HPTN 035:
What have we learnt?

Presenter:
Salim Abdool Karim on behalf of the HPTN 035 team

MTN Regional Meeting
Cape Town, South Africa
19-23 October 2009

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HPTN 035 study team

Sponsors:	NIH (R Black, L Soto-Torres, S Estep), Indevus Pharmaceuticals (A Profy), ReProtect (T Moench)
Protocol Chair:	Salim S Abdool Karim
Blantyre, Malawi:	T Taha, N Kumwenda, B Makanani, S Hurst, C Nkhoma, E Kachale
Durban & Hlabisa, SA:	G Ramjee, R Govinden, N Coumi, N Dladla-Qwabe, S Ganesh, N Morar
Harare, Zimbabwe:	ZM Chirenje, N Padian, A van der Straten, T Magure, M Mlingo, N Mgodi
Lilongwe, Malawi:	I Hoffman, F Martinson, T Tembo, L Chinula, T Mvalo
Lusaka, Zambia:	G Parham, M Kapina, C Reid, M Kasaro, A Brahmi
Philadelphia, USA:	L Maslankowski, J Prince, S Whittington, E Yu
Coordinating Center:	W Cates, A Coletti, K Gomez, R White
Statistical Center:	M Cianciola, C Kelly, C Miller, B Mâsse, B Richardson, T Fleming
Network Laboratory:	S Hillier, E Piwowar-Manning, L Rabe

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Overview

1. Phase IIb vs Phase III design: phase IIb delivers
2. Meet pairwise target in 4-arm trial
3. Community engagement benefits study
4. Vigilance for co-enrolment
5. Protocol safety review team: Great for safety
6. Contraception provision reduces pregnancies
7. Measuring adherence: Strengths & weaknesses
8. Good governance is good for trials
9. Results dissemination: good news travels fast
10. Conclusions

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1a. Is the phase IIb design appropriate? – should we rather do a phase III trial?

- Traditional trial phases not readily applicable to microbicides - no marker of biological activity
- Should we jump from small or moderate sized safety trials (Phase I) to a large efficacy trials (Phase III)?
- Debated in the vaccine & microbicide fields:
  - Should we first get signal for protection in phase IIb intermediate size trial for effectiveness?
  - Should we proceed without this to a large phase III trial?
- HPTN 035 shows the value of phase IIb approach
- HPTN 035 also shows limitation of phase IIb trial:
  - Not able to achieve statistical significance for borderline effects
  - Easy to misinterpret the power of the trial

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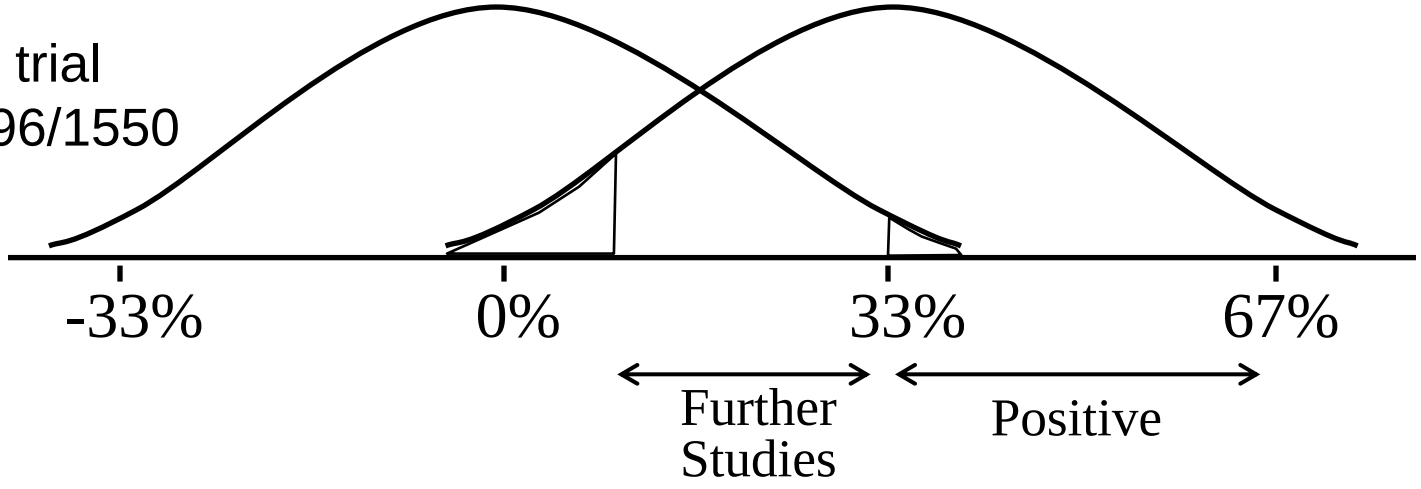
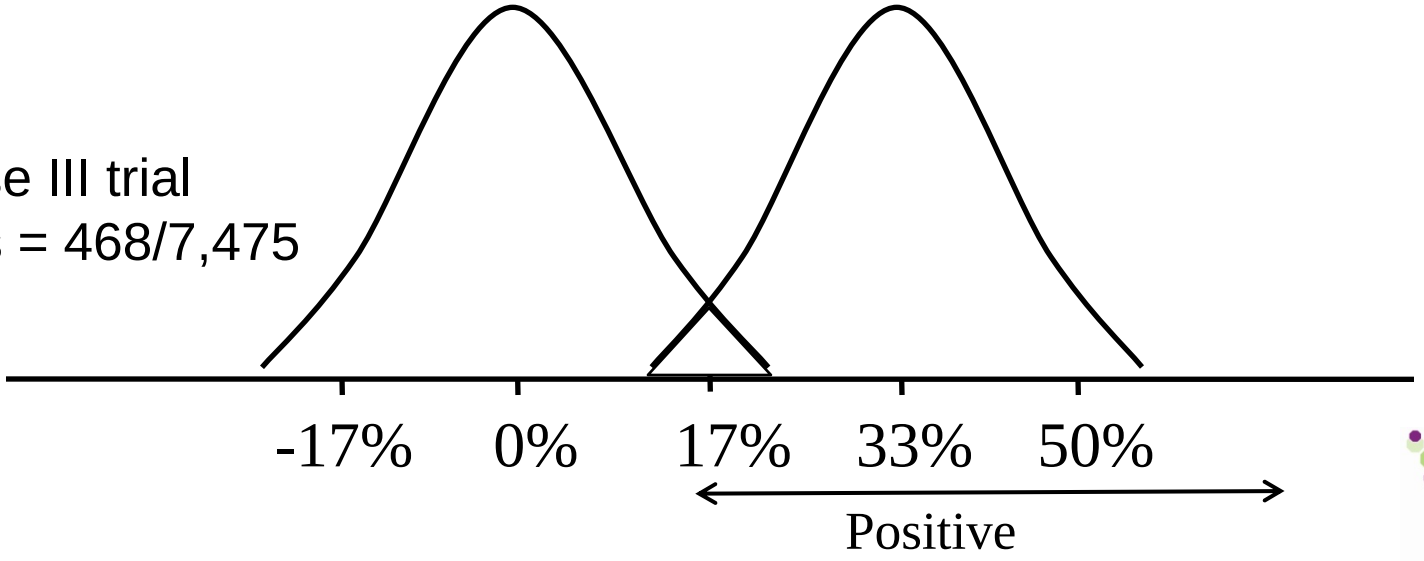
1b. Phase IIb vs Phase III design: phase IIb delivers

Phase IIb trial
endpoints = 96/1550



Phase III trial
endpoints = 468/7,475



2. Meet pairwise target in 4-arm trial

- **HPTN 035 was designed with the goal of obtaining 96 HIV endpoints per pairwise comparison ie. 96X2=192 overall**
- **However, when the trial was stopped at 192, only 87 (36 vs 51) endpoints in the PRO 2000 vs placebo comparison**
- **With 87 endpoints, trial needed 36% effectiveness (34 vs 53) to be statistically significant (ie. p<0.05)**

Hypothetical possible outcomes of a 2-way comparison in a trial with 87 endpoints

PRO2000 vs Placebo	Hazard ratio	p-value	effect
36 vs 51	0.69	0.1	30%
35 vs 52	0.66	0.06	34%
34 vs 53	**0.64**	**0.04**	**36%**
33 vs 54	0.6	0.02	40%

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3a. Community engagement benefits study

AFRICA

USA

- **HPTN 035 - a partnership between US & African researchers**
- **Partnership between researchers & the study communities**
- **Local ownership and engagement allowing sites flexibility**
- **Strong relationships translate to enrolment and retention**

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3b. Community relationship improves retention

- Women took part in the study for 12-30 months (20 months on average)
- 94% of women successfully completed their participation in the study, with similar rates across groups

BufferGel	PRO 2000	Placebo	No Gel
93.5%	93.6%	93.1%	94.0%

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4. Vigilance for co-enrolment

- **96 participants from HPTN 035 co-enrolled in CAPRISA 004**
- **Reasons for co-enrolment:**
  - R150 financial incentive
  - Access to quality health care
  - Altruism: want to contribute to AIDS research
  - Want to increase chances of getting active gel
  - Peer influence (waiting rooms: source of info)
- **Exercise vigilance for telltale signs**
- **Common database with ID works well**
- **Finger-print system now in place - works**

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5. Protocol safety review team: Great for safety

- Protocol Safety Review Team had monthly teleconferences
- Dedicated team of review clinicians
- Reviewed > 19,000 adverse events
- PSRT responded to > 100 queries:
  - 35 product use management
  - 25 adverse event reporting
  - 18 eligibility/withdrawal from study
  - 8 clinical management

6. Contraception provision reduces pregnancies

- Pregnancy Rate: 11.28 per 100 wys
- Percent ever pregnant: 17.9%
- 55 % of women on reliable contraception at baseline
- Pregnancy outcomes – no difference between arms
- 233 person-years on product hold – 5.9% of follow-up
- 82% of product hold due to pregnancy
- Future trials: require hormonal contraception at enrolment

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7. Measuring adherence: Strengths & weaknesses

- Reported gel use (in three groups): 81%
- Need more data on timing of gel in relation to sex
- ACASI finds lower adherence:

	FTFI	ACASI
Gel Use*	77.4%	73.5%
Condom Use**	65.7%	60.3%

- Pregnancy rate in high condom (≥85%) users is 7.9 per 100 wys vs 14.8 per 100 wys in low condom users – some reliability in self-report
- HPTN 035 should have collected more than self-reports - should have included applicator counts; even though dye test limited on HTI applicator

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8. Good governance is good for trials

- Protocol Co-chairs from each site important
- Trial management followed principles of good governance and democratic participation
- All opinions heard and considered seriously
- Robust study decisions were achieved based on the totality of the experience, knowledge and opinions
- Excellent study manager dedicated to project

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9a. Countdown to public release: The embargo period

Feb. 5, 6 *(Thursday/Friday)*

NIAID informs primary stakeholders

- Feb. 5 - Indevus, ReProtect, FDA, MRC
- Feb. 6 - other stakeholders

Feb. 6 *(Friday)*

Sites inform MoH and IRB/EC chair

Feb. 9 *(Monday a.m., local time)*

Sites inform drug regulatory agencies

Feb. 9 ***(Monday, 3:30 p.m., local time)***

Embargo lifts after CROI press conference

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9b. Results dissemination: good news travels fast

- Despite challenges, communications plan successfully implemented with good results
- Sites worked hard and their efforts were responsible for successful dissemination
- Media response good & coverage positive. Reporting mostly fair, balanced and accurate
- Inclusion of participants successful
- Study results – and the positive response –

  …provided a needed boost to the field

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Conclusion – what have we learnt?

- Even moderate success is success
- PRO2000 reduced HIV by 30% in trial (p=NS)
- HEC placebo is inert and lots more…
- Undertaking a trial of this magnitude has many challenges – working with wonderful people who share a deep sense of commitment to the study participants and to turning the tide on HIV is the greatest pleasure and honour that I treasure as Protocol Chair of HPTN 035 ….

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Acknowledgements

Sponsors: US National Institutes of Health (R Black, L Soto-Torres, S Estep), Indevus Pharmaceuticals (A Profy), ReProtect (T Moench)

Protocol Chair: Salim S Abdool Karim

Blantyre, Mal **khoma, E Kachale**

Durban and H **mi, N Dladla-Qwabe**

Harare, Zimb **agure, M Mlingo, N Mg**

Lilongwe, Ma **Mvalo**

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The HPTN 035 Protocol Team gratefully acknowledges the dedication and commitment of the 3099 study participants without whom this study would not have been possible.

HIV Prevention Trials Network

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Acknowledgements

HPTN 035 was funded by the US National Institutes of Health (NIH). The study was designed and implemented by the HIV Prevention Trials Network (HPTN) and the Microbicide Trials Network (MTN). The HPTN (U01AI46749) has been funded by the National Institute of Allergy and infectious Diseases (NIAID), National Institute of Child Health and Development (NICHD), National Institute of Drug Abuse (NIDA), and National Institute of Mental Health (NIMH). The MTN (U01AI068633) has been funded by NIAID, NICHD, and NIMH.

The study products were provided free of charge by Indevus Pharmaceuticals, Inc. and ReProtect, Inc.

The US Agency for International Development (USAID) provided funding for manufacturing of BufferGel for this study.

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