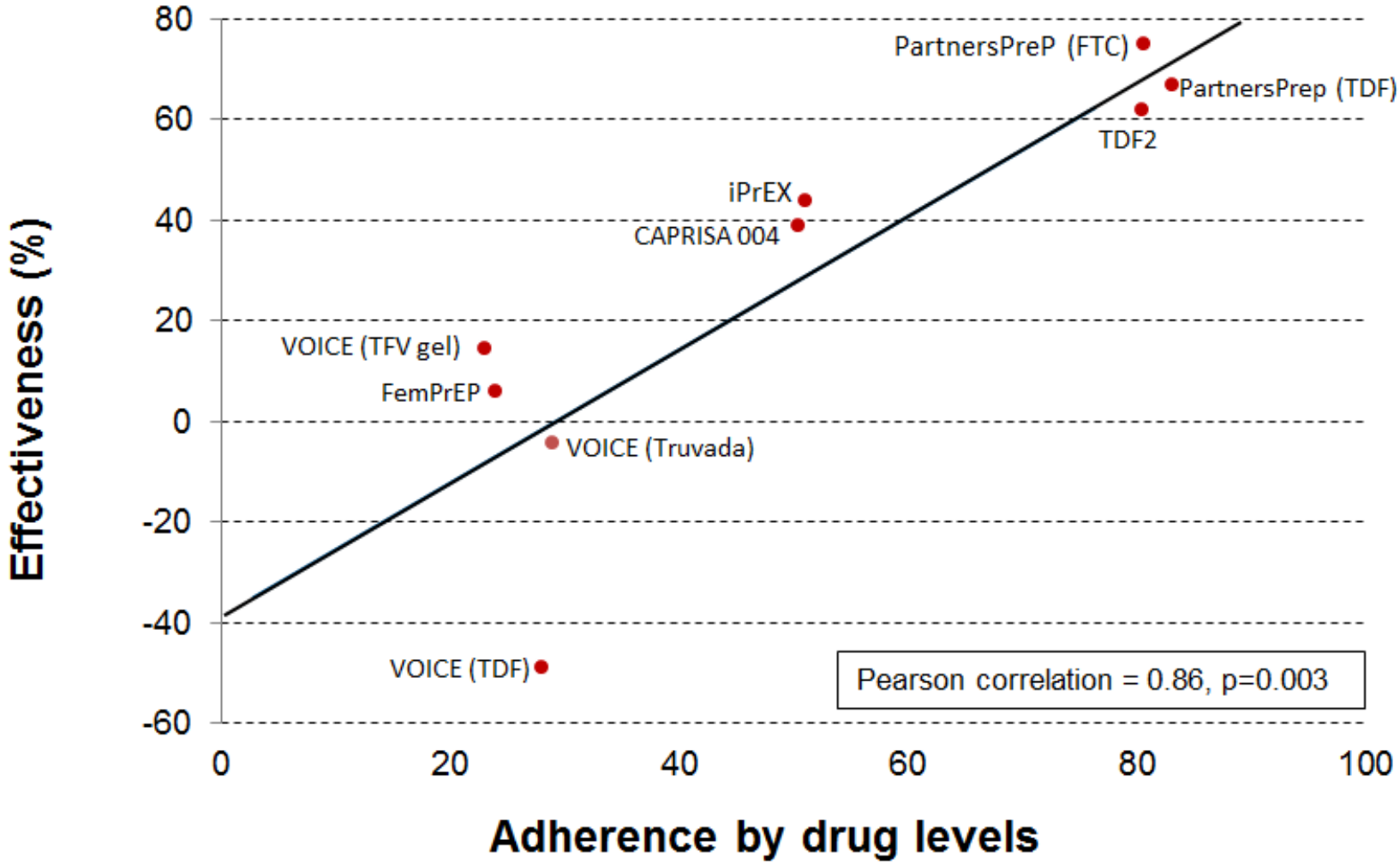
Lessons from CAPRISA 004

Anneke Grobler

Head of statistics: CAPRISA

CAPRISA

Effectiveness by adherence



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Tenofovir gel effectiveness by levels of adherence

Adherence	N	Incidence Tenofovir	Incidence Placebo	IRR
Returned used applicator				
High (>9)	158 (18%)	8.1	17.9	0.46 (0.2; 1.0)
Moderate (>5-9)	335 (38%)	6.4	9.4	0.68 (0.3; 1.3)
Low (<5)	396 (44%)	3.7	5.6	0.67 (0.3; 1.5)
Self-report last sex act				
High (100%)	250 (28%)	3.7	10.3	0.36 (0.1; 0.9)
Moderate (80 < 100%)	374 (42%)	4.5	6.1	0.73 (0.3; 1.5)
Low (<80%)	265 (30%)	9.6	13.0	0.74 (0.4; 1.4)
Applicator based (formula)				
High (>80%)	337 (38%)	4.2	9.3	0.45 (0.2; 1.0)
Moderate (50-80%)	180 (20%)	6.3	10.2	0.61 (0.2; 1.6)
Low (<50%)	367 (41%)	6.2	8.6	0.72 (0.4; 1.4)

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3 strategies

- **Run-in period**
- **Drop sites that do not adhere**
- **Drop individuals that do not adhere**

- **Disclaimers**
  - No p-values
  - Adherence not by drug levels

Coitally dependent vs daily dosing

- **Largest challenge**
- **Drug levels: No expected value**
- **No sex + no gel = 100% adherent**
- **Formula: Gels used / sex**
- **Negates ‘objective’ assessment, since sex cannot be counted objectively**

1

Run-in period

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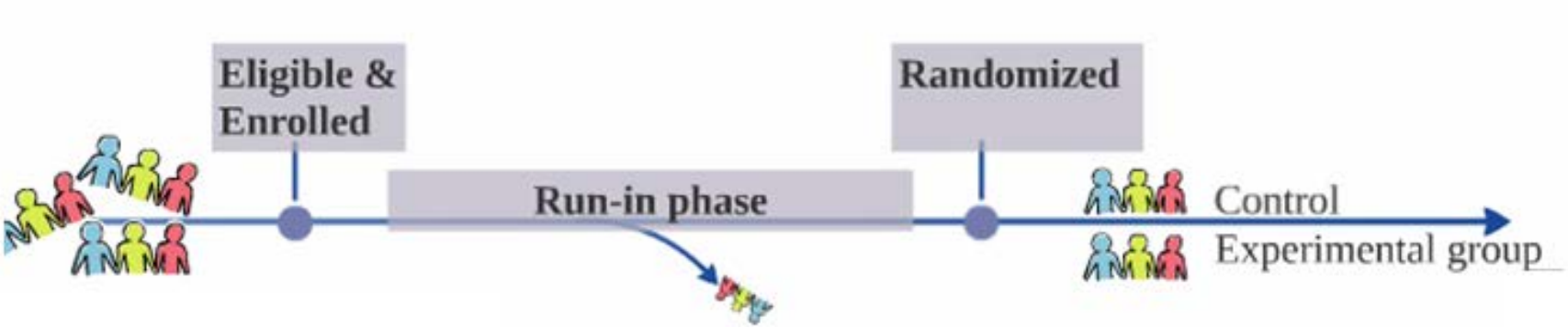
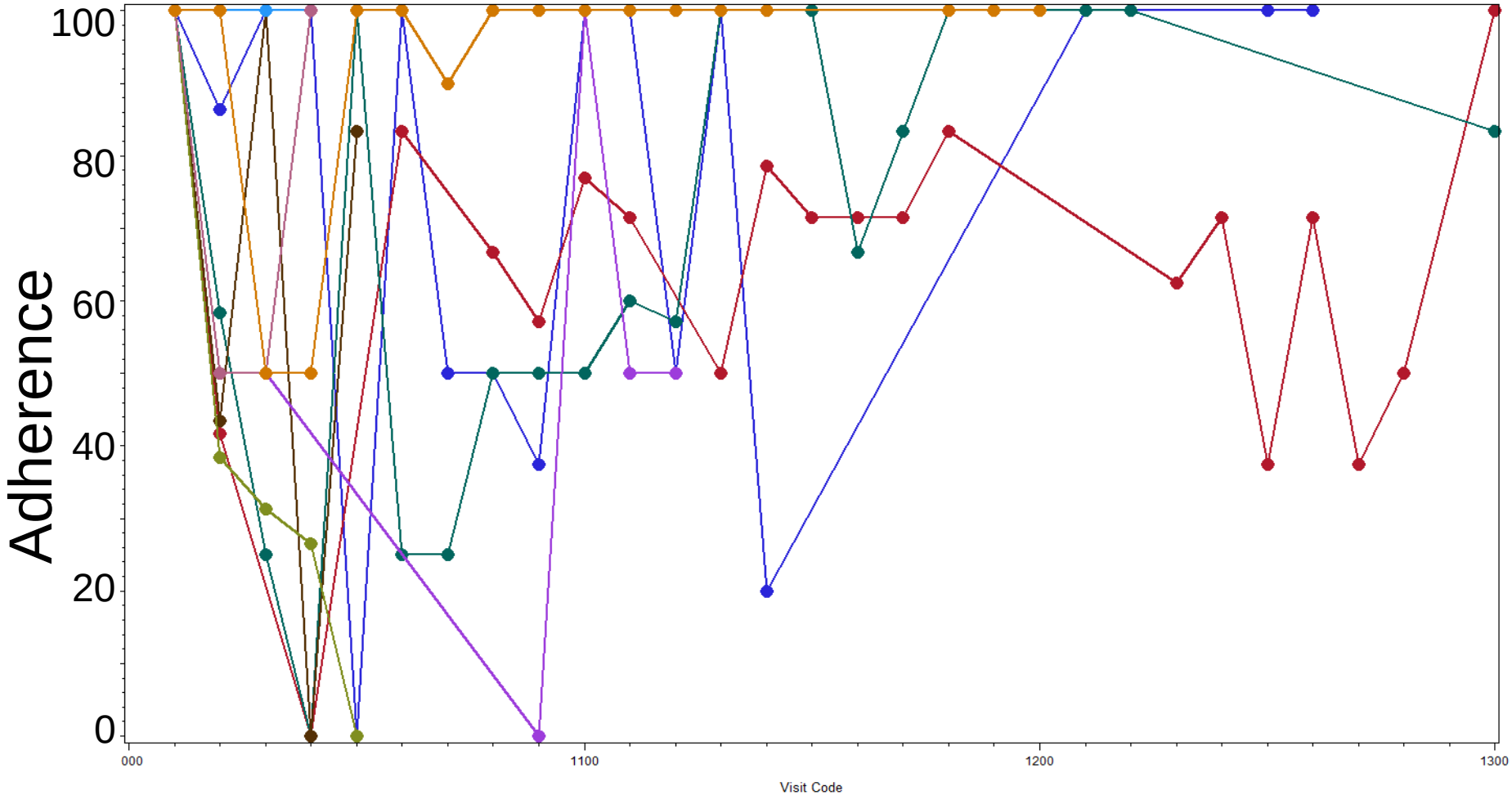
Run-in period

- **Period prior to randomisation during which potential participants who have met all entry criteria for an RCT are assigned to the same regimen, either the control or experimental treatment.**



Run-in: Participants selected for 100% adherence at Visit 1 or 3



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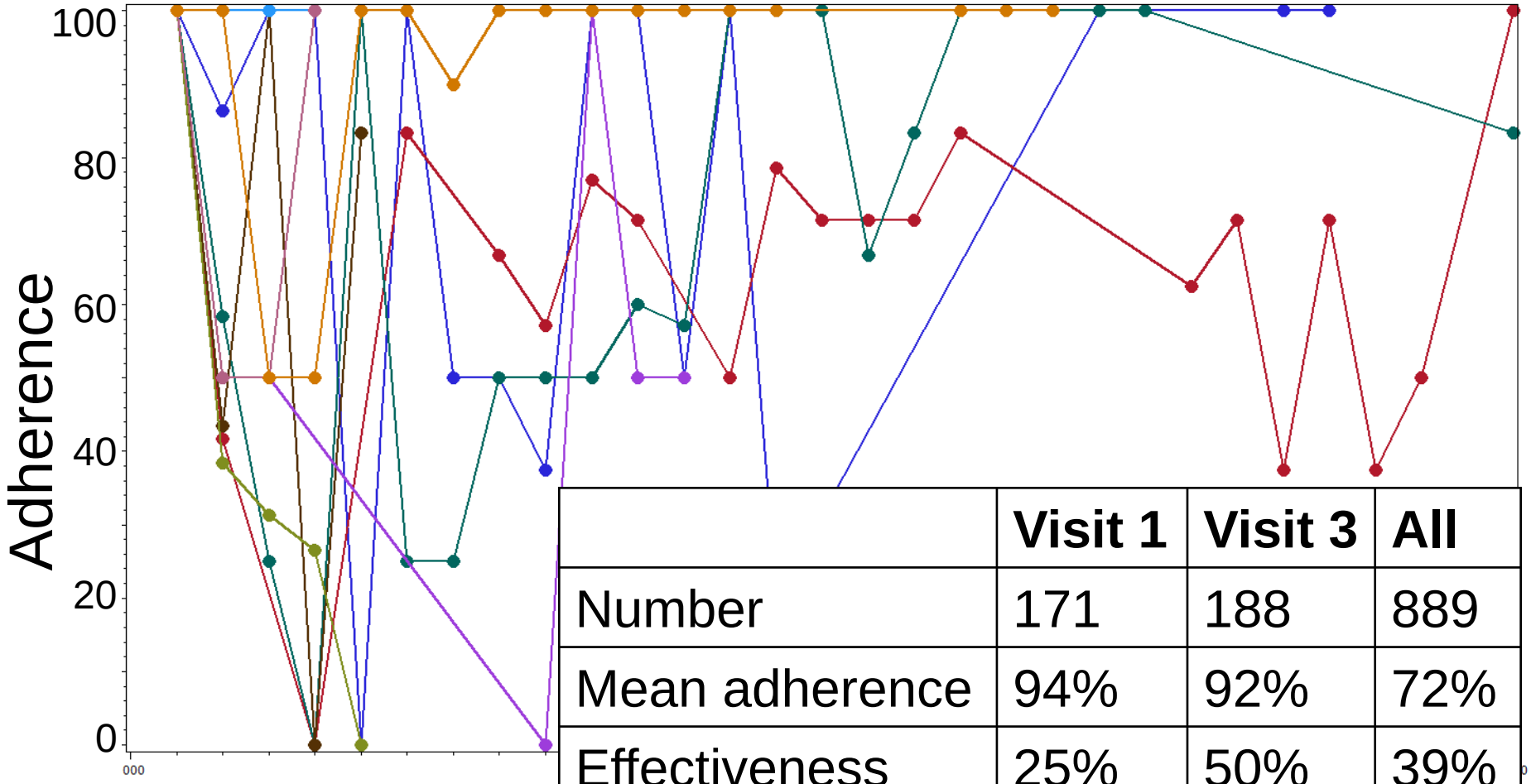
Run-in: Participants selected for 100% adherence at Visit 1 or 3



	Visit 1	Visit 3	All
Number	171	188	889
Mean adherence	94%	92%	72%
Effectiveness	25%	50%	39%

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Run-in period: Acceptability

- **Product acceptability predicted adherence**
- **Less likely to adhere if:**
  - Disliked something about the gel
  - Found the gel messy
  - Found the gel interrupted sex
  - Found it difficult to hide gel use

AIDS Behav (2014) 18:849–854
DOI 10.1007/s10461-014-0696-0

ORIGINAL PAPER

Disclosure of Microbicide Gel Use to Sexual Partners: Influence on Adherence in the CAPRISA 004 Trial

Kathryn Therese Mngadi · Silvia Maarschalk · Anneke C. Grobler · Leila E. Mansoor · Janet A. Frohlich · Bernadette Madlala · Nelisiwe Ngcobo · Salim S. Abdool Karim · Quarraisha Abdool Karim

- **Run-in period with gel (active or placebo) and only randomise women who find the gel acceptable**

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2

Select sites that adhere

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Site differences in CAP 004

- **Rural site had higher adherence**
- **Rural site had lower HIV rates**
- **Rural site had higher effectiveness**

	# HIV	N	HIV incidence		Effect	Adherence
			TFV	Placebo		
Rural	67	611	5.2	9.1	**43%**	**69%**
Urban	31	278	6.6	9.0	**26%**	**50%**

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Adherence differences by site

Site	Adherence % gel use last sex act	HIV incidence rate Per 100 person years
Malawi: Blantyre	82.6	3.67
Malawi: Lilongwe	**75.4**	1.42
South Africa: Durban	79.0	4.60
South Africa: Hlabisa	79.2	9.10
USA: Philadelphia	76.7	0.48
Zambia: Kamwala	82.5	4.10
Zimbabwe: Chitungwiza	**93.5**	2.45
Zimbabwe: Harare	91.0	2.49

Safety and effectiveness of BufferGel and 0.5% PRO2000 gel for the prevention of HIV infection in women

Salim S. Abdool Karim[a,b], Barbra A. Richardson[c], Gita Ramjee[d], Irving F. Hoffman[e], Zvavahera M. Chirenje[f], Taha Taha[g], Muzala Kapina[h], Lisa Maslankowski[i], Anne Coletti[j], Albert Profy[k], Thomas R. Moench[l], Estelle Piwowar-Manning[m], Benoît Mâsse[n], Sharon L. Hillier[o], Lydia Soto-Torres[p], on behalf of the HIV Prevention Trials Network (HPTN) 035 Study Team

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Adherence differences by site

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H.,
Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S., Albert Y. Liu, M.D., M.P.H.,
Lorena Vargas, Pedro Goicochea, M.Sc., Martín Casapía, M.D., M.P.H.,
Juan Vicente Guanira-Carranza, M.D., M.P.H., Maria E. Ramirez-Cardich, M.D.,

Subgroup	FTC–TDF (no. of patients)	Placebo (no. of patients)	FTC–TDF (no. of events)	Placebo (no. of events)	Hazard Ratio (95% CI)	P Value
Region						0.62
Andean	850	850	32	55	0.59 (0.38–0.91)	
Non-Andean	401	398	4	9	0.43 (0.13–1.39)	

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3

Terminate non-adherent participants

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Terminate participant if non-adherent

- **Unbiased**
- **Same criteria used in both arms**
- **Perfectly blinded placebo**

Terminate participant if non-adherent

- First time adherence is less than 70% at 4 consecutive visits
- Terminated 404 participants (45%)
- Person time: 866 person years (65%)
- Median follow-up: 10 months
- 63 HIV infections (64%)
- Effectiveness: 45%

Summary

	Number screened	Number enrolled	Effectiveness
CAPRISA 004	2160	889	39%
Run-in with 100% adherence	10800	889	50%
Select adhering sites	2160	889	40%
Analyse adhering sites	2160	889	43%
Terminate non-adherent participants	3323	1367	45%
Adherent subgroup	2160	889	55%

Forum for Collaborative HIV Research

Workshop on Adaptive Enrichment Trial Design for Microbicides

Co-sponsored by CONRAD, AVAC, and FCHR

CONRAD
Leaders in Reproductive Health and HIV Prevention

AVAC
Global Advocacy for HIV Prevention

Forum for Collaborative HIV Research

June 23, 2014

Planning Group

- Ben Hauschild
- Gustavo Doncel
- Annette Larking
- Christine Mauck
- Veronica Miller
- Jill Schwartz
- Mitchell Warren
- Sarah Zugschwerdt

The Issue

- High cost of prevention trials
- Donor fatigue
- Ability to demonstrate efficacy and safety only if adherence is high
  - Drugs don't work if they are not taken

For Discussion

- What are clinical trial design options?
  - Adaptive design increasingly used in clinical research
- Will adaptive trial designs be acceptable for registration?

Session 1

- Craig Hendrix MD, JHU
  - Adherence impact on study results
- Benoit Masse PhD, U Washington
  - Biostatistical considerations
- Dionne Price PhD, FDA
  - Regulatory perspective on adaptive designs

Adherence : Impact on Study Results

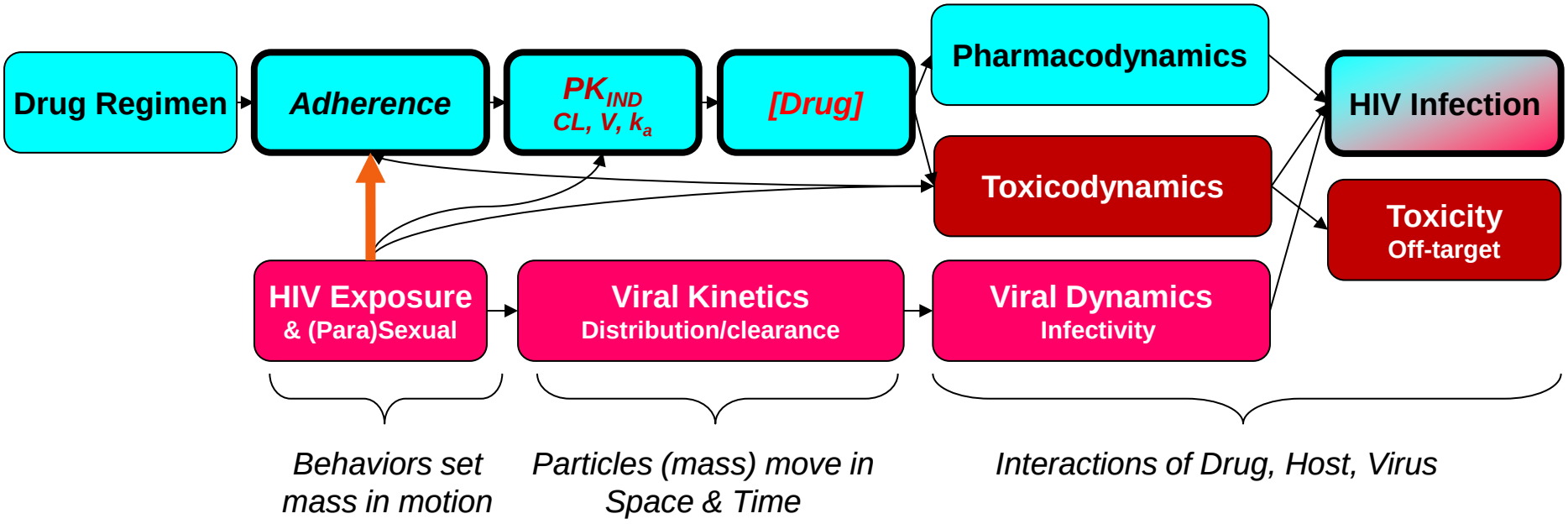
Craig W. Hendrix, MD
Johns Hopkins University

Major Points

- Poor adherence is common and may reduce efficacy
- Most selective definition of “adherence” requires consideration of drug PK and PD
- Each adherence measure has limitations & correlation among measures is modest
- PK & EMS highly complementary
- On study PK-based adherence monitoring is feasible, but time-consuming

What is the impact of adherence on outcome?

Relating Adherence, PK, PD, Toxicity

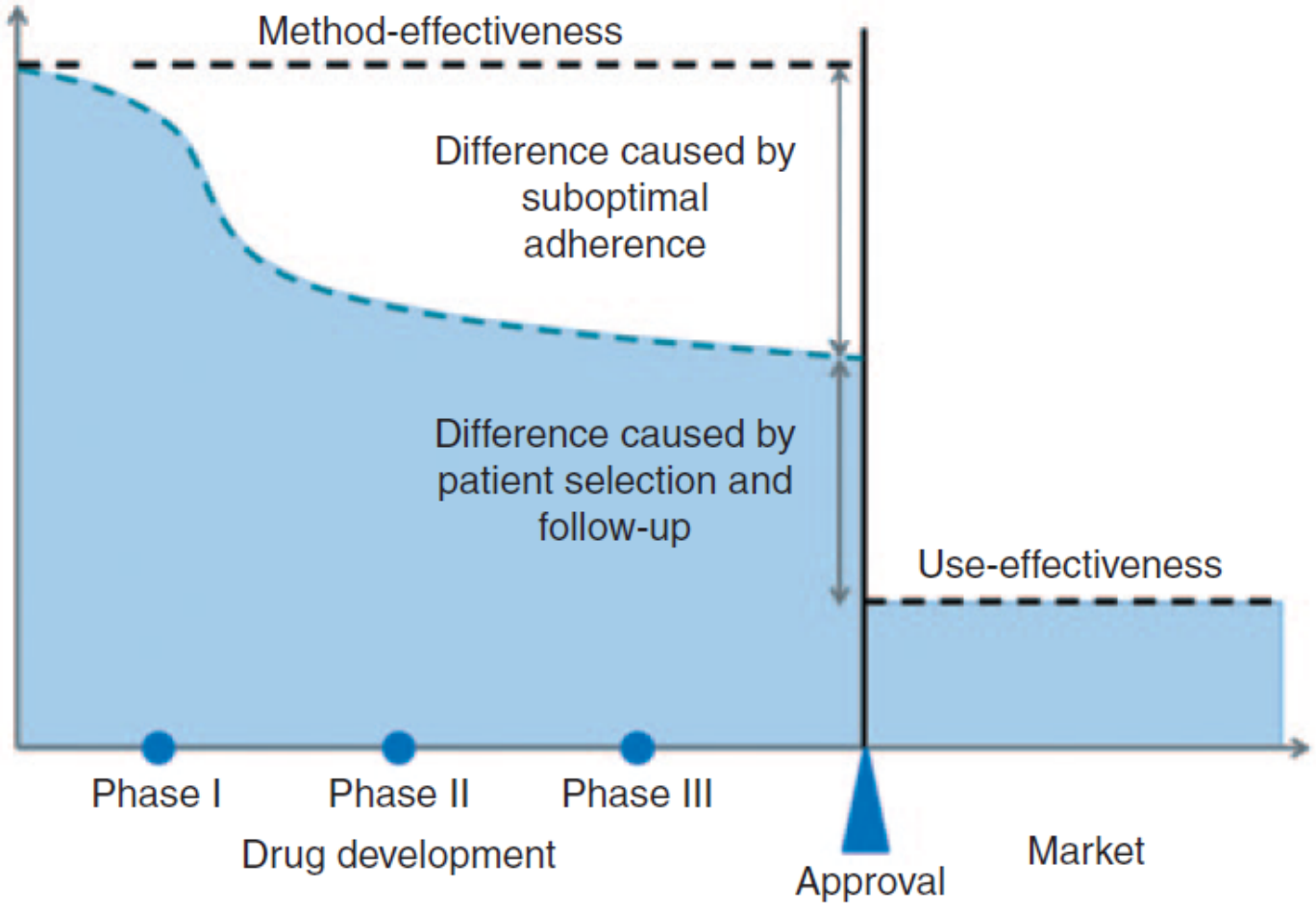


Non-Adherence Impacts

- Failed treatment
- Inappropriate dose escalation
- Emergence of drug-resistance
- Hazardous rebound or recurrent first-dose effects
- Misdiagnosis (drug response is a diagnostic criterion)
- underestimated drug efficacy/trial failure
- underestimated incidence of AEs
- Overestimated dosing requirement

Blaschke TF, et al. Ann Rev Pharmacl Toxic 2012

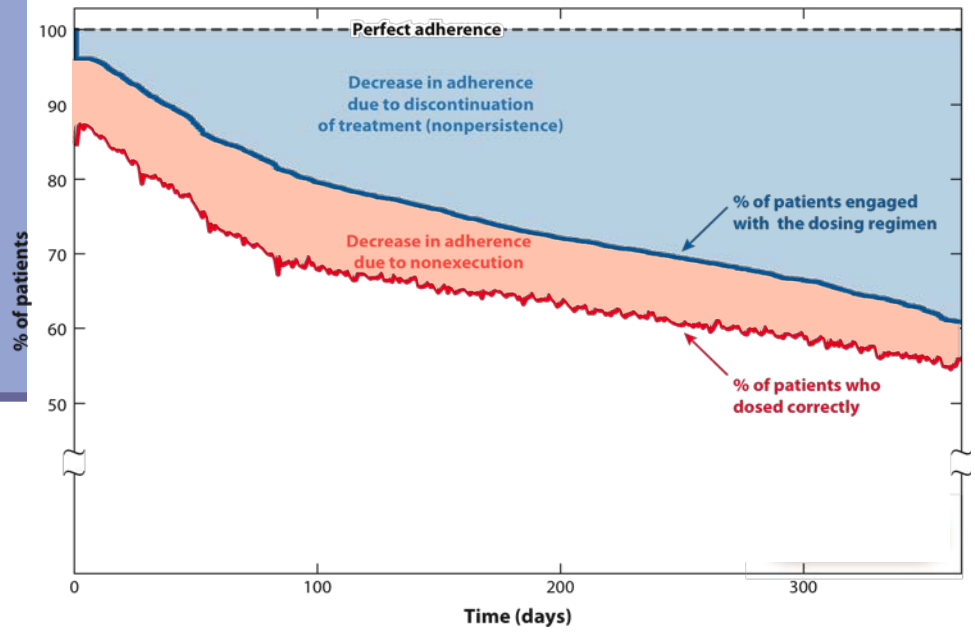
Adherence impact in drug development

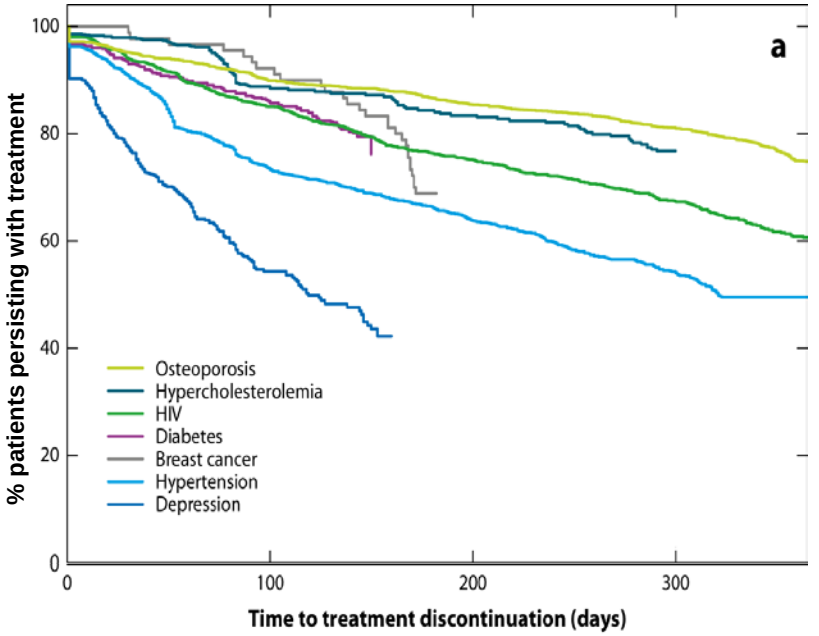


Vrijens & Urquhart. *CPT* 2014

Adherence (EMS) in RCTs

- N=16,907, variety of medical conditions in 95 studies
- Discontinuation is greater problem than nonexecution
- Decreases occur in all therapeutic categories

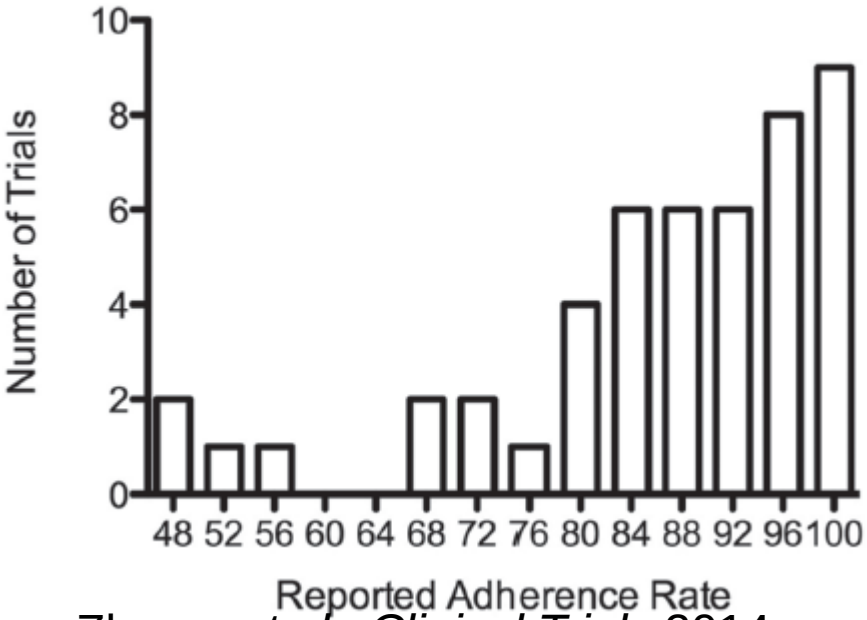




Blaschke TF, et al. Ann Rev Pharmacol Toxic 2012

Adherence reporting in RCTs

- 111 RCT 2010, 10 high impact journals
- 51 (46%) reported adherence assessment
- More likely reported if ineffective Rx
- PrEP RCT adh. reported 100% (not by protocol)



Method	% (# / 51)
Pill count	57
Self-report	24
Electronic	11
Drug concentration	5
Direct observation	3

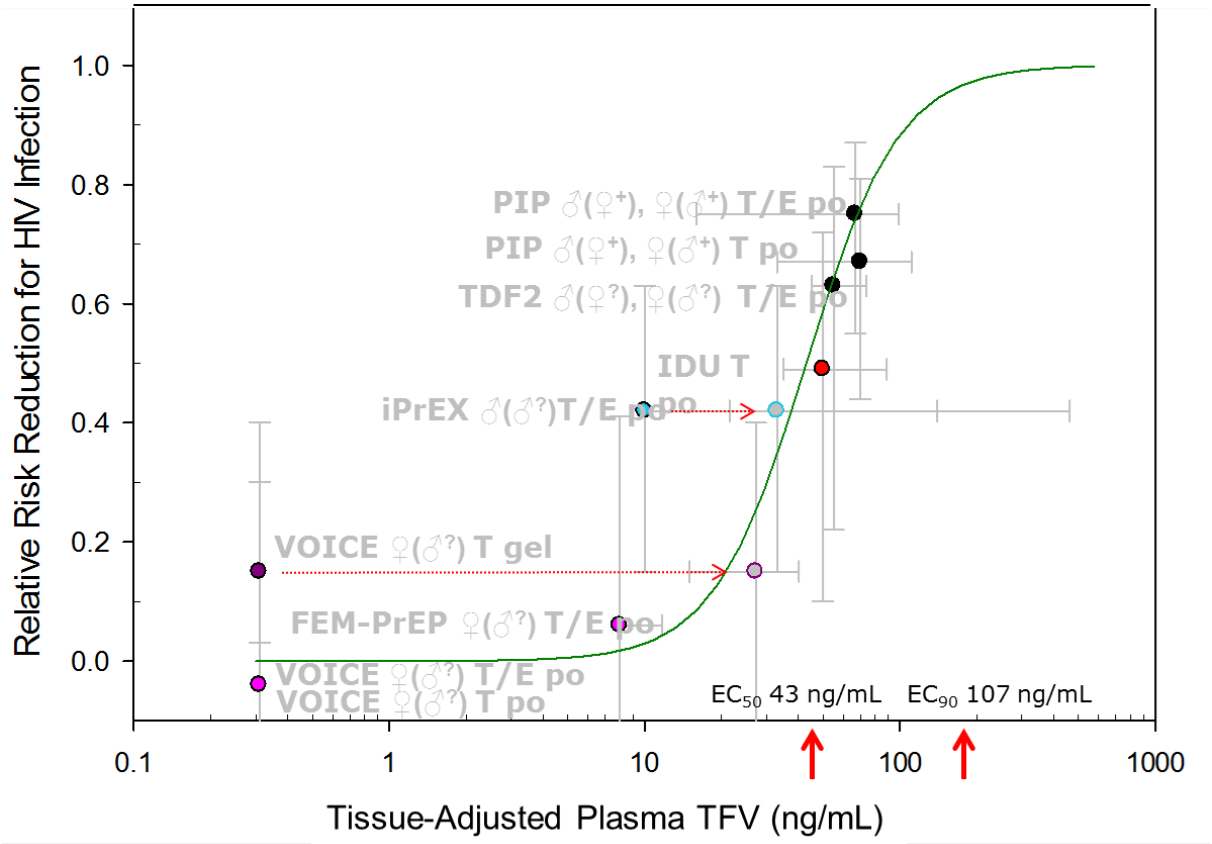
Zhang, *et al., Clinical Trials* 2014

PrEP Conc,n-Response Within RCT

Study	Population	Regimen	Relative Risk Reduction (95% CI)	
			All Subjects	Drug Detectible
Partners	women, men	TDF po qd	0.67 (0.44 – 0.81) ↗	0.86 (0.57–0.95); BLQ 0.3
		TDF/FTC po qd	0.75 (0.55 – 0.87) ↗	0.90 (0.56–0.98) ; BLQ 0.3
CDC TDF2	women, men	TDF/FTC po qd	0.62 (0.22 – 0.83)	50% SC, 80+% NSC; BLQ 0.3
iPrEX	MSM	TDF/FTC po qd	0.42 (0.15 – 0.63) ↗	0.92 (0.40 – 0.99) ; BLQ 10
FEM-PrEP	women	TDF/FTC po qd	0.06 (-0.41 – 0.52)	No diff. 25% v 35% (BLQ 10)
VOICE	women	TDF po qd	*-0.49 (-1.30 – 0.035)*	No difference (BLQ 0.3)
		TDF/FTC po qd	*-0.04 (-0.50 – 0.30)*	No difference (BLQ 0.3)
CAPRISA 004	women	TFV gel BAT24	0.39 (0.04 – 0.60) ↗	>1,000 CVF increased RRR
VOICE	women	TFV gel qd[e]	*0.15 (-0.20 – 0.40)* ↗	0.43 (0.20-0.92); BLQ 0.3
Bangkok IDU	men, women	TDF po qd	0.49 (0.10 – 0.72) ↗	0.70 (0.02–0.91); BLQ 0.3

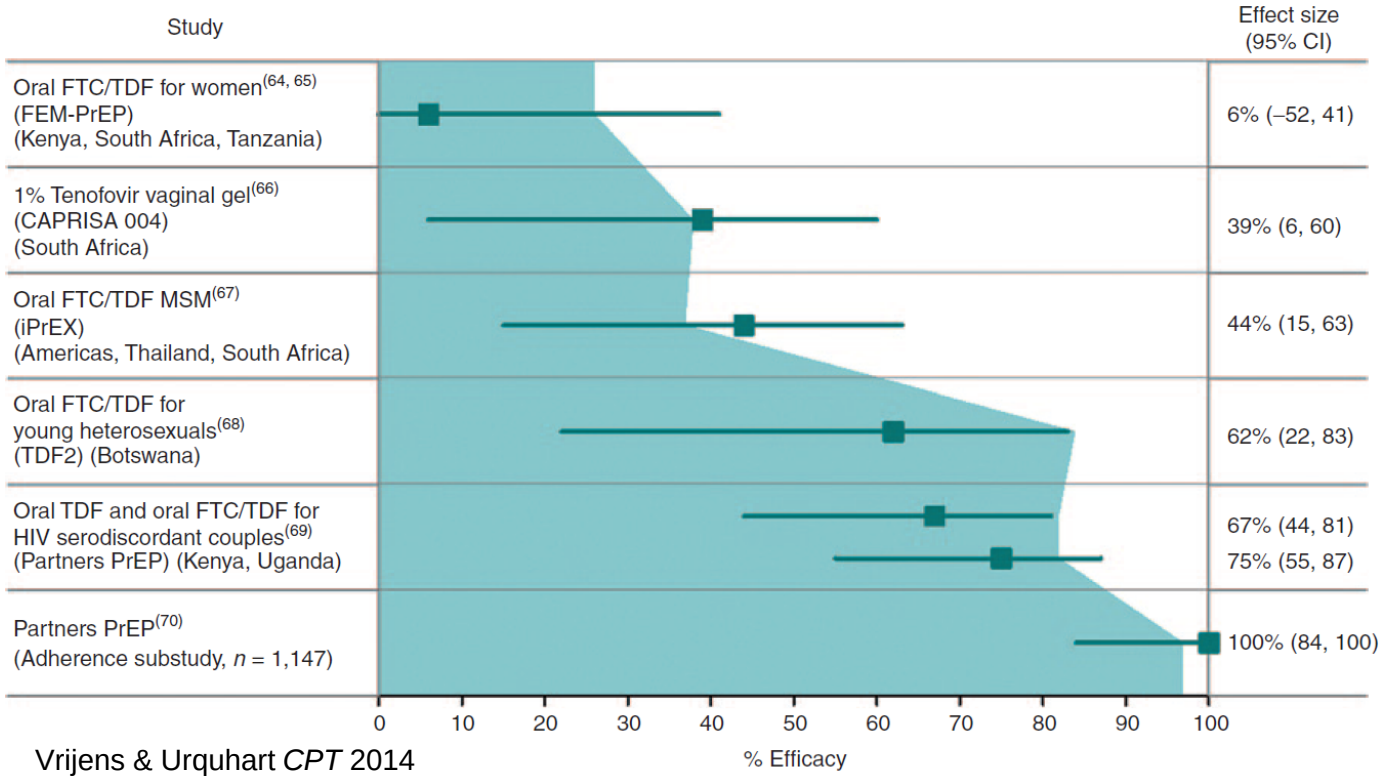
- Even in VOICE gel, presence of drug increases efficacy
- Most concentration-related adjustments controlled for HIV risk covariates

PrEP Conc'n-Response Among RCTs



- Concentration (±IQR) provides additional actionable PK-PD information
- Variation too large to be PK differences, attributed largely to adherence
- Reference to benchmarks (STRAND, HPTN066) gives dose frequency context

PrEP Outcome & Adherence



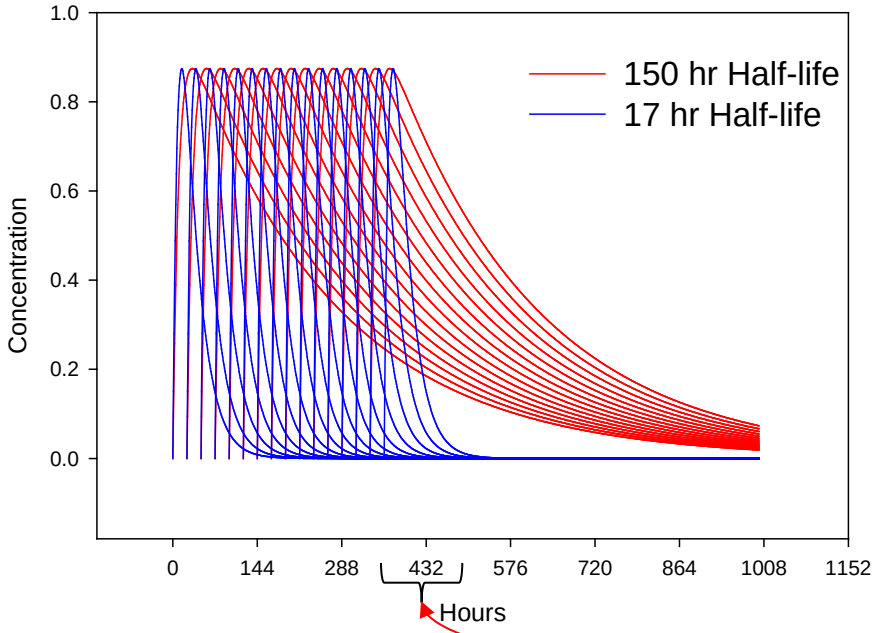
Vrijens & Urquhart *CPT* 2014

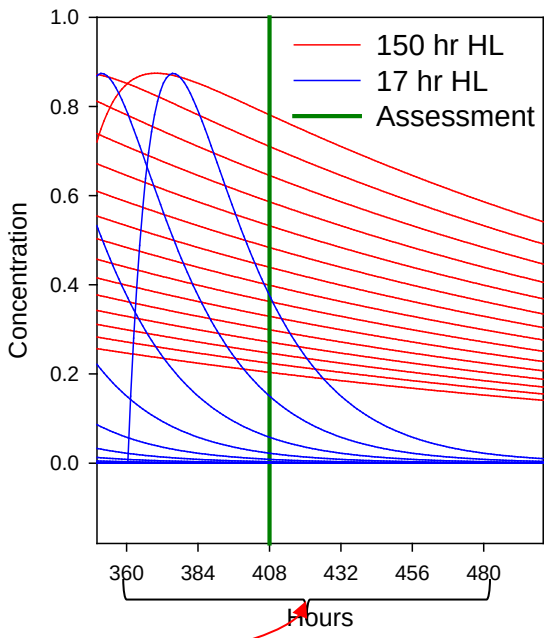
- Adherence associated with seroconversion rate
- Adherence % based on yes/no plasma LLOQ cut-off (varies)
- Variability not shown
- No account of concentration associated with efficacy (dilutes influence)
- Ignores influential (for TFV) pattern of dosing

How to objectively assess adherence?

Influence of Half-life in Matrix/Moiety

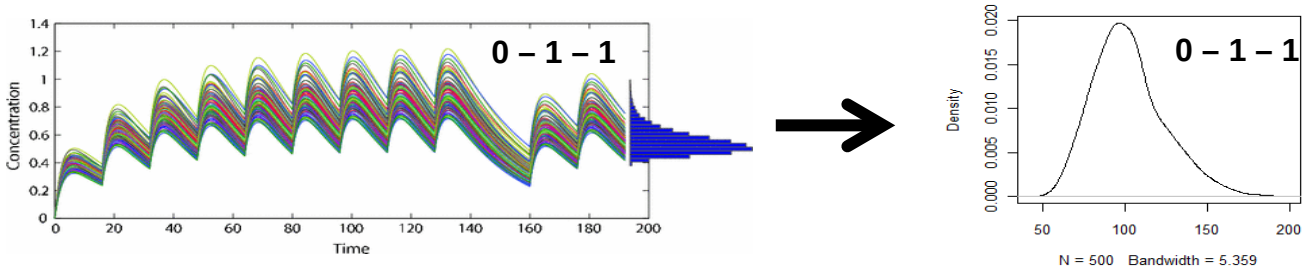
- Both PBMC & plasma associated with PrEP outcome
- ↑ HL drug, more doses influence each observation
- ↑ HL, changes slow with missed doses
- ↓HL drug, more influence of most recent dose
- None sensitive to drug holidays unless recent (only ↓HL)
  - Pattern (holidays) influential for ↑ HL drug (TFV-DP)





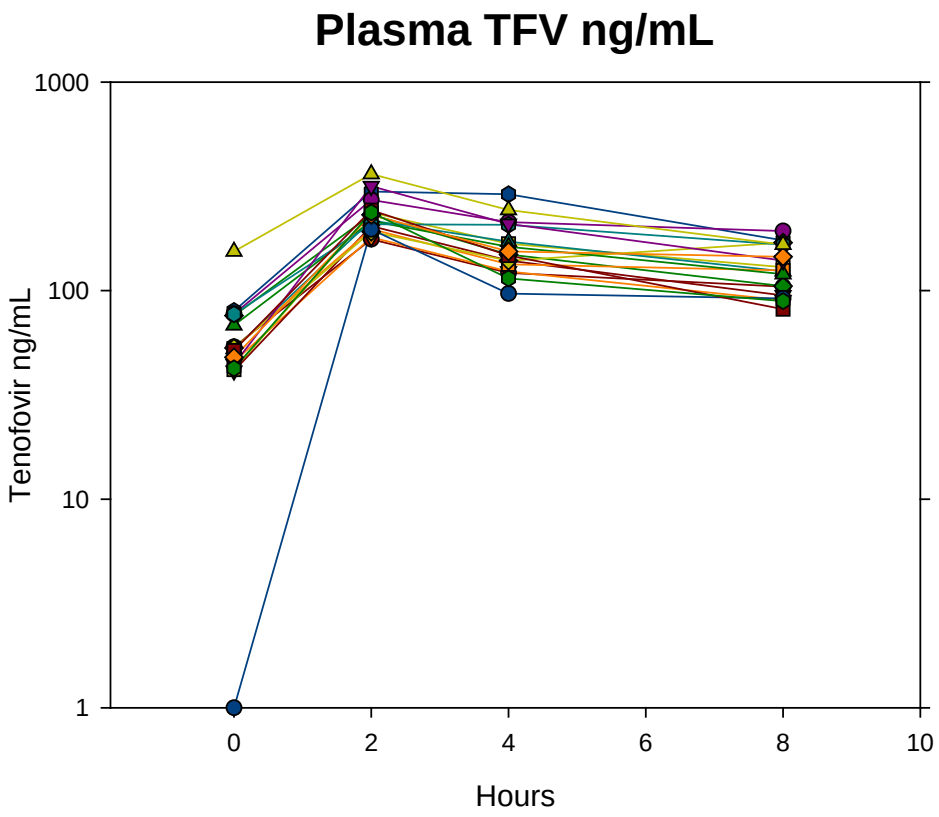
Cannot Decode Patterns with PK

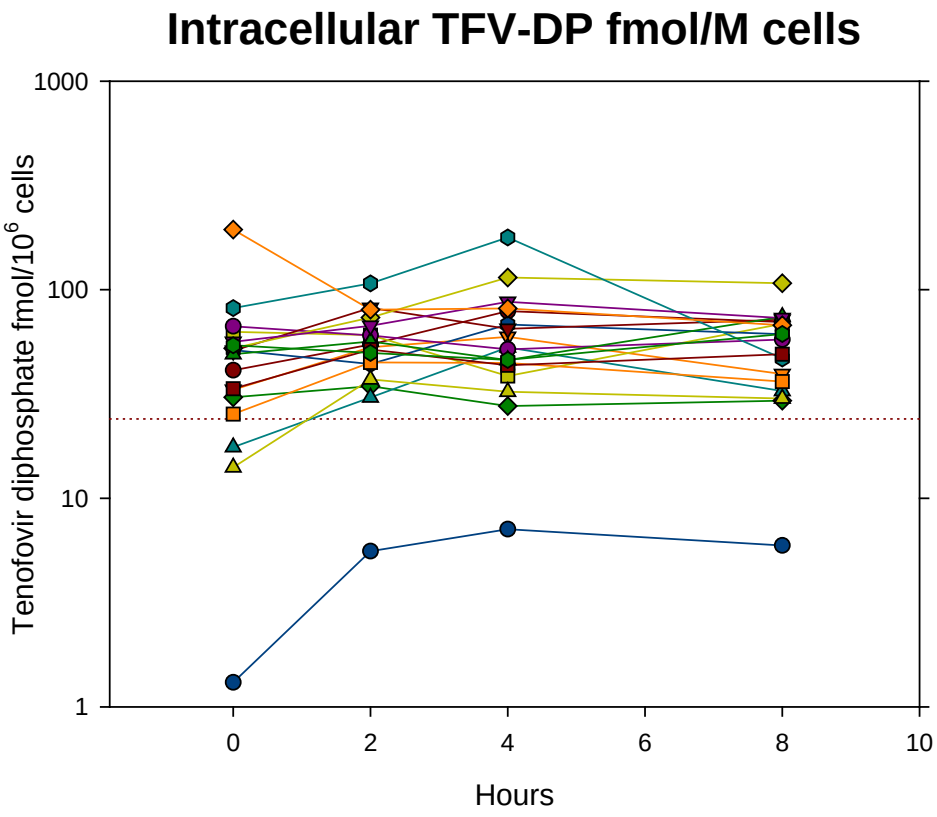
- POP PK model built to calculate PK_{IND}, σ
- Establish Bayesian likelihood of prior dose pattern based on observed concentration and PK_{IND}



- Select most probability sequence (among 8)
  - 1-1-1 full compliance, 0-0-0 full non-compliance
- Observed values
  - 51% consistent with full compliance (MTN-001)
  - Identifies few “white coat” effects (too high)
  - Only 79% within 60% - 140% of actual
  - ***PK cannot decode adherence patterns***

Decoding concentration
White Coat Effect & Matrix





- Plasma indicates adherence,
- PBMC TFV-DP indicates single very recent dose or very distant last dose (long Tss)
- Combination indicating "*white coat adherence*"

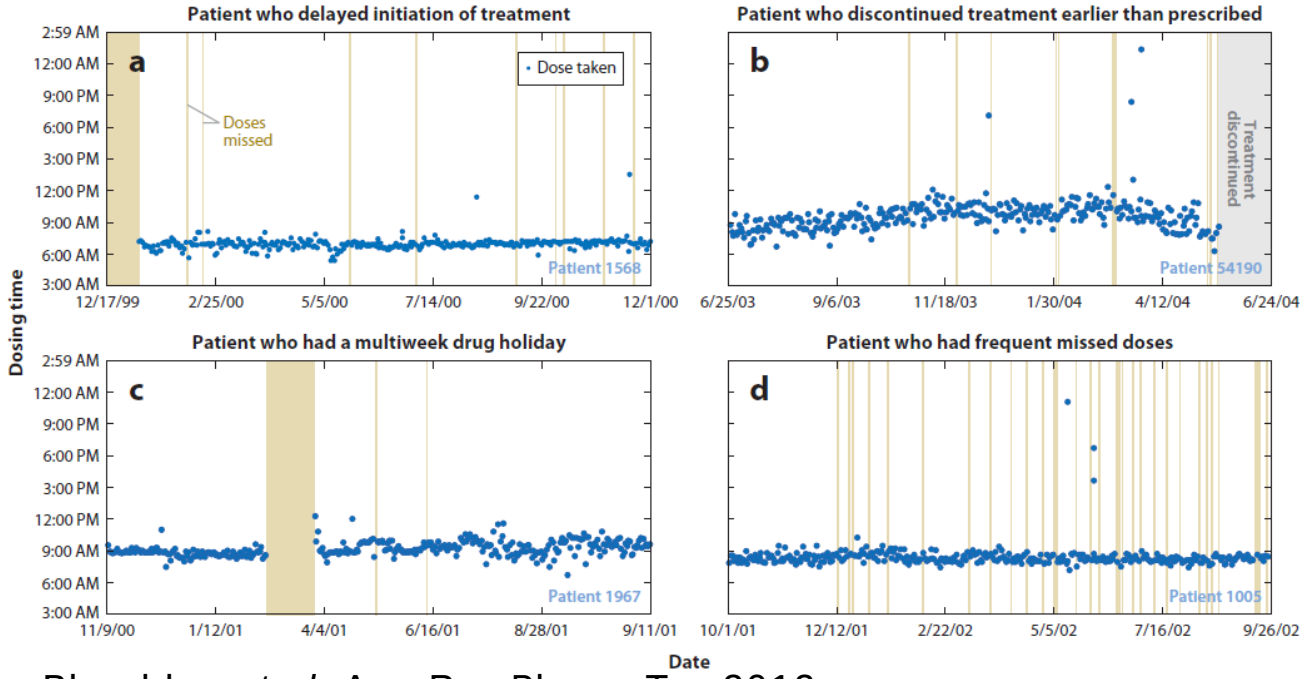
Source: TDF2 (CDC Botswana PrEP, TDF 300 mg qd, steady-state, men & women)

Adherence Measures Concordance

- Only modest correlation among adherence measures
  - plasma, PBMC, hair, MEMS
  - Data not shown (under publication review)
- All “objective” adherence methods capture somewhat different information
- Selection as adherence measure should be based on specific use intended

Variable Patterns of Adherence

- "90% Adherence" takes many forms

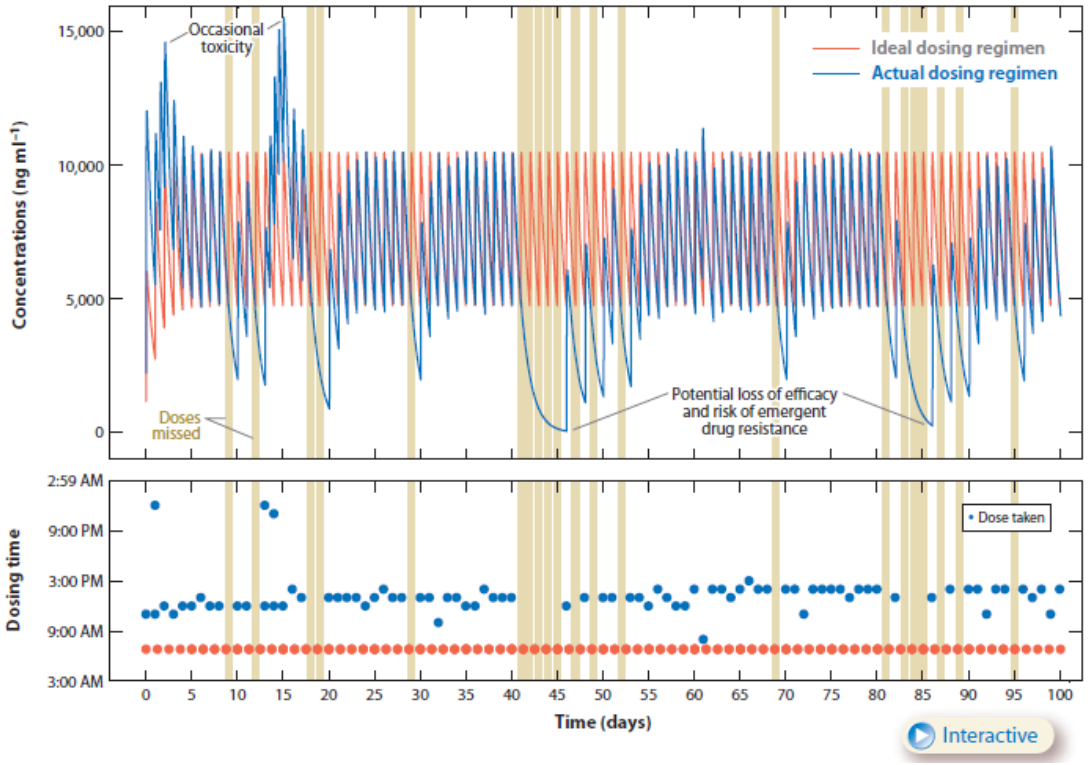


Blaschke, *et al*. Ann Rev Pharm Tox 2012

- Pattern informs adh. intervention & outcome interpret.
- All PK methods "average" holidays, lose information
- Simple "Adherence %" biggest least relevant for ↑HL drug

Optimal Information: EMS & PK_{IND}

- Adherence patterns vary
- At same level of overall adherence, some patterns riskier than others
- "On average" may oversimplify "adherence"
- Need event monitoring for *both drug and sexual exposure (e.g., Yc)*
- EMS+PK >> EMS > PK especially for individual, but also for explanatory value in population



Blaschke, *et al*. Ann Rev Pharm Tox 2012

- Useful for selection of "adherence" criteria & clinical trial simulation

Clinical Trial Simulation

- Describe adherence, PK, PD, viral dynamics as related equations to enable RCT simulation
- Compete varied adaptive RCT designs to select most efficient, least ambiguous design
- Allows exploring “what if?” scenarios
- Explore RCT sensitivity to
  - Adherence
  - Enriched population selection
  - Site/individual performance thresholds

Is PK-adherence assessment feasible on study?

On Study PK testing feasibility

- MTN-020: 1 month, 6037 (since 3/20/13)
- MTN-017
  - 218 since 1/14/2014
  - Sites ship q2w; lab TAT 6 d (range 2-10)
  - Results available at next visit (1 month)
- Minimizing TAT
  - Significant time commitment to coordinate/track 6 sites
  - Frequent communication between site (clinical & lab), MTN, central lab
  - Expedited runs possible if needed
  - Equipment failure (redundancy)

Major Points

- Poor adherence is common and may reduce efficacy
- Definition of “adherence” requires consideration of drug PK and PD
- Each adherence measure has limitations & correlate among measures is modest
- PK & EMS highly complementary
- On study PK-based adherence monitoring is feasible, but time-consuming

Thank You

Workshop on Adaptive Enrichment Trial Design for Microbicides

Alternative Designs: Adherence Based Enrichment

Jill Schwartz, M.D.
Medical Director, CONRAD
Associate Professor of Obstetrics and Gynecology
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Rationale for Enriched Trial Design

- Drug development is a lengthy and costly process
- It is becoming more difficult to support the cost of new drug development
- The current model for clinical testing may no longer be sustainable
- Need for cost-saving and efficient trial designs to test safety and efficacy

Pitfalls of Poor Adherence

Adherence to treatment is essential for the reliable evaluation of drug treatment

Variable adherence can:

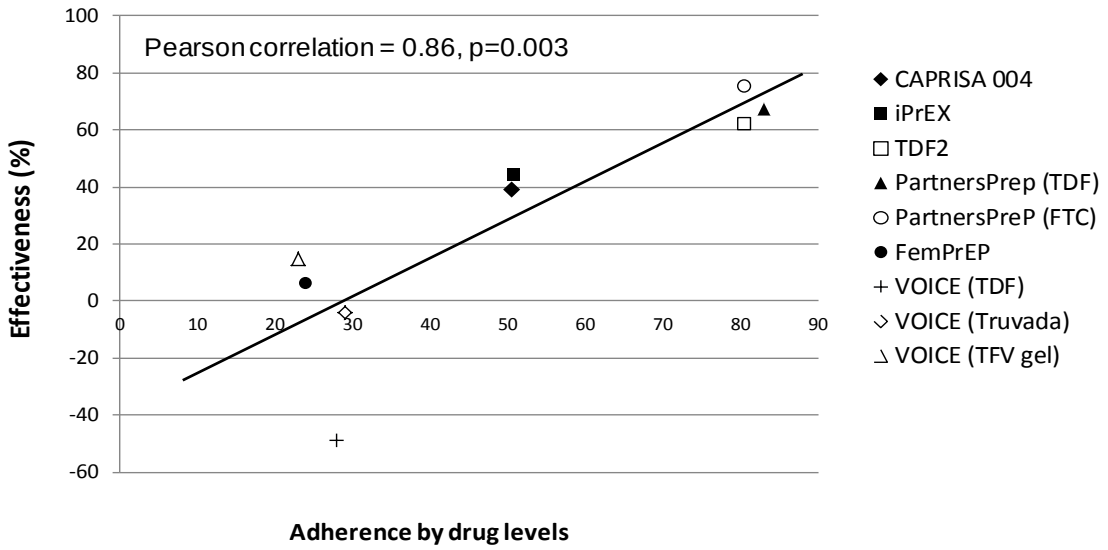
- Underestimate the efficacy of the drug
- Confuse the interpretation of clinical trials
- Influence the path of drug development

A potentially effective drug can be erroneously judged to be ineffective

Vrijens and Urquhart, Clinical Pharmacology and Therapeutics, 2014

Relationship Between Adherence and Effectiveness

Relationship between drug detection and protection



Karim S, unpublished

Identify and select adherent volunteers

- Across different studies, adherence strongly influences effectiveness
- Great need to identify and select volunteers likely to adhere to the protocol-specified regimen

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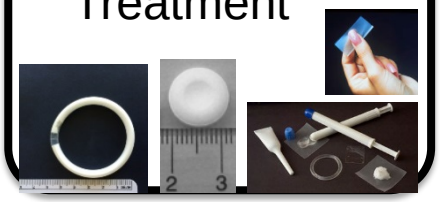
Adherence Based Enrichment Concept

Enrichment Phase

- Proven adherers
- Run-in period
- Predictors of adherence

Enrollment

- Randomize to Placebo and Treatment



Monitoring Adherence

- Objective markers of adherence

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Adherence Based Enrichment TFV gel example

Pre-trial Enrichment

- Select volunteers from previous microbicide trials who have demonstrated >80% adherence –known adherers

Trial

- Randomize enriched population to TFV gel vs placebo

Monitor Adherence

- Identify non-adherers by objective marker of adherence

Monitoring Adherence

- Measure objective marker that determines adherence to both placebo and TFV gel (non-differential)
  - Marker of applicator insertion feasible now
  - Electronic monitoring (e.g. smart sensors)
  - Important to have close to real-time assessment
- Threshold for non-adherence: < 80% adherence for 3 consecutive months
- If <80%, discontinue from gel and place in "standard of prevention" (no-gel arm)

Underlying Assumptions

- 3.5% HIV incidence in placebo
- 90% efficacious product
- 25% drop of participants due to lower adherence (equally distributed in placebo vs TFV arm) and LTFU
- 21 HIV endpoints would provide 80% power to detect a 75% reduction in risk

Enroll a total of 690 women for up to 24 months to get about 520 adherent women

Limitations of Enrichment Strategies

- Intent-to-treat is the conventional approach to test safety and effectiveness
- High adherence may be associated with lower risk of HIV infection
- Dropping participants post-randomization may introduce confounders and can decrease generalizability
- Need additional study to determine product use and adherence in target population

Advantages of Enrichment Strategies

- ITT does not account for non-adherent volunteers
- Determination of efficacy among high adherers minimizes trial size and cost and maximizes efficiency
- Adherence monitoring enables testing of true efficacy in a setting where women use the product consistently
- After confirmation of efficacy, efforts can focus on:
  - discerning barriers to product use
  - testing the product under conditions that improve adherence, consistent use, and product uptake more broadly (e.g., messaging/counseling under open label; target populations, etc.)

Acknowledgements

DEVELOPMENT OF NOVEL ON-DEMAND AND LONGER-ACTING MICROBICIDE PRODUCT LEADS

Workshop on Adaptive Enrichment Trial Design for Microbicides

AVAC/CONRAD/Forum for Collaborative HIV Research

Washington, DC, 23 June 2014

How to measure adherence by objective markers

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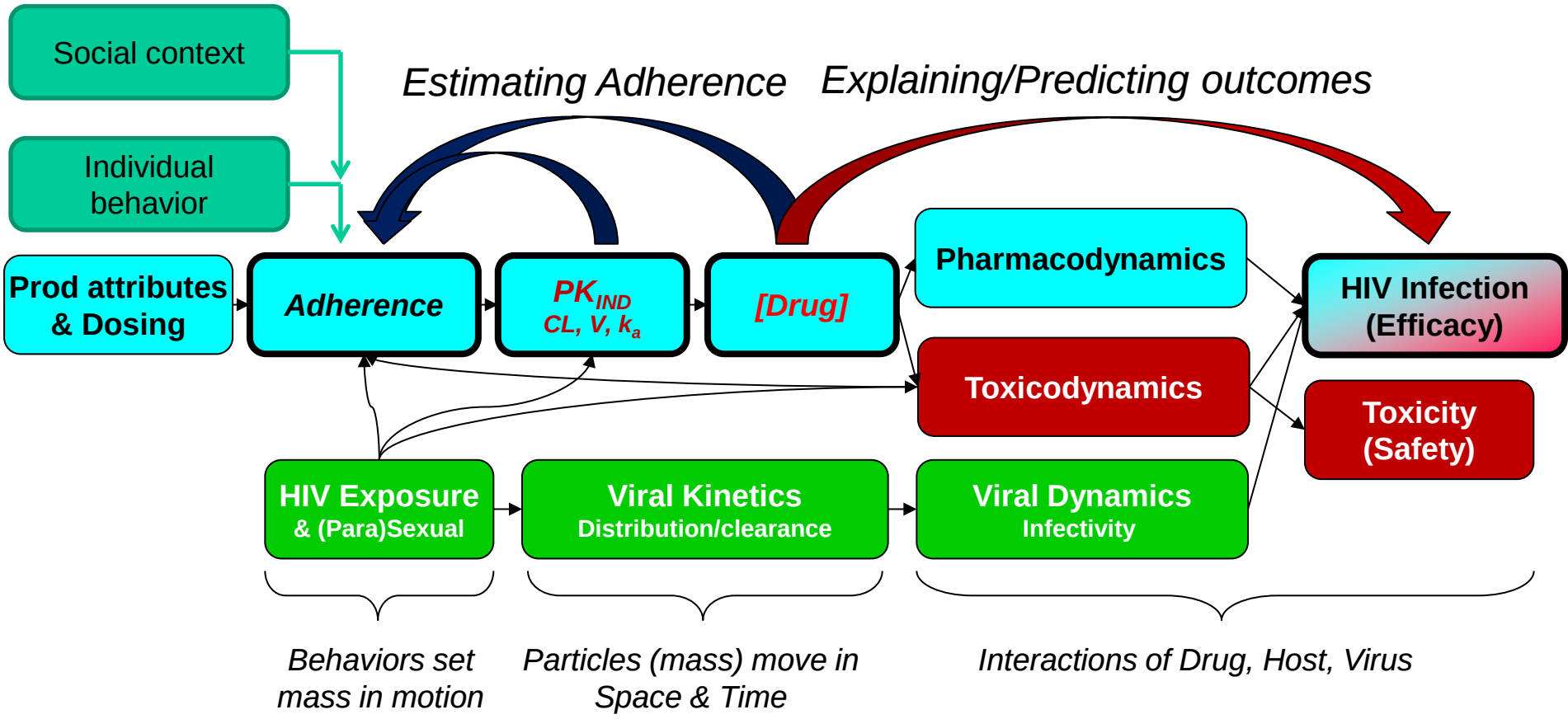
Adherence, PK/PD and HIV infection



Modified from Hendrix 2009

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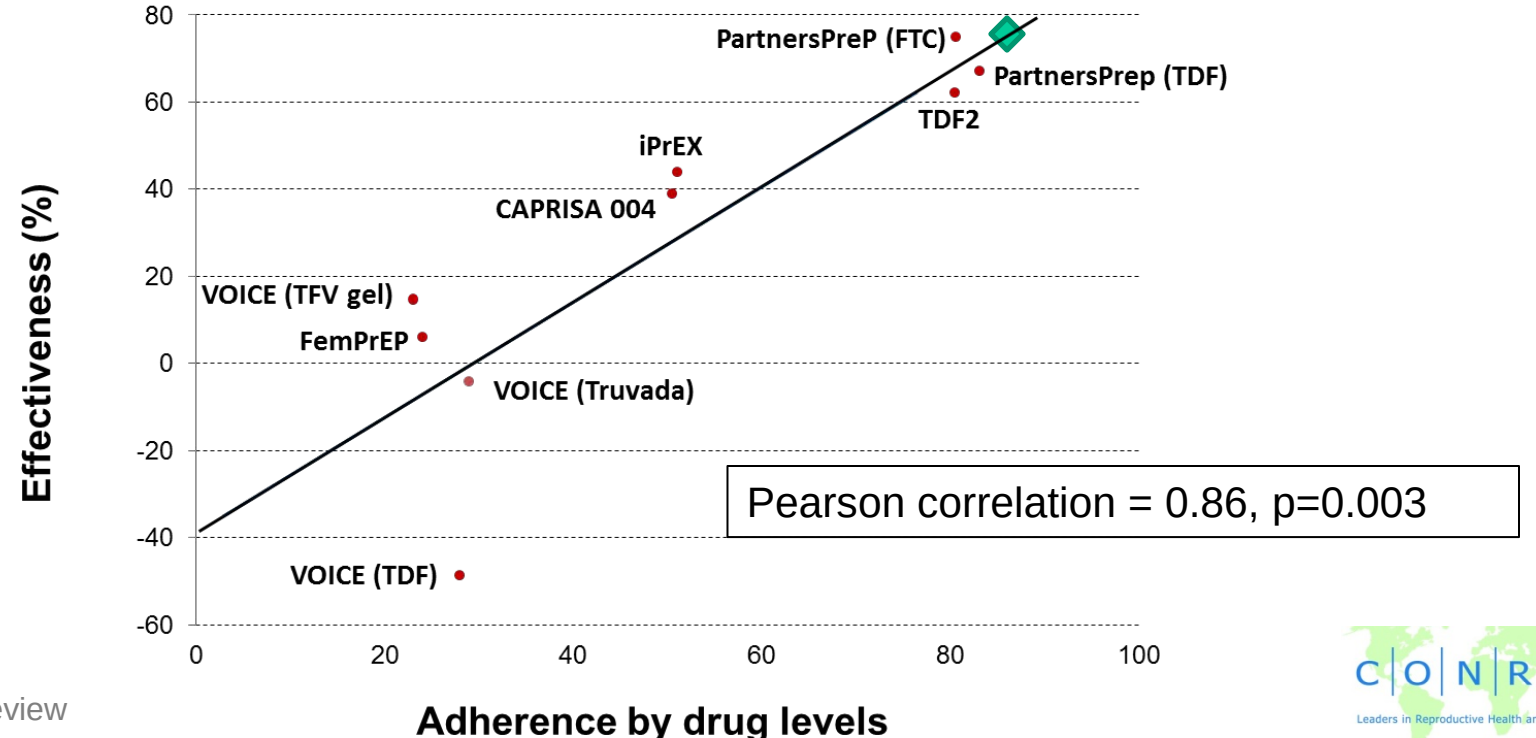
Adherence and effectiveness in PrEP trials

Relationship between drug detection and protection

Oral TFV (TDF,Truv) trials	Blood sample TFV detected*	Effectiveness - HIV protection
Partners PrEP FTC/TDF arm	81%	75%
TDF2	79	62
iPrEx	51	44
FEM-PrEP	35	6

* controls



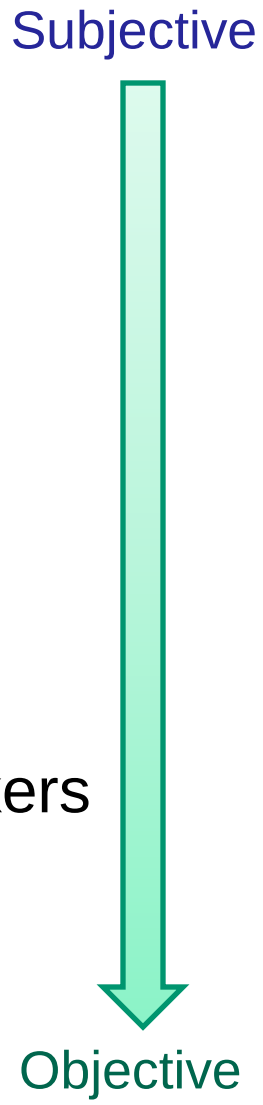
Karim S, under review

Measures of adherence

- Self-report
- FTF interview
- ACASI
- Cell phone (SMS/IVR)

- Pill/applicator count/pharmacy refill
- Electronic monitoring (e.g., MEMS, WiseBag)

- Biomarkers (e.g., drug in biological matrices, markers of vaginal insertion)
- Physicochemical markers (e.g., changes in pH, taggants, tracers)



Self-Report

- Major strengths:
  - Inexpensive
  - Simple to implement
  - Not product specific
  - Applicable to both active and placebo groups
  - May provide information (e.g., reasons and mode) on incorrect or non-use
  - May allow for monitoring of pattern of use
- Major weaknesses:
  - **Social desirability bias (or purposeful deceptiveness?)**
  - Retrospective (typically)
  - Low accuracy

"My short-term goal is to bluff my way through this interview. My long-term goal is to invent a time machine so I can come back and change everything I've said so far."

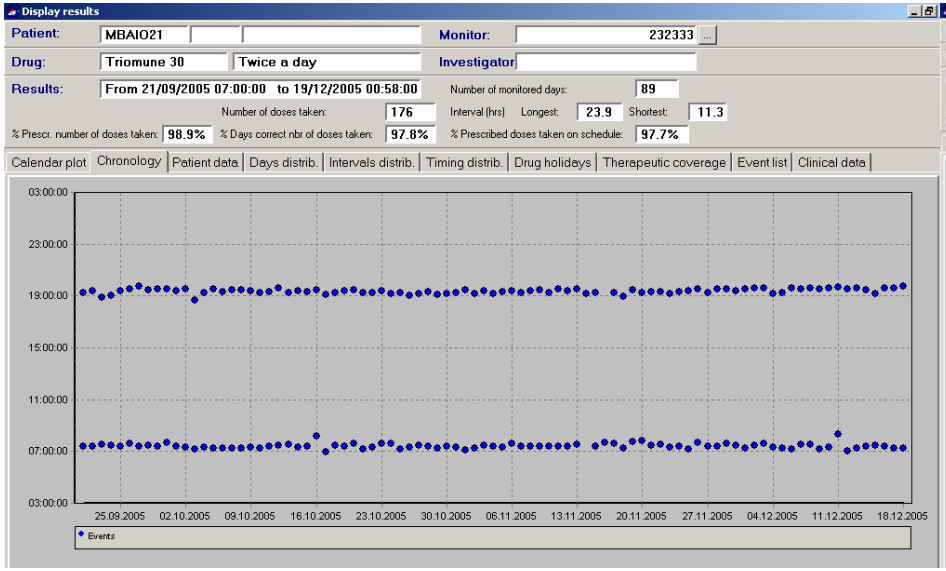
Modified from van der Straten, M2012

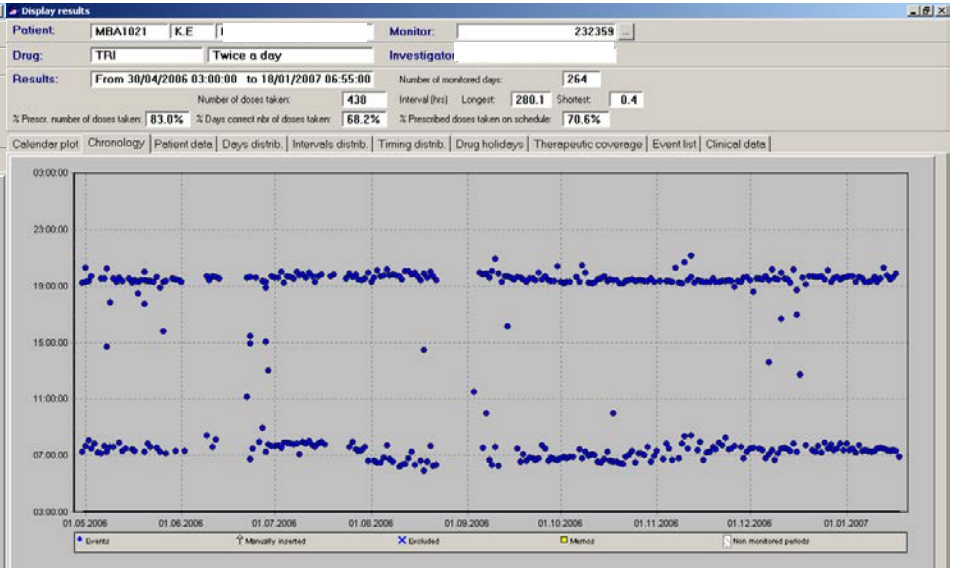
In PrEP studies self report has not been reliable

- FEM-PrEP (Van Damme, 2012)
  - Self-report: 95% of participants took the drug usually or always
  - Pill-count: 85% of the days
  - Drug-levels in blood (cohort):
    - Uninfected: ~36%
    - Infected: ~23%
- Other studies with similar discrepancy: VOICE, iPrEX, Carraguard
- PREDICT study: child self-report of missed doses associated with virologic failure

Medication Event Monitoring System (MEMS)

- Used in >200 studies for >25 years
- Date-and-time stamp for each opening/closure
- Data downloaded via USB cable





Medication Event Monitoring System (MEMS)

- Used in >200 studies for >25 years
- Date-and-time stamp for each opening/closure
- Data downloaded via USB cable

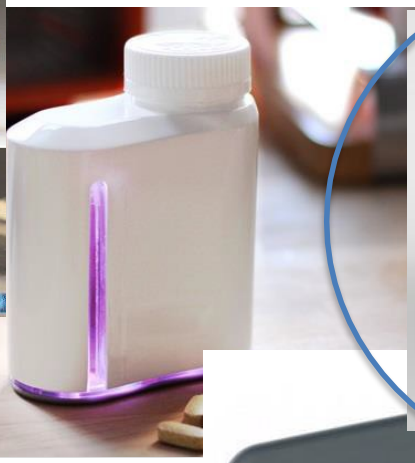
PROS

- Likely more objective measure of behavior
- Provides patterns of adherence

CONS

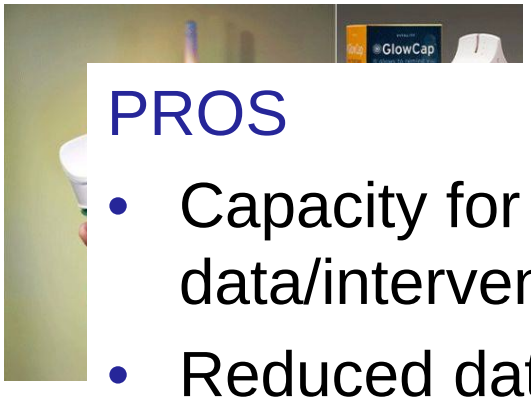
- Curiosity openings and pocket doses
- Requires adherence to the adherence measurement
- Potential for Hawthorne effect
- Expensive
- Not compatible with pill boxes

Wireless electronic adherence monitors



The SIMpill® SMART

Wireless electronic adherence monitors



PROS

- Capacity for real-time data/intervention
- Reduced data loss

CONS

- Cost
- Increased data management
- Cellular reception
- Batteries, SIM cards
- Potential for unintended disclosure
- Hawthorne effect may be high

Physico-chemical markers Taggants/tracers

- Products marked with an inert detectable taggant
- Adherence measured through breath test
- Xhale, Inc. (SMART)
  - Reminders sent to breathe into the device
  - Taggant recorded and transferred via USB for adherence management

- Ester taggant for vaginal gel (TFV and placebo) use shown to be feasible among 8 US women *(Morey, J Clin Pharm, 2013)*
  - *Taggants: 2-butyl acetate, 2-pentyl acetate, others*
  - *Breath collected before and up to 1 h after vaginal administration*
  - *Taggants and metabolites measured by mGC and GC/MS*
  - *Clear detection in breath after use*
  - *Side effects: burning sensation, bubblegum taste*
  - *Variable PK depending on taggants, gels, individuals*

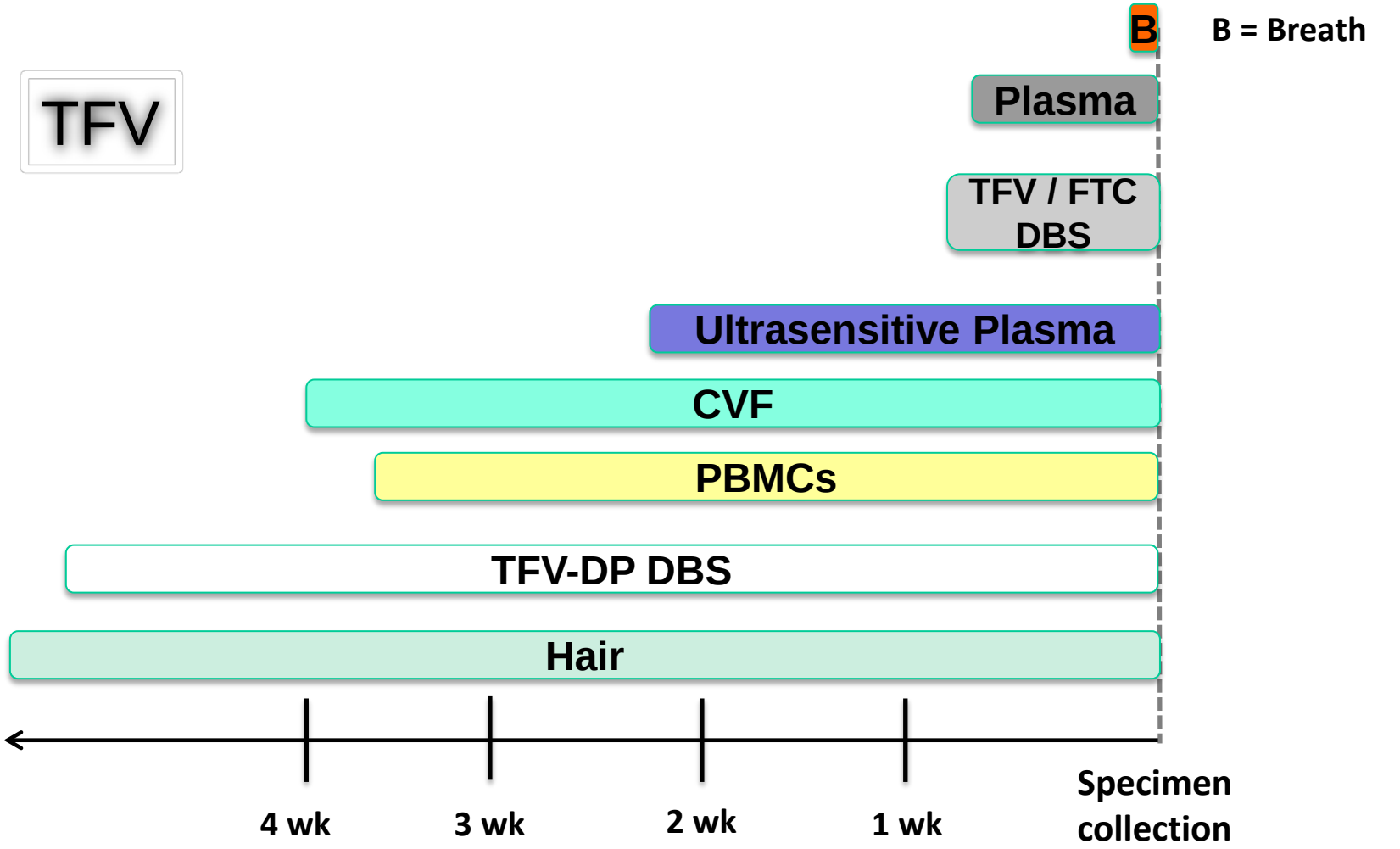
Biomarkers of adherence

Drug detection

- Major strengths
  - Direct measure of active product taken
  - Link between adherence and outcome (HIV infection)
- Major weaknesses
  - Requires specialized lab
  - Subject to individual biological variation
  - Need more empirical data on dose proportionality with topical PrEP (plasma, PBMC, CVFs, tissue, ECC)
  - Logistically challenging to implement in real-time in RCT
- Monitoring of pattern of use: limited (by combining biomarkers with long or short half-life)
- Biological samples/matrices:
  - \+ plasma, CVF, RBC
  - \- hair, PBMC, ECC

Modified from van der Straten, M2012

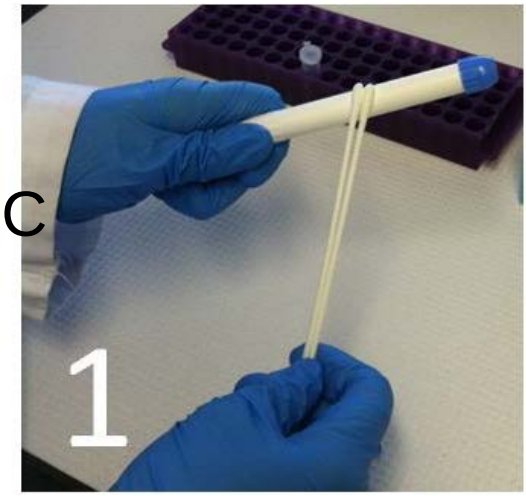
Drug detection windows
Informative of non-persistence



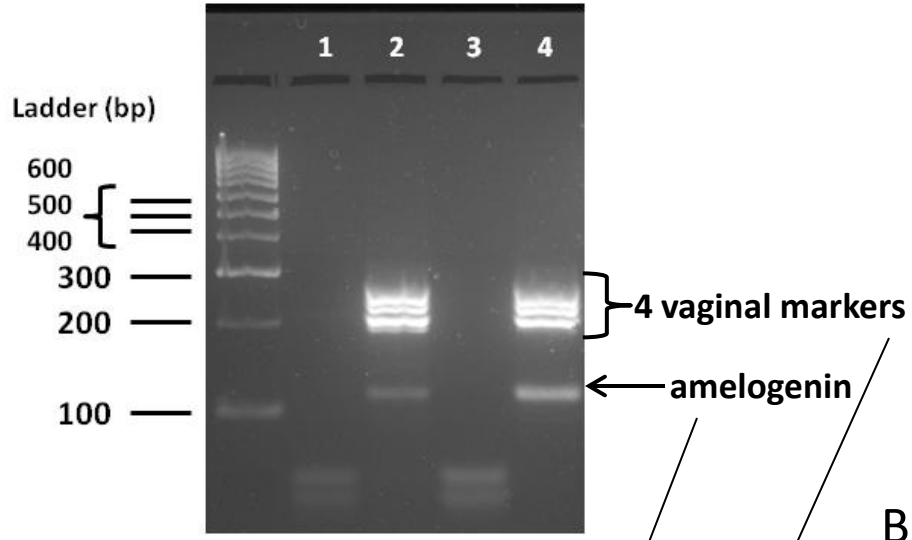
Modified from Liu, M2012

Composite measure of adherence using vaginal applicators

- Ideal: objective markers of vaginal insertion, semen/HIV exposure, drug deployment
- Vaginal insertion (existing methods): VIRA, UVL, DSA
- New biomarkers of vaginal insertion and semen exposure
- DNA and protein extracted from surface of applicators (swabs)
- Markers detected by multiplex PCR or IHC
- Detection of TFV (by LC/MS/MS)



DNA-based biomarkers collected from vaginally inserted and sham applicators

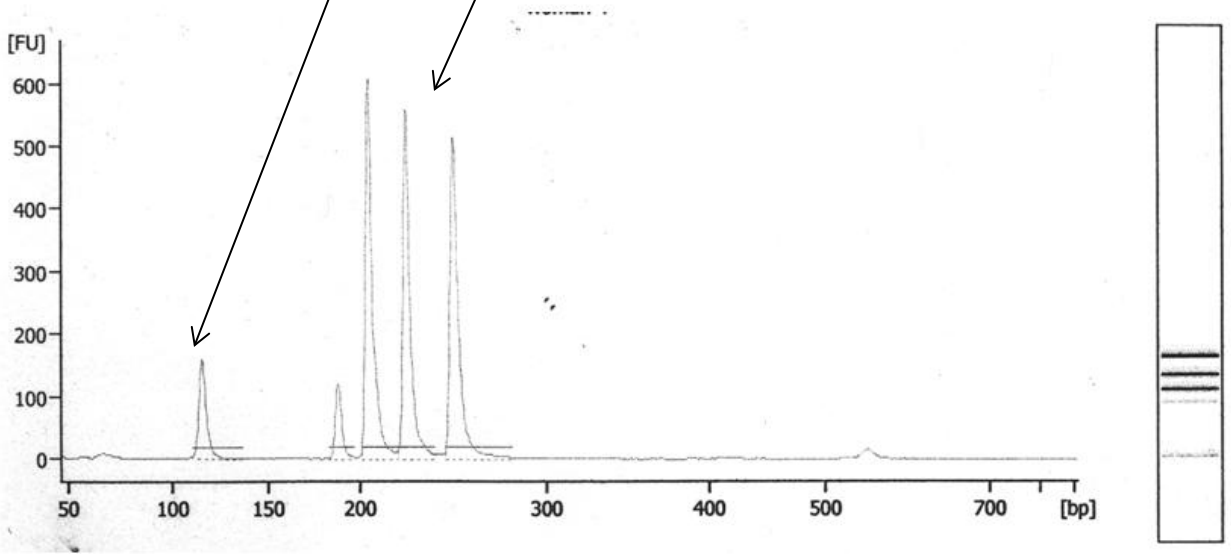


Lane 1: Sham applicator
Lane 2: Inserted applicator
Lane 3: Negative control
Lane 4: Vaginal Swab

Multiplex PCR

Jacot, under review

Bioanalyzer 2100/Lab Chip



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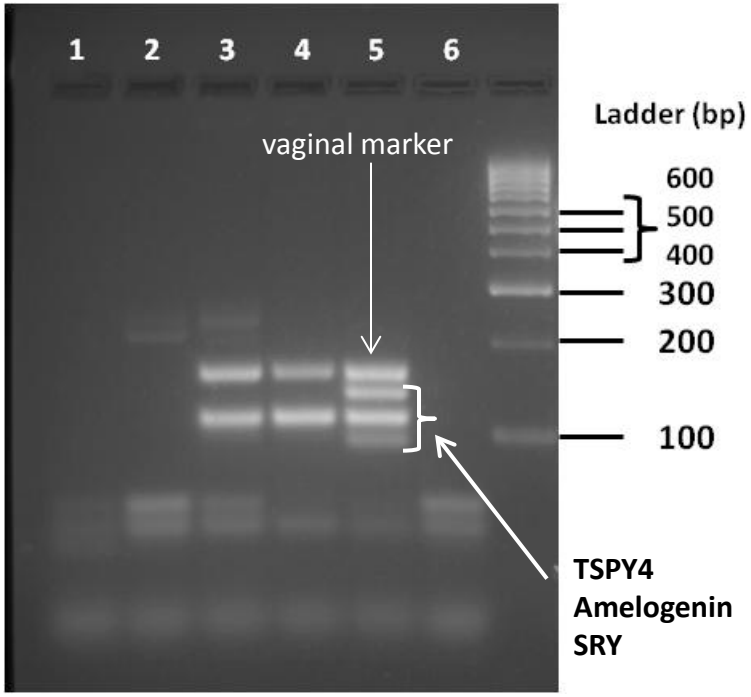
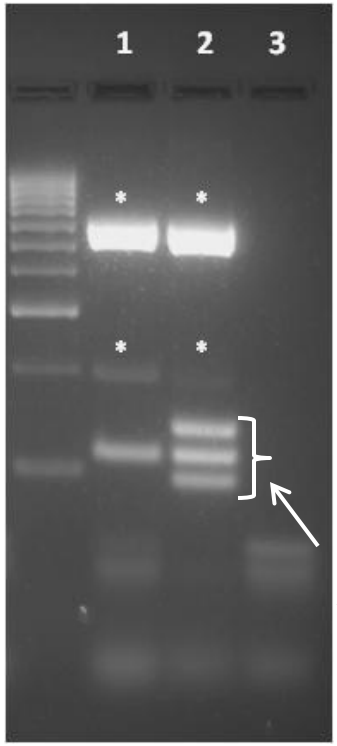
DNA-based biomarkers from vaginally inserted and sham applicators with and without semen exposure

Lane 1: No contact (control) applicator
Lane 2: Sham applicator
Lane 3: Inserted applicator
Lane 4: Vaginal Swab
Lane 5: Inserted applicator + semen exposure
Lane 6: Negative control



Jacot, under review

DNA biomarkers can determine vaginal insertion pre- and post-semen exposure



* vaginal markers

TSPY4
Amelogenin
SRY

Lane 1: Inserted applicator – before coitus
Lane 2: Inserted – after coitus
Lane 3: Negative control

Jacot, under review

DNA/Protein biomarkers show robust, high sensitivity and specificity

Variable	7 Days	30 Days
Sensitivity (%)		
All Inserted Apps	98.3	98.3
No prior gel	100	100
With prior gel	100	100
Wiped	95	95
Specificity (%)		
All Sham	100	100

Data expressed as %

Thurman, STD, in press

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CONRAD 125 study results

DNA/Protein Biomarkers Increased Sensitivity/Specificity at 30d

Variable	VIRA or UVL	DNA/Protein	p value
VIRA - 30 DAYS			
Sensitivity All Applicators	187/360 (51.9%)	117/119 (98.3%)	**<0.0001**
Sensitivity Wiped	34/120 (28.3%)	37/39 (95%)	**<0.0001**
Specificity (Sham)	94/120 (78.3%)	40/40 (100%)	**0.0013**
UVL Light - 30 Days			
Sensitivity All Applicators	332/360 (92.2%)	117/119 (98.3%)	**0.02**
UV Specificity (Sham)	79/120 (65.8%)	40/40 (100%)	**<0.0001**

Thurman, STD, in press

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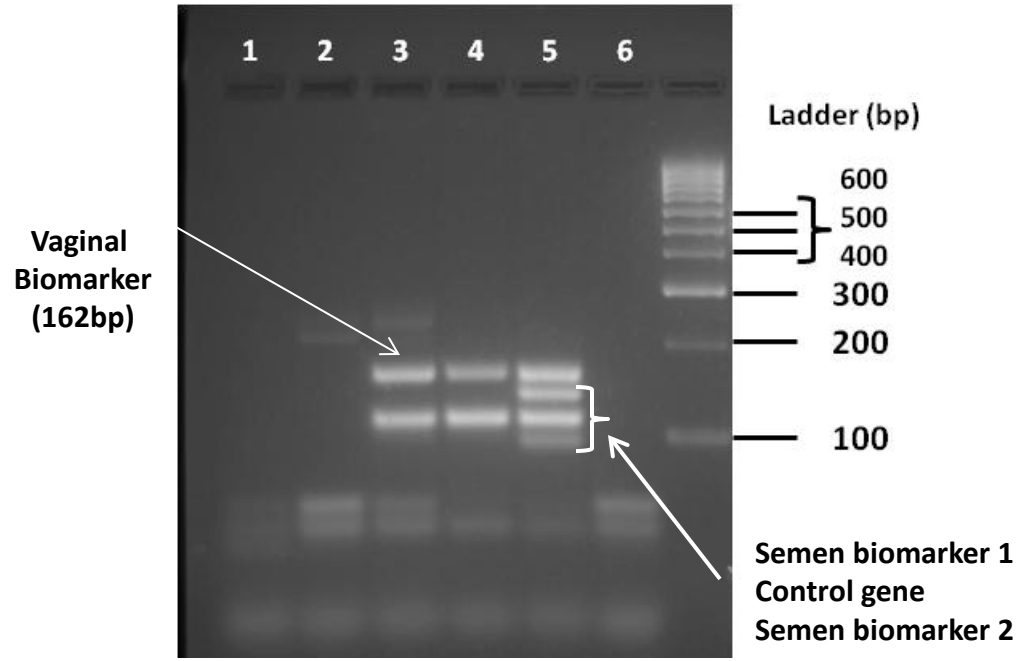
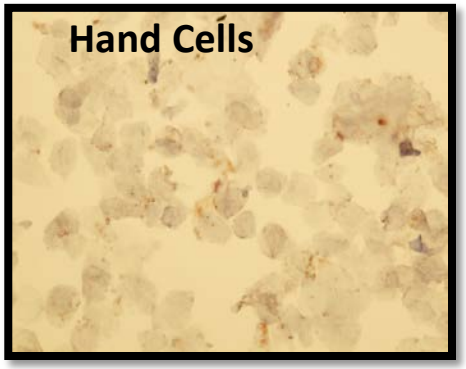
New objective markers of adherence

DNA Biomarkers



Protein Biomarker



Jacot, under review

Drug Expulsion

	Vaginally Inserted				Controls (n=2)	
	1	**2**	**3**	**4**	**Sham**	**Blank**
TFV (ng)	1120	1250	659	577	BLD	BLD
Storage (days)	32	55	33	13	-	-

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Summary and Conclusions

- Adherence is a complex process influenced by multiple factors (TPP, biological, behavioral, socio-cultural, etc.), which impacts PK/PD and PrEP effectiveness
- Adherence can be measured by different methods
- Traditional methods (e.g., self-report) are easier to implement but highly subjective
- More objective measures of adherence include biological endpoints such as drug presence/concentration
- Composite objective measures of vaginal insertion, semen exposure and drug/placebo release are in development/validation
- Different measures and markers offer complementary information; best measure of adherence likely to result from combination of various types of evaluations

Collaborators and Acknowledgements

CONRAD Intramural Research

- Terry Jacot
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- Ariane van der Straten

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EVMS
Eastern Virginia Medical School

Thank you


USAID
FROM THE AMERICAN PEOPLE


PEPFAR


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Alternative trial designs in other fields

Robert Cuffe *June 23, 2014*

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Scott Berry (Berry Consultants)*

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ViiV Healthcare

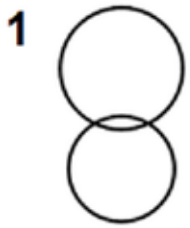
Alex Rinehart

Kim Smith

Jim Goodrich

Outline

- Seamless studies
- Post-hoc enrichment
- Adaptive enrichment (in theory)
- Platform trials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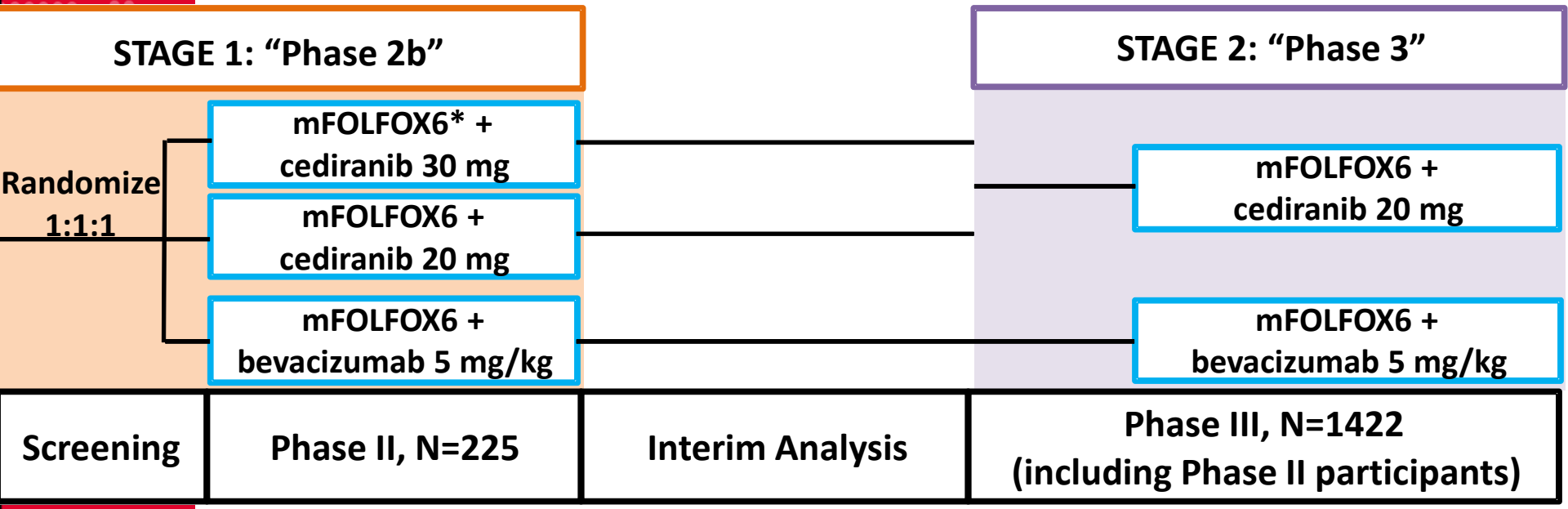
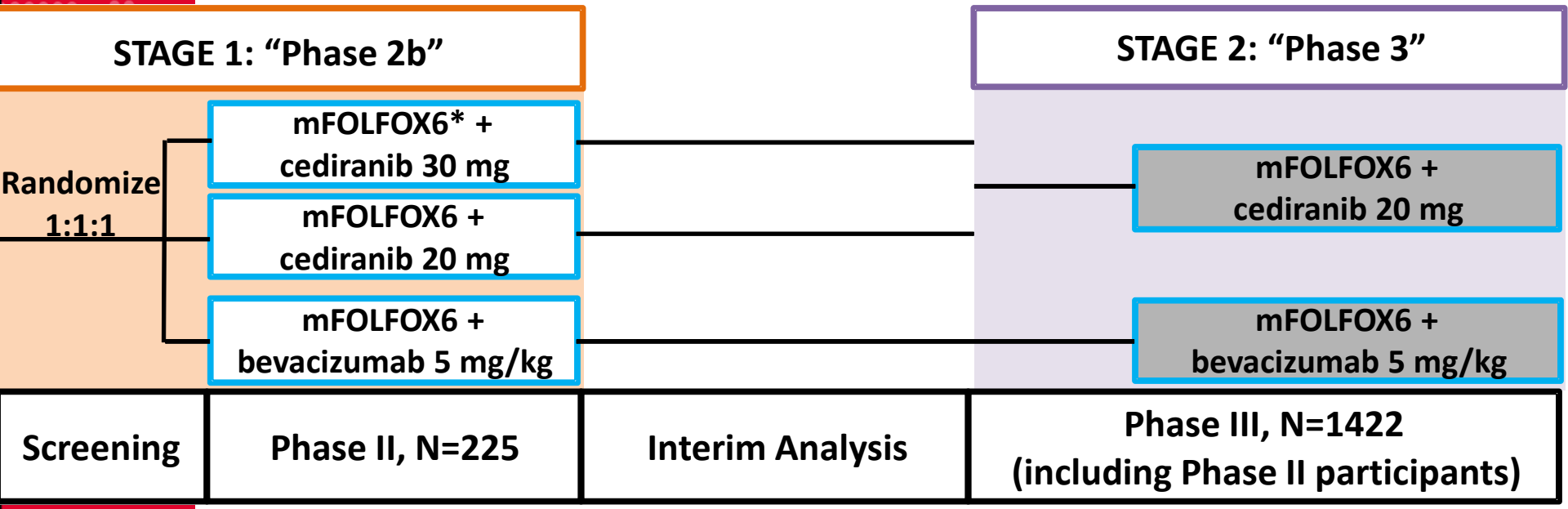
Seamless studies

DOI: 10.1002/pst.1622

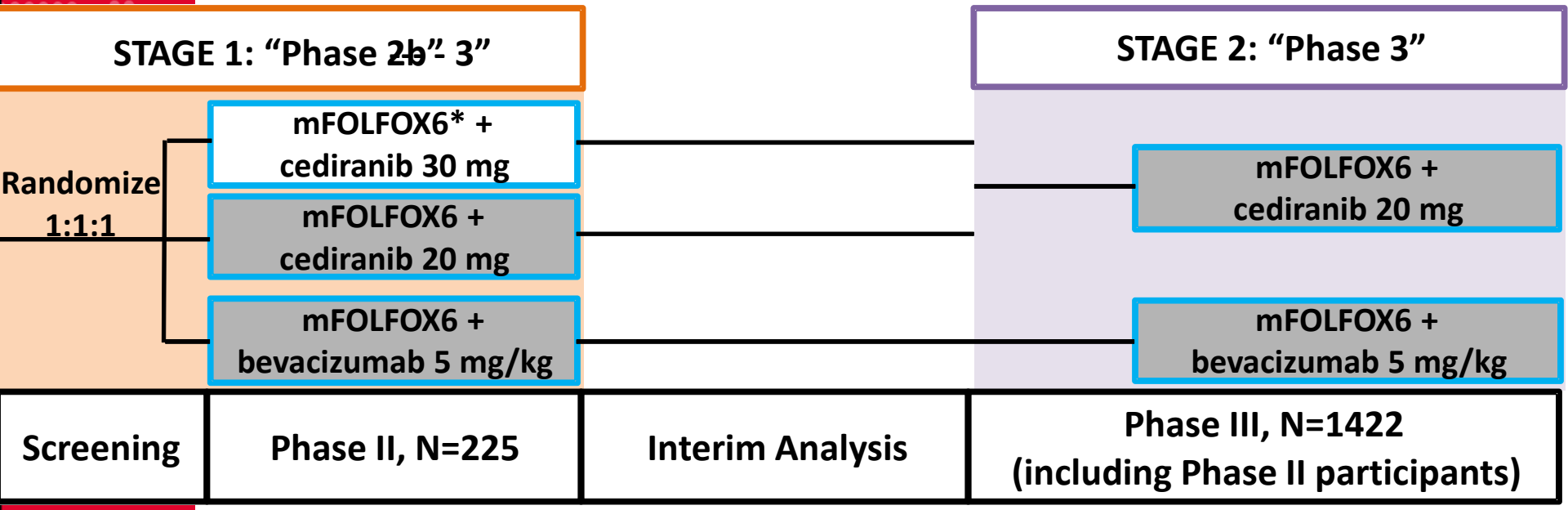
HORIZON: cediranib for MCRC



HORIZON: cediranib for MCRC



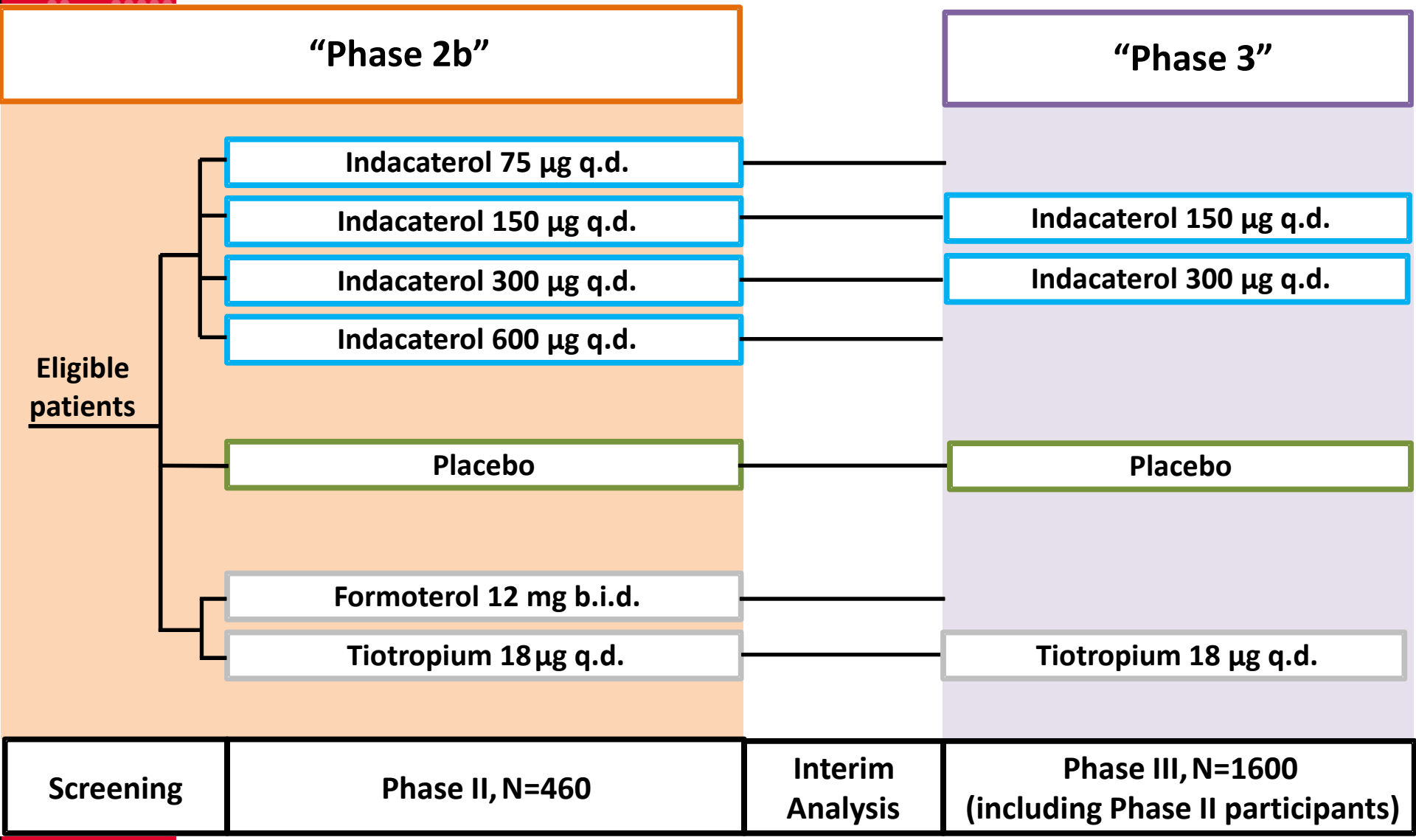
HORIZON: cediranib for MCRC



Lessons

- Visualise label at outset of Phase ~~2b~~ 3 portion
- Cannot incorporate lessons of 2b without access to data
- Cannot change clinical management without changing the question

INHANCE: indacaterol for COPD



Post-hoc enrichment

Accumulating *KRAS* Evidence in mCRC

Phase II Studies

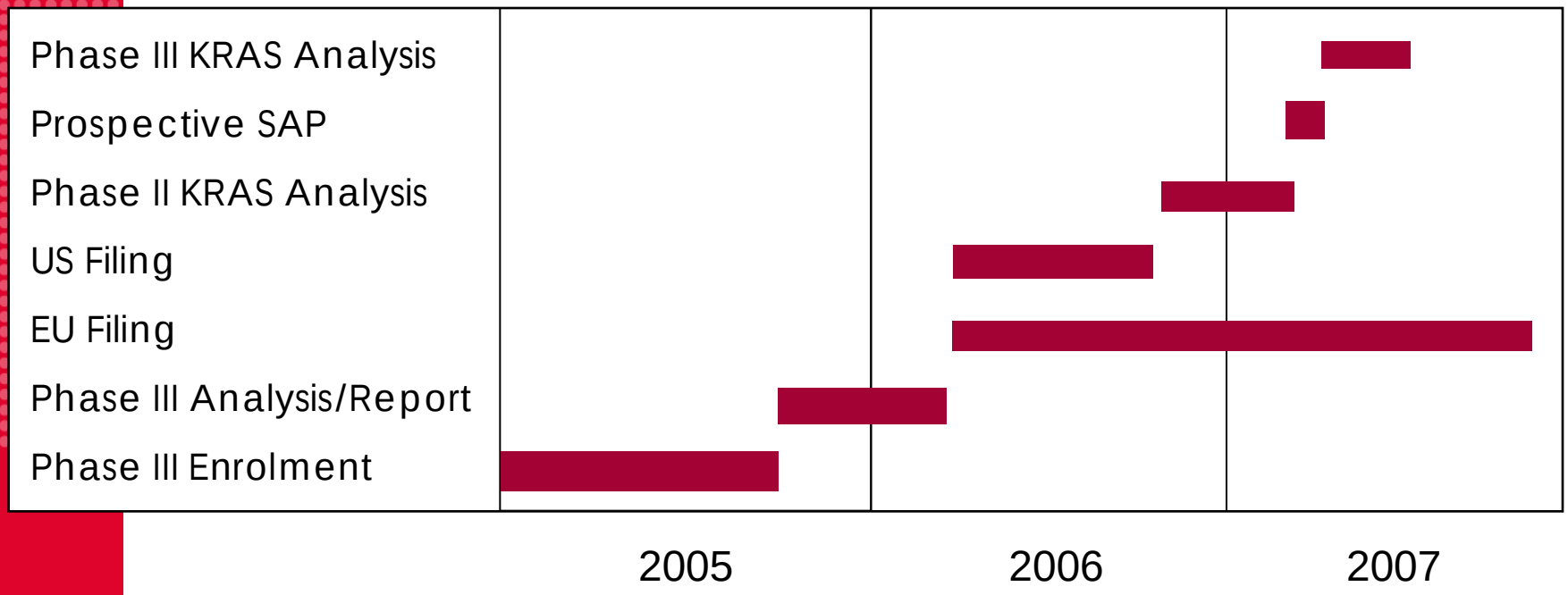
Publication	Treatment	N	KRAS Status	
			Mutant	Wild-Type
Moroni et al (2005)	Pmab, Cmab ± CT	31	2/10 (20%)	8/21 (38%)
Benvenuti et al (2007)	Pmab, Cmab ± CT	48	1/16 (6%)	10/32 (31%)
De Roock et al (2007)	Cmab ± CT	37	0/17 (0%)	8/17 (46%)
Di Fiore e al (2007)	Cmab + CT	59	0/16 (0%)	12/43 (28%)
Finocchiaro et al (2007)	Cmab ± CT	81	2/32 (6%)	13/49 (27%)
Khambata-Ford et al (2007)	Cmab	80	0/30 (0%)	5/50 (10%)
Lievre et al (2007)	Cmab ± CT	78	0/27(0%)	24/49 (49%)

- All single arm studies
- Different *KRAS* assay kits used

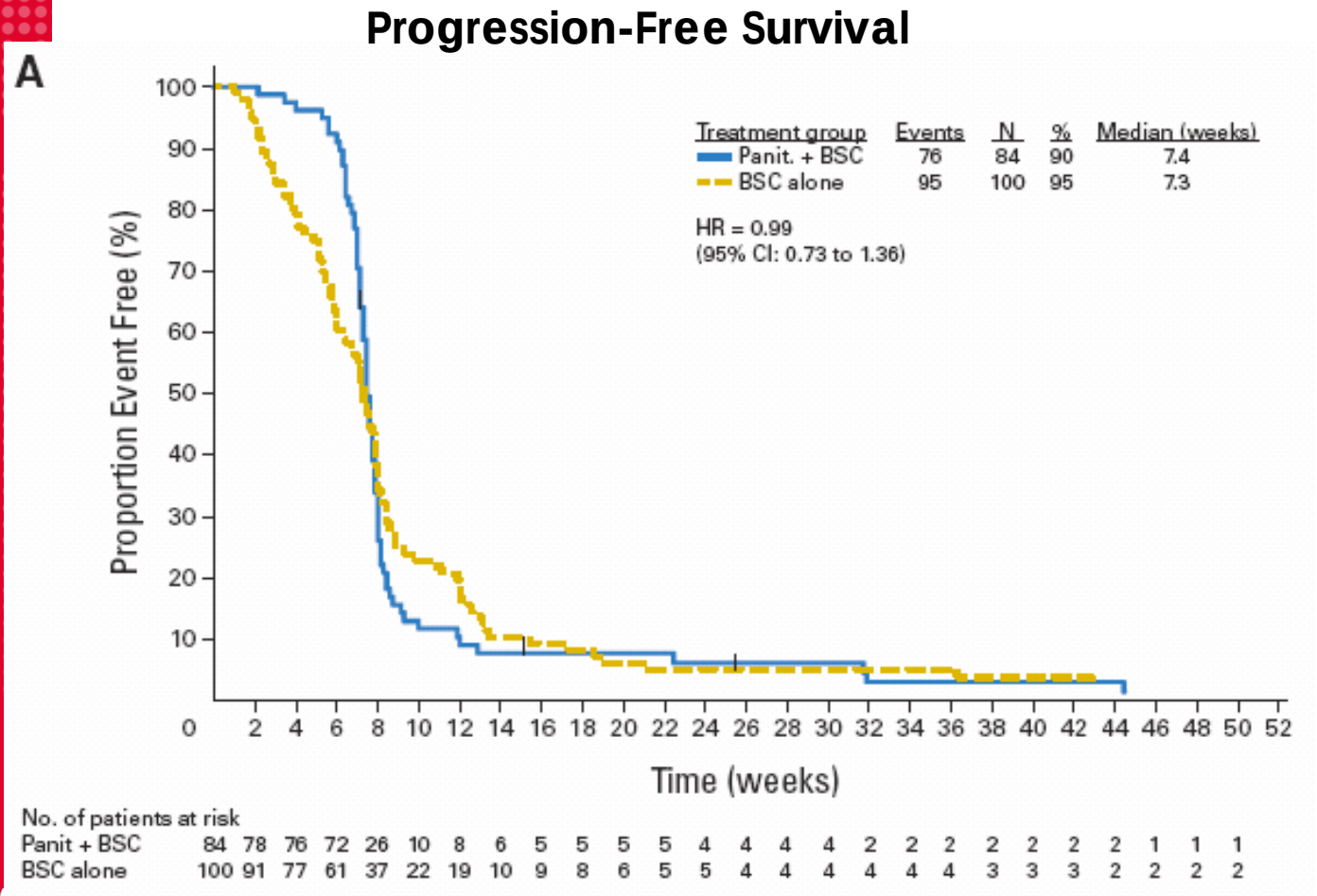
ViiV Healthcare

Activity Timeline

Timeline for *KRAS* Evidence

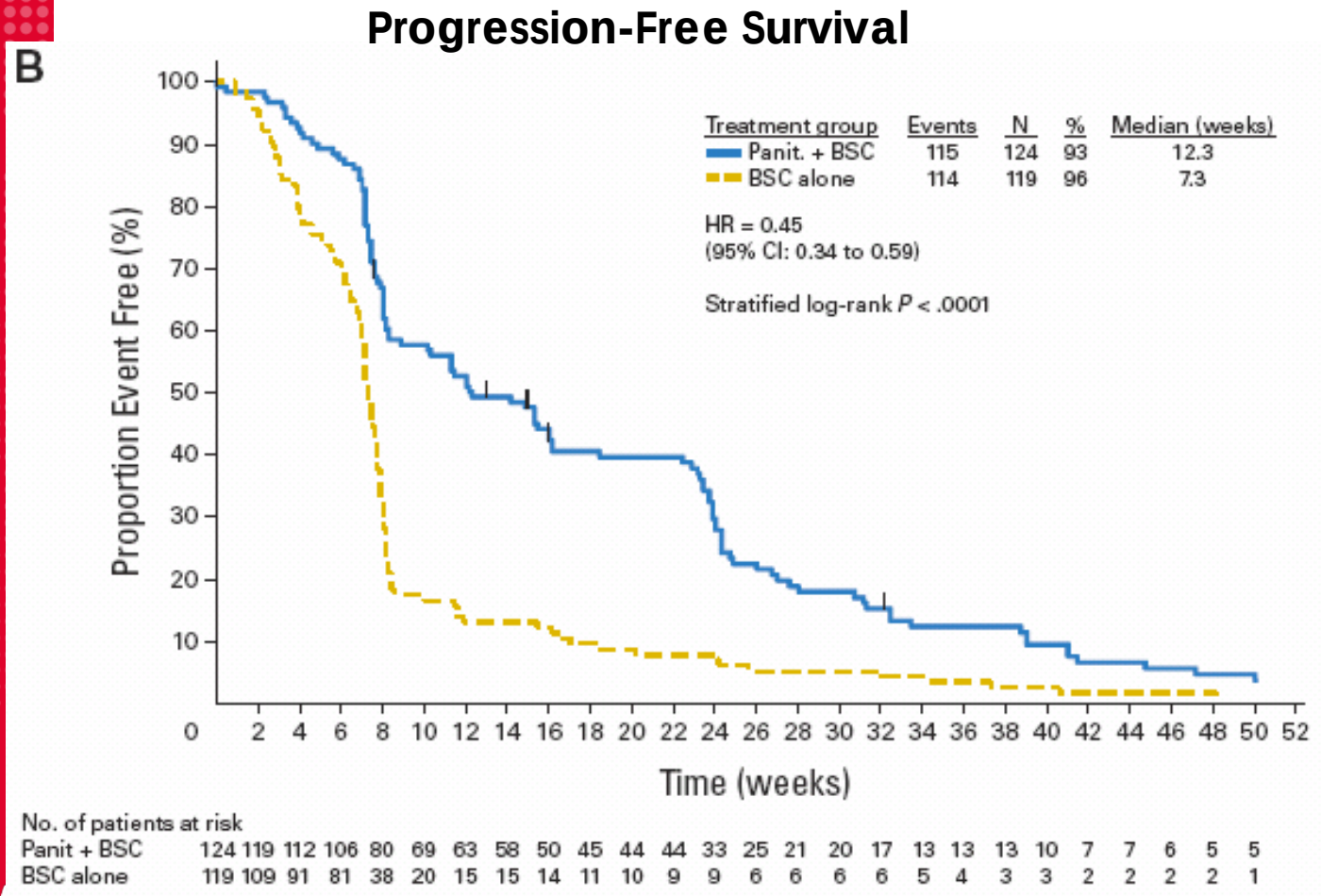


Outcome in Patients with *KRAS* Mutant Tumours



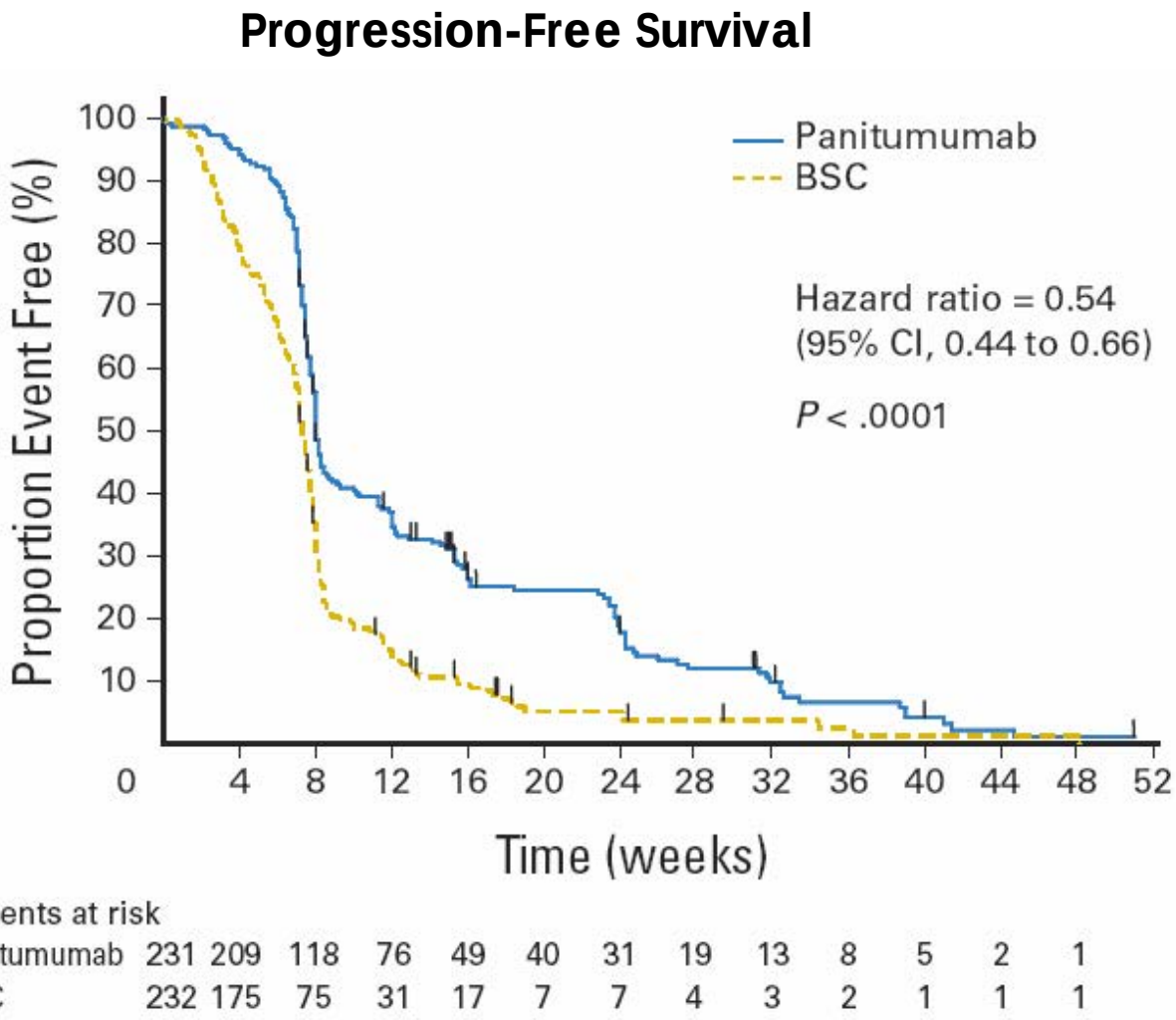
Amado et al (2008) JCO, 26

Outcome in Patients with *KRAS* Wild-Type Tumours



Amado et al (2008) JCO, 26

Confirmatory Trial Result



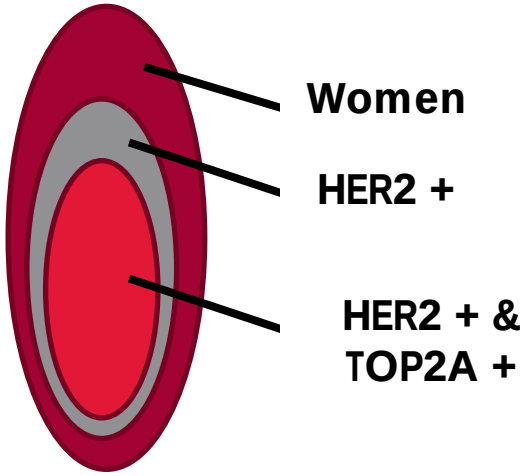
Van Cutsem et al (2007) JCO, 25

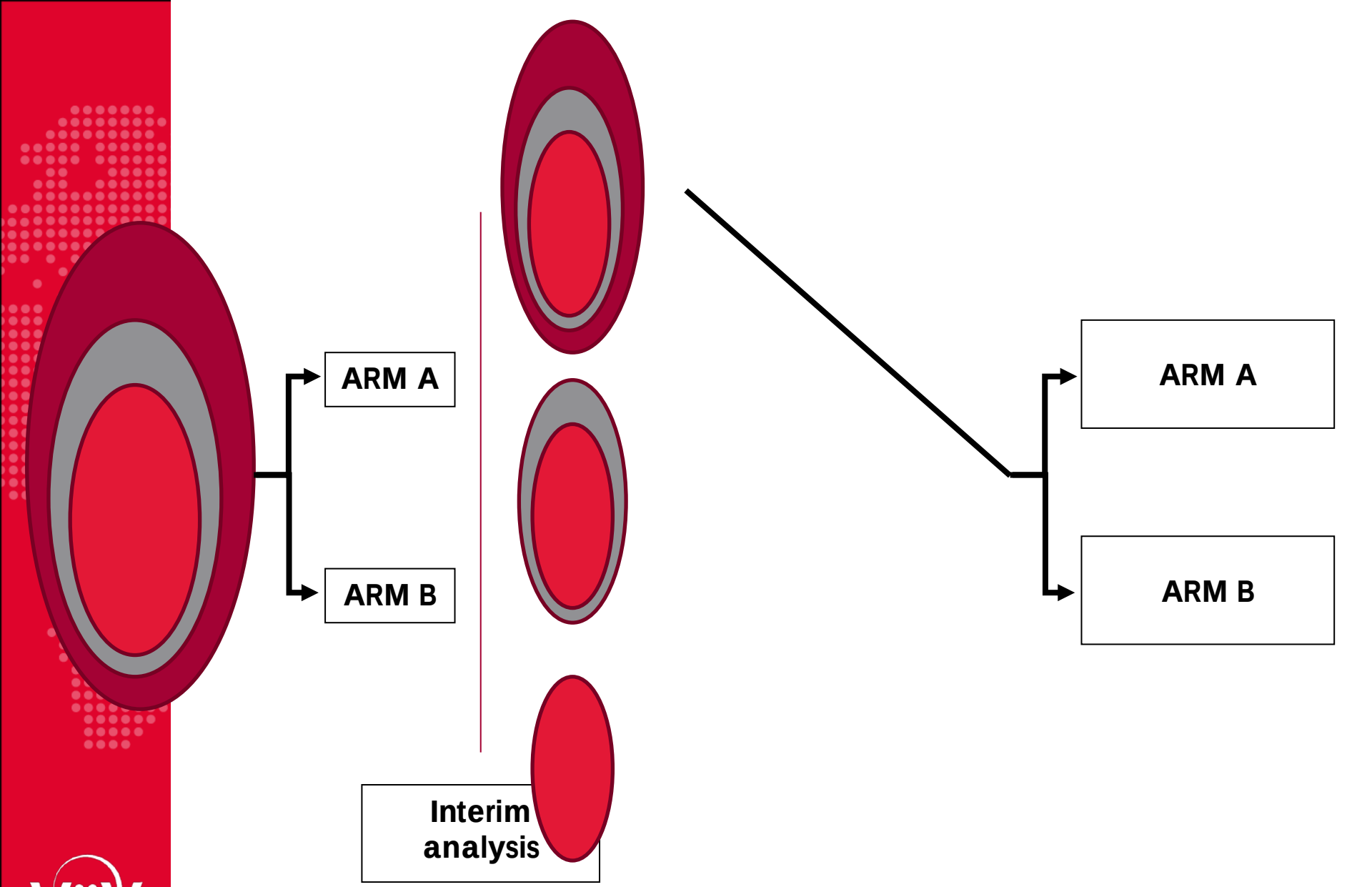
Lessons

- Post-hoc enrichment improved a successful trial
- Biomarkers are pre-randomisation

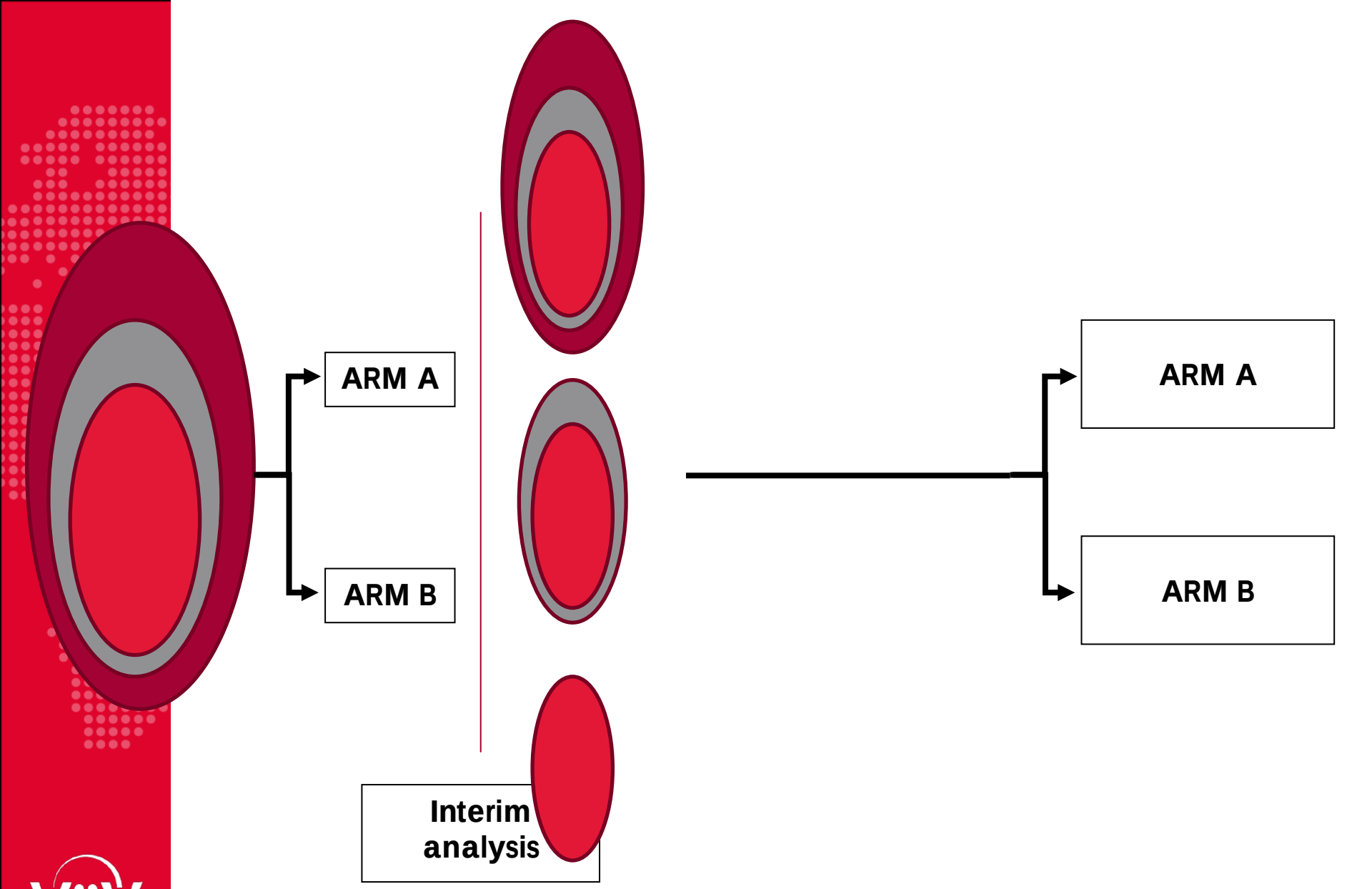
Adaptive enrichment

Theoretical example in metastatic breast cancer

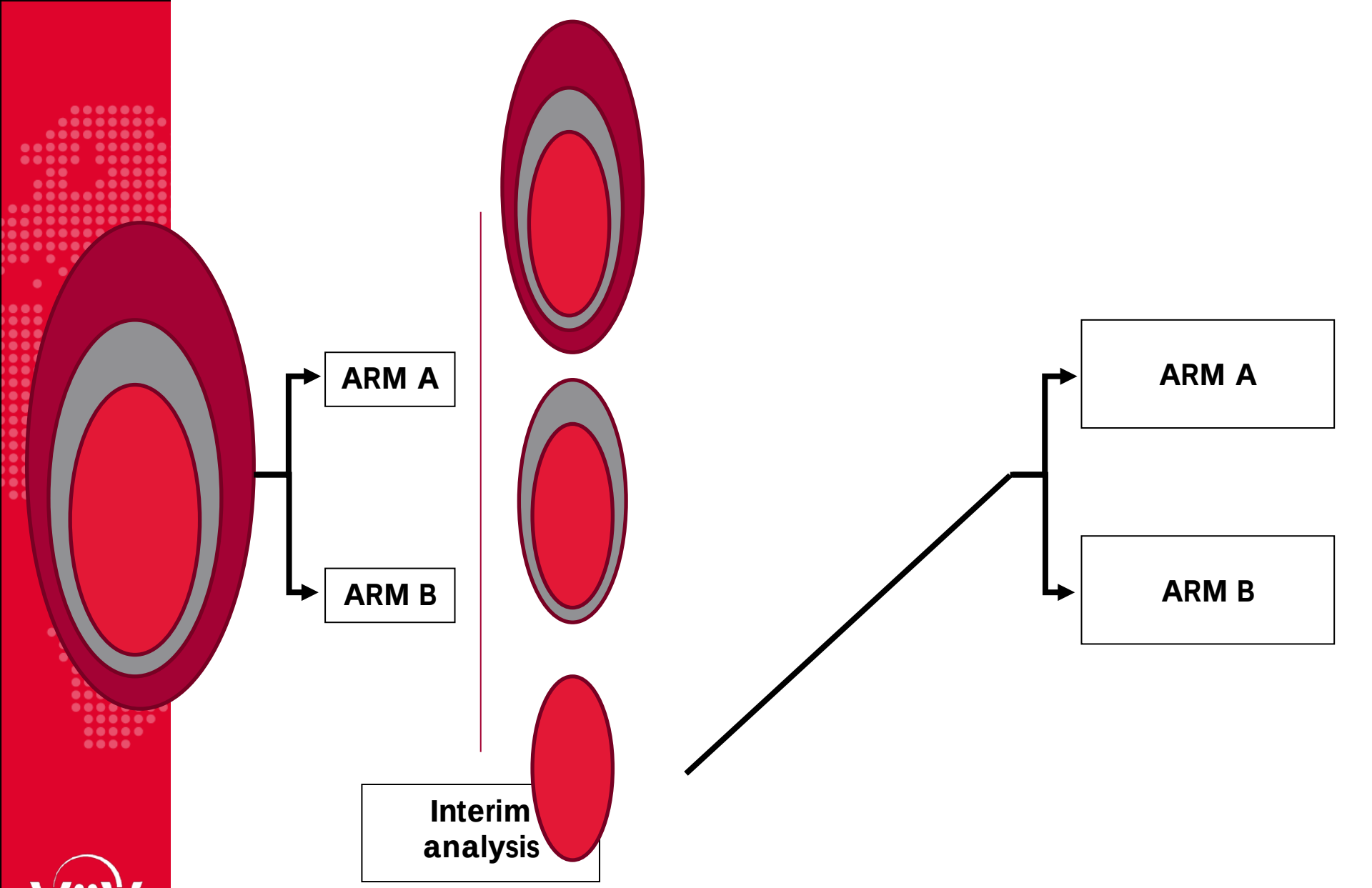




DOI: 10.1002/bimj.200900003



DOI: 10.1002/bimj.200900003

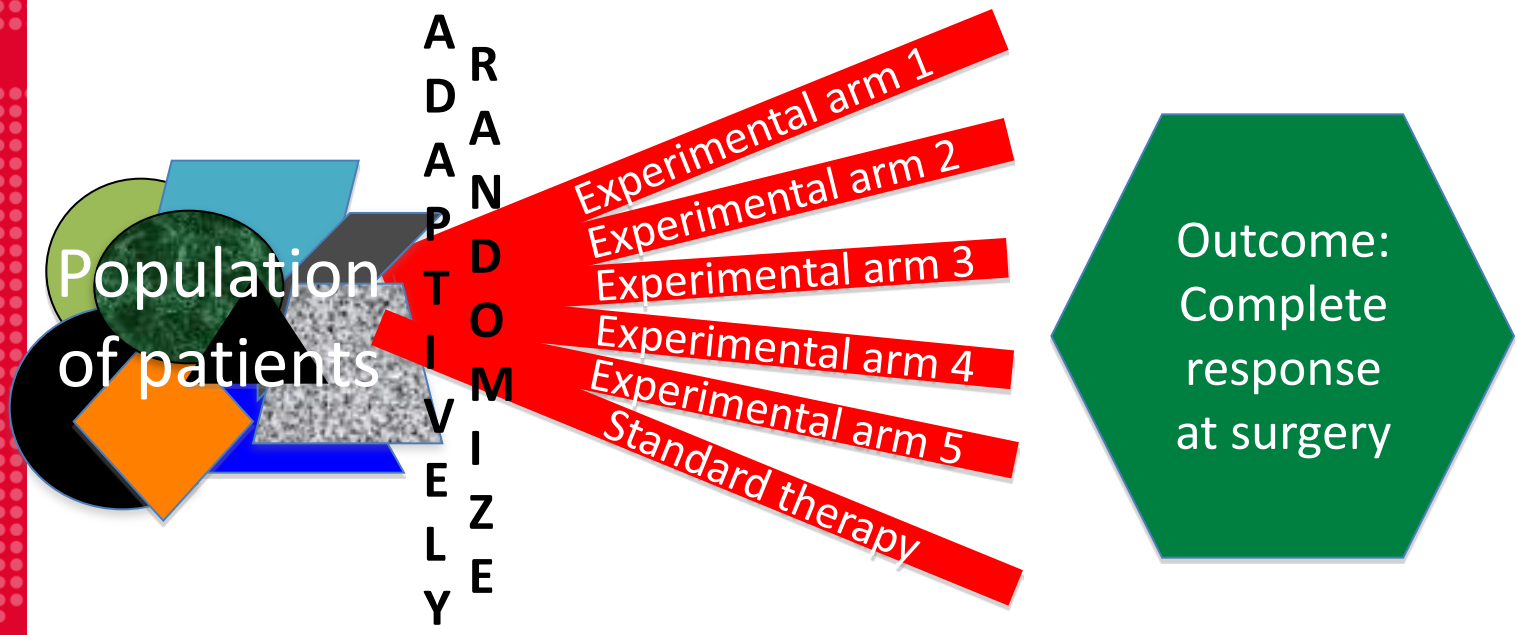


DOI: 10.1002/bimj.200900003

Platform trials

lspy2.org

I-SPY 2 trial: phase 2 study in LABC



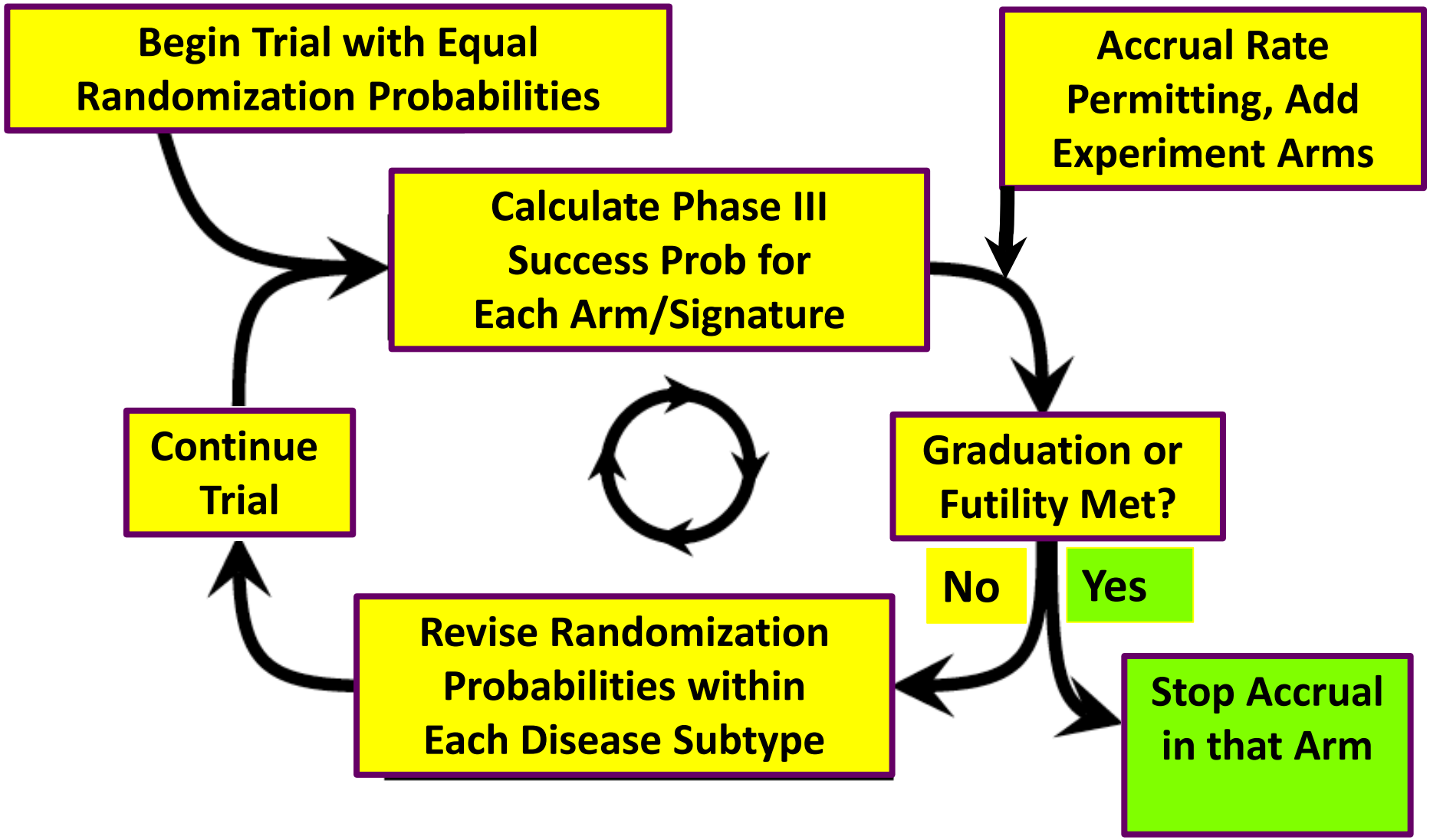
Subtypes

- Mamma print (+/-), HR (+/-), HER2 (+/-)

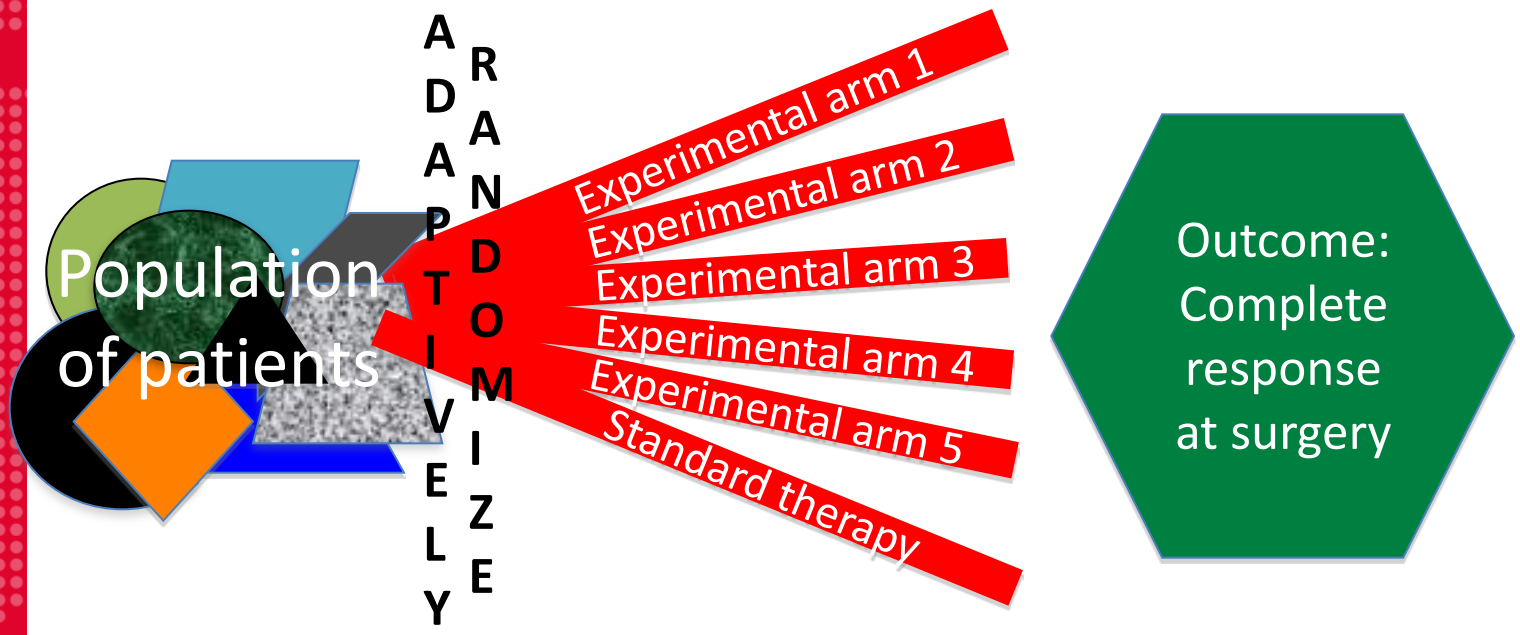
- Qualifying biomarkers
  - "Assays with promise to predict response to standard chemotherapy and novel agents"
  - Performed under CLIA conditions, may be used for stratification

- Exploratory biomarkers

I-SPY 2 Adaptive Process



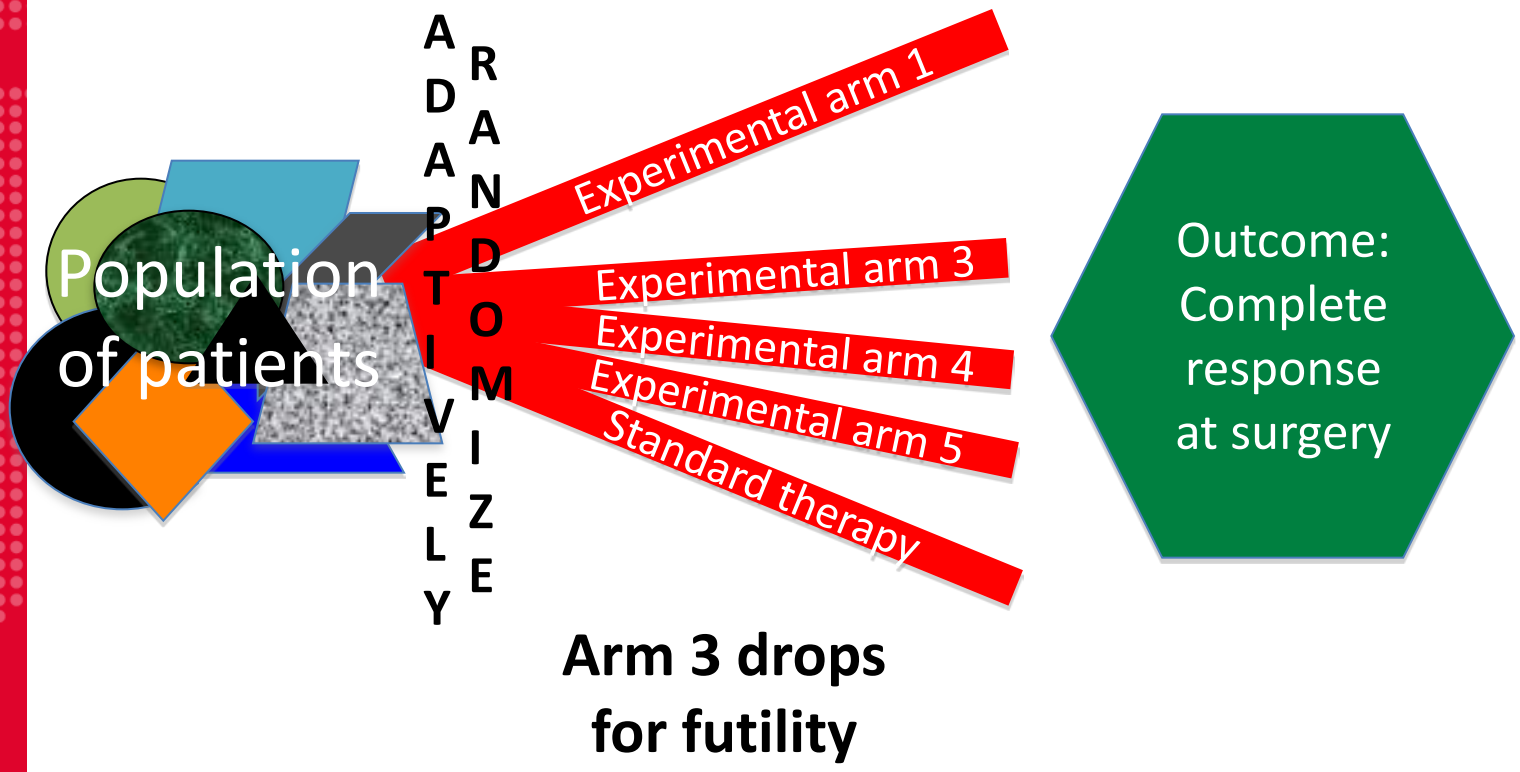
I-SPY 2 trial


Population of patients
ADAPTIVELY
RANDOMIZE
Experimental arm 1
Experimental arm 2
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy
Outcome: Complete response at surgery

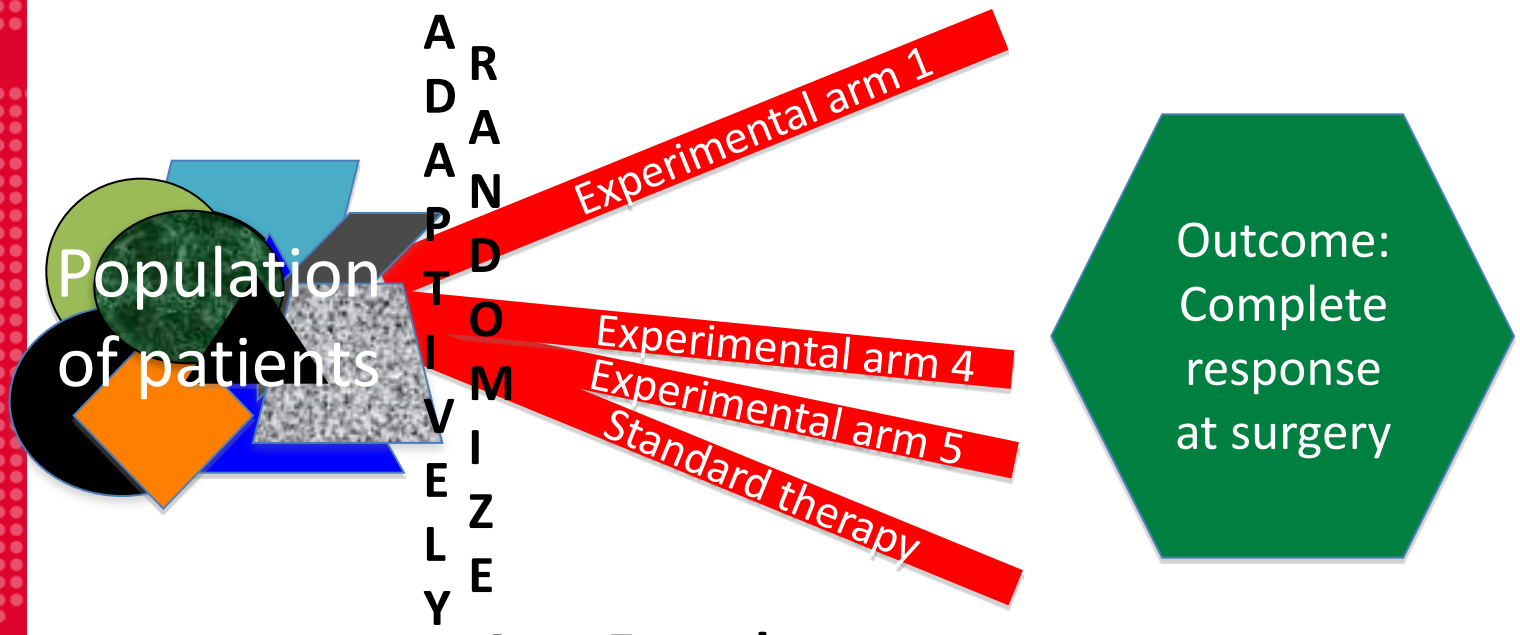
I-SPY 2 trial

Arm 2 graduates to small focused Phase 3 trial

I-SPY 2 trial

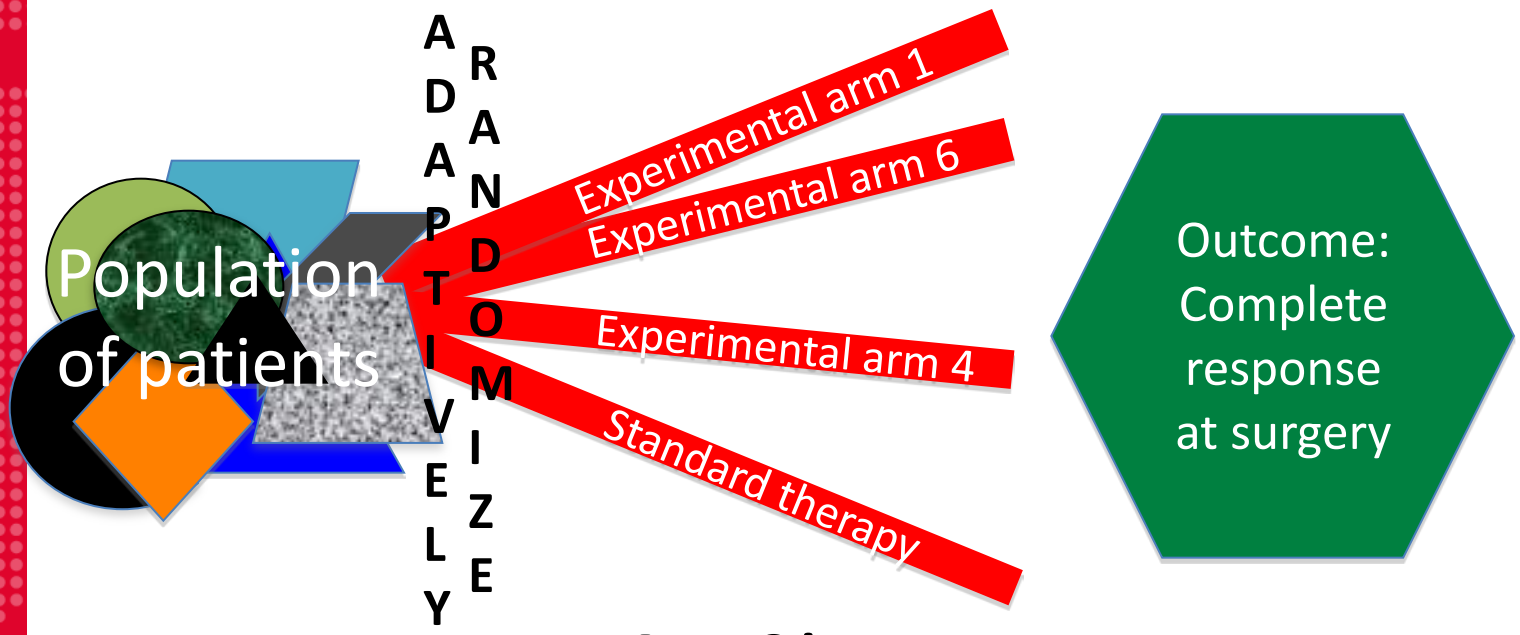

Population of patients
ADAPTIVELY RANDOMIZE
Experimental arm 1
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy
Outcome: Complete response at surgery
Arm 3 drops for futility

I-SPY 2 trial



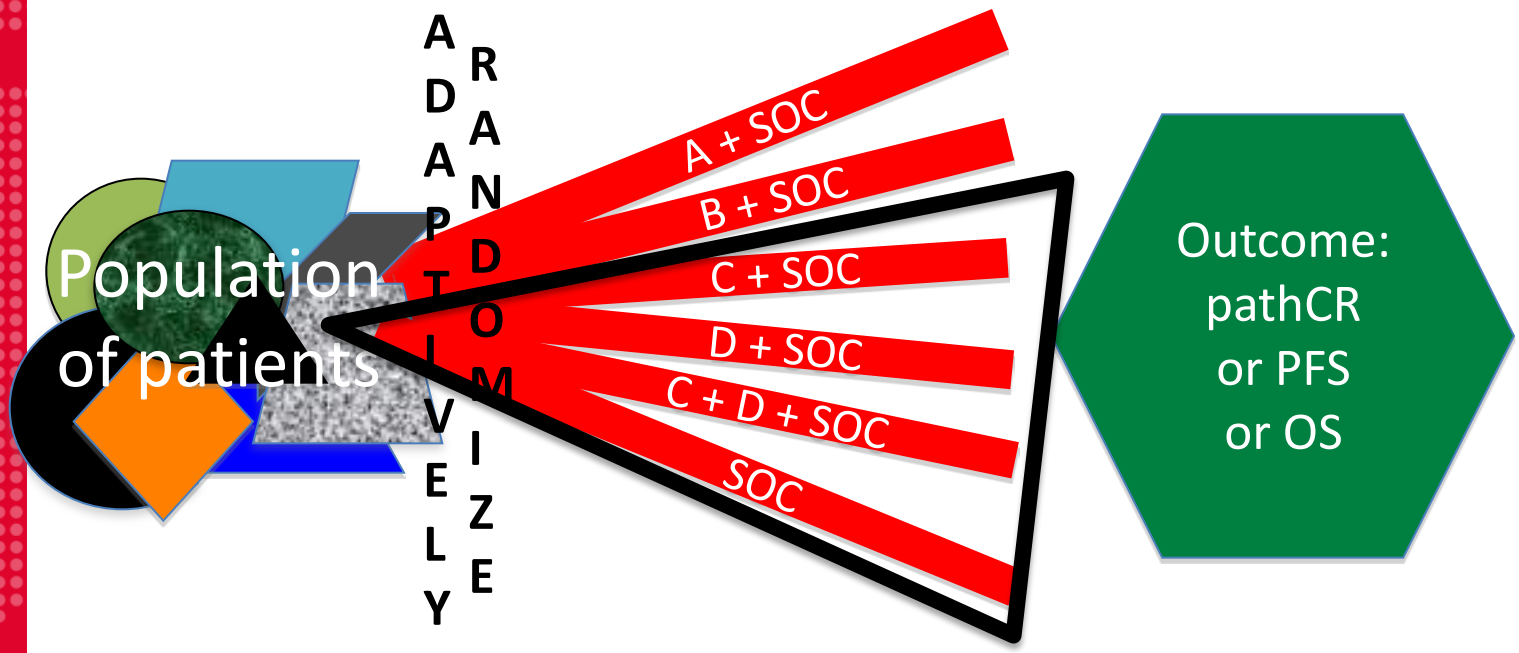
Arm 5 graduates to small focused Phase 3 trial

I-SPY 2 trial



Arm 6 is added to the mix

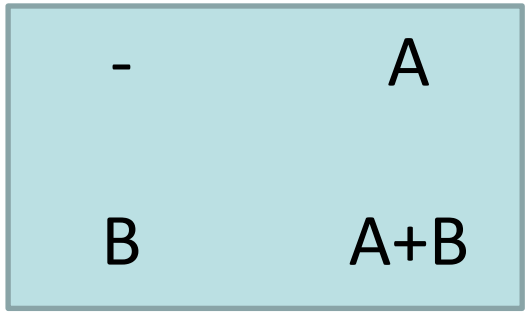
I-SPY 2 trial (multiple evaluations)



Substudy: Adaptively randomized factorial

Factorial designs

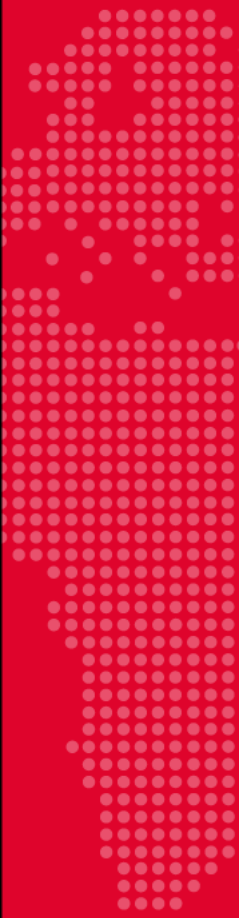
- Normal design: 4 arms x N/2
  - Study 1: A vs. -
  - Study 2: B vs. -
- Multi-arm: 3 arms x ~N/2
  - A vs. B vs. -
- Factorial: 4 arms x ~N/4
  - A+B vs. A vs. B vs. -



Conclusions

- Adaptive trials allow you to tweak a parameter
- Pivotal evidence is a) statistical and b) for the label
- Enrichment is prospective for patients, can be retrospective for studies
- Can evaluate multiple agents efficiently in single studies

ViiV Healthcare



- Phase 3/pivotal/confirmatory:
  - Is there an identifiable group of individuals for whom the decision to prescribe in this way will lead on average to more benefit than harm (compared to available therapy)?

- Phase 2/learnatory:
  - Does this thing work?

Workshop on Adaptive Enrichment Trial Design for Microbicides:

Regulatory perspective on adaptive designs

Dionne L. Price, Ph.D.
Division of Biometrics IV
OB/OTS/CDER/FDA

June 23, 2014

Outline

- Adaptive Designs
- Enrichment Strategies
- Adaptive Enrichment
- Microbicides: Enriching for Adherence
- Concluding Remarks

The views expressed pertaining to enriching for adherence in trials of microbicides are those of the author and should not be construed to represent FDA's views and policies.

Guidance for Industry

Adaptive Design Clinical Trials for Drugs and Biologics

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Robert O'Neill or Sue-Jane Wang at 301-796-1700, Marc Walton at 301-796-2600 (CDER), or the Office of Communication, Outreach and Development (CBER) at 800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2010

Adaptive Design Guidance

- **Definition – Adaptive design clinical study**
  - a study that includes a *prospectively* planned modification of one or more aspects of the study design and hypothesis based on accumulating data from subjects in the study

- **Possible adaptations**
  - Study eligibility criteria
  - Randomization procedure
  - Treatment regimens
  - Sample size
  - Primary endpoint
  - Analytic methods

Adaptive Design Guidance

- **Generally well understood adaptations**
  - Eligibility criteria based on pre-treatment data
  - Maintain power based on blinded analysis of aggregate data
  - Interim results of an outcome unrelated to efficacy
  - Group sequential methods and unblinded analyses for early study termination
  - Analytic adaptations not dependent on within study, between group outcome differences

Adaptive Design Guidance

- **Less well understood adaptations**
  - Dose selection
  - Outcome dependent adaptive randomization
  - Sample size modification based on interim-effect size estimates
  - Patient population based on treatment-effect estimates
  - Endpoint selection based on interim estimate of treatment effect
  - Multiple study design features in a single study
  - Non-inferiority studies

Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Robert Temple, 301-796-2270, (CBER) Office of Communication, Outreach and Development, 301- 827-1800, or (CDRH) Robert L. Becker, Jr., 301-796-6211.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
December 2012

Enrichment Strategies Guidance

- **Definition - enrichment**
  - the *prospective* use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population
- **Strategies**
  - Prognostic enrichment
    - identify high risk population
  - Predictive enrichment
    - identify likely responders
  - Decrease heterogeneity
    - encourage compliance
    - reduce placebo response and spontaneous improvement

Enrichment Strategies Guidance

- **Generally accepted ways to decrease heterogeneity**
  - Define entry criteria carefully
  - Identify and select patients likely to comply
    - **Note:** Removing poor compliers identified post-randomization is not acceptable
  - Use placebo lead-in periods prior to randomization
  - Enroll patients who give consistent baseline values
  - Exclude patients unlikely to tolerate treatment
  - Exclude patients who are likely to drop out for non-medical reasons.

Enrichment Strategies Guidance

Adaptive enrichment, from the Guidance

- **Definition – Adaptive enrichment**
  - An adaptive design that employs an enrichment strategy during the course of the study
- Should be explicit in the protocol
- Analysis should adequately account for adaptation
- Example:
  - Interim analysis with goal of potentially changing entry criteria to emphasize a better-responding subgroup.

Microbicides: Enriching for adherence

- **One possible example**:
  - Randomize from broad population
  - Pre-specify what constitutes a sound definition of poor complier or what predicts adherence
  - At interim analysis, restrict enrollment to those likely to comply and possibly increase the sample size for subgroup
  - Final analysis on both overall population and subgroup of those likely to comply

- Utility if baseline measures that predict adherence can be used to identify subgroup(s) of responders

Concluding Remarks

- Adaptive enrichment designs may be useful in some scenarios

- Challenges may include
  - Logistical issues
  - Determination of appropriate baseline characteristics to "predict" response
  - Rate of recruitment may decrease in enriched subgroup
  - Statistical methods for design and analyses may be more complex
  - Generalizability of results
  - Interpretation of results

Concluding Remarks

- **Adaptive Design Guidance**
  - " The increased complexity of some adaptive design studies and uncertainties regarding their performance characteristics may warrant earlier and more extensive interactions than usual"

- **Enrichment Strategies Guidance**
  - "Given the potentially complex interpretation of studies using enrichment designs, we strongly recommend early discussions with the Agency on plans to use them."