

HPTN / IMPAACT Plenary Session

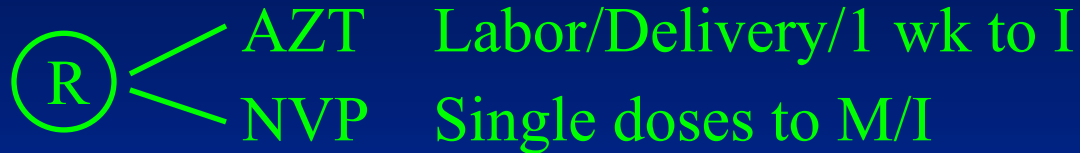
When is Clinical Trials Evidence Sufficient to Change Clinical Practice?

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University of Washington

When is Clinical Trials Evidence Sufficient?

- **Illustrations**
- Need for Confirmatory Trials
- Phase 2b Screening Trials
- Extrapolating to Related Settings
- Conclusions

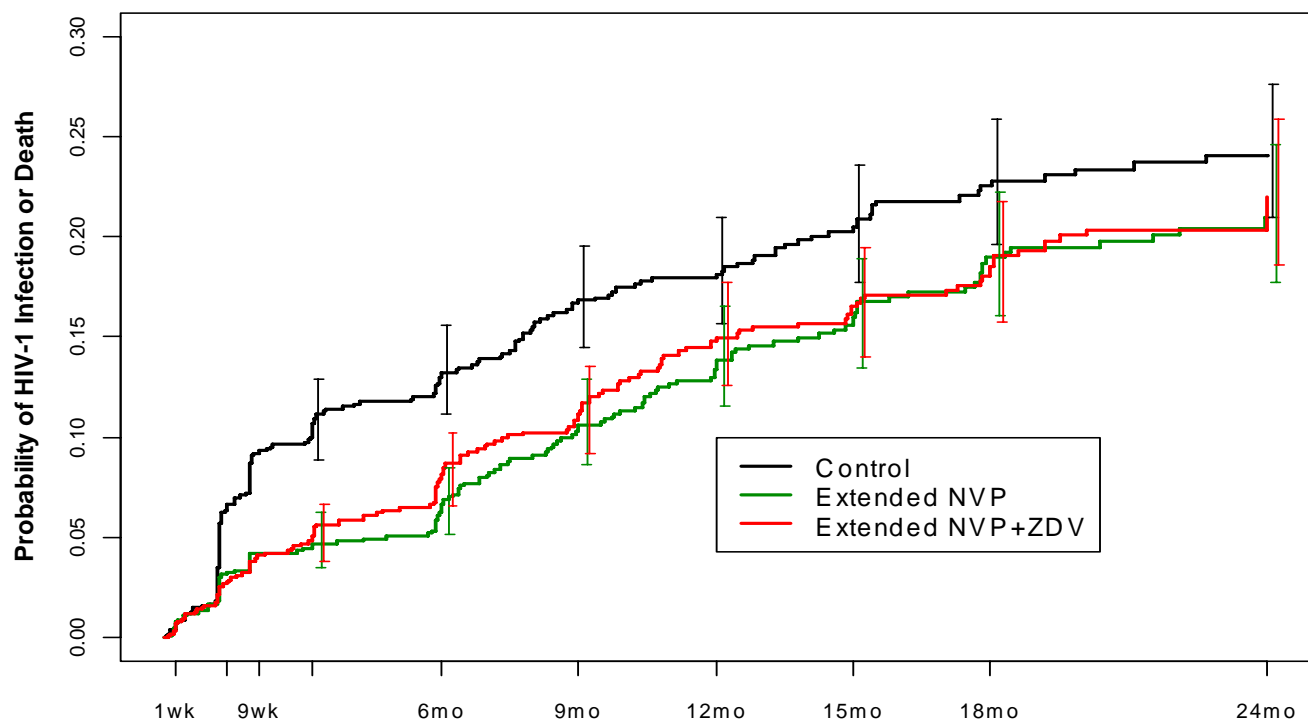
HIVNET 012: MCT in Uganda



- 8/99 Results *Lancet* 1999; 354: 795-802

		<u>HIV Infection</u>	
	<u>N</u>	<u>6-8 wks</u>	<u>14-16 wks</u>
AZT	302	59 (21.3%)	65 (25.1%)
NVP	307	35 (11.9%)	37 (13.1%)
		2p = 0.0027	2p = 0.0006

Probability of HIV-1 Infection or Death in Infants Uninfected at Birth by Treatment Arm: PEPI-Malawi



Age	1 wk	6 wks	9 wks	14 wks	6 mos	9 mos	12 mos	15 mos	18 mos	24 mos
Estimates (%)										
Control	0.6	6.7	9.3	10.7	13.2	16.8	18.1	20.5	22.6	24.1
Extended NVP	0.6	3.3	4.2	4.7	6.6	10.6	13.9	16.0	19.0	20.9
Extended NVP+ZDV	0.5	2.8	4.1	5.1	8.2	11.2	15.0	16.5	18.6	22.0

Male Circumcision - RCTs

	Orange Farm	Rakai	Kisumu
Population	Semi-urban	Rural	Urban
MC Rate	20%	16%	10%
HIV Incidence	1.6%	1.3%	1.8%
Age Range	18-24 yrs	15-49 yrs	18-24 yrs
Sample size	3,274	4,996	2784
DMC Stopped	Nov. 2004	Dec. 2006	Dec. 2006
RR	0.40	0.52	0.47

HPTN 035 Phase 2b Screening Trial

Prevention of HIV Infection

	No. HIV Infections	Women-Years of Follow-Up	Incidence Rate (95% CI)
PRO 2000 Gel	36	1332	2.7 (1.9 - 3.7)
BufferGel	54	1304	4.1 (3.1 - 5.4)
Placebo Gel	51	1305	3.9 (2.9 - 5.1)
No Gel	53	1318	4.0 (3.0 - 5.3)
ITT Analysis	Hazard Ratio vs. Placebo		Hazard Ratio vs. No Gel
PRO 2000 Gel	0.70 (0.46-1.08)		0.67 (0.44-1.02)
BufferGel	1.10 (0.75-1.62)		1.05 (0.72-1.55)

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- **Need for Confirmatory Trials**
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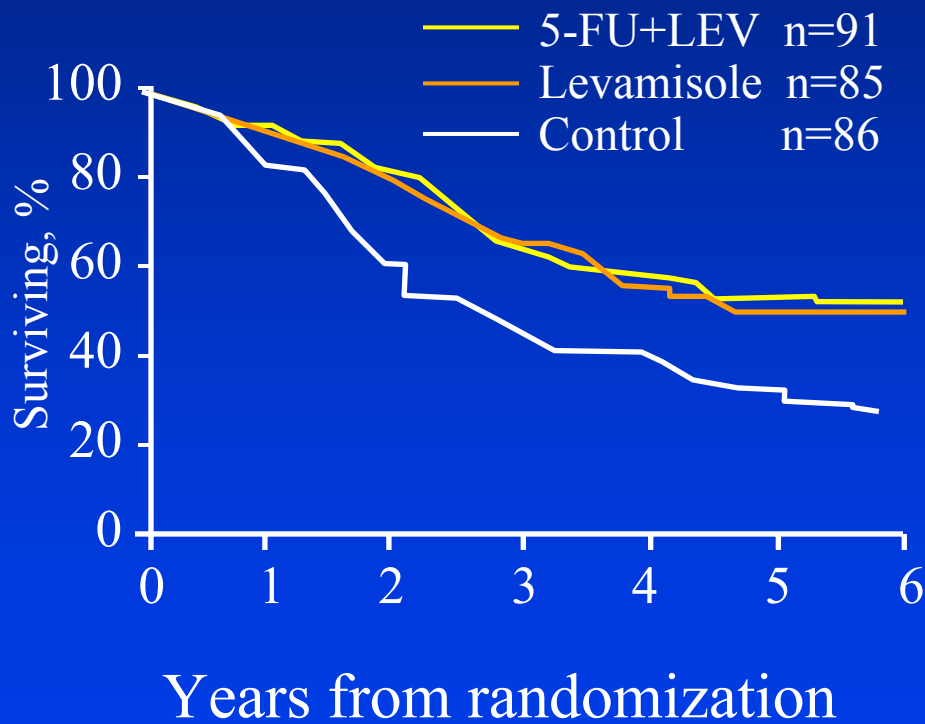
Importance of Multiple Independent Trials

CPCRA 023 Trial: April 1993 – July 1995
 Oral Gancyclovir: Prevention of CMV Symptoms

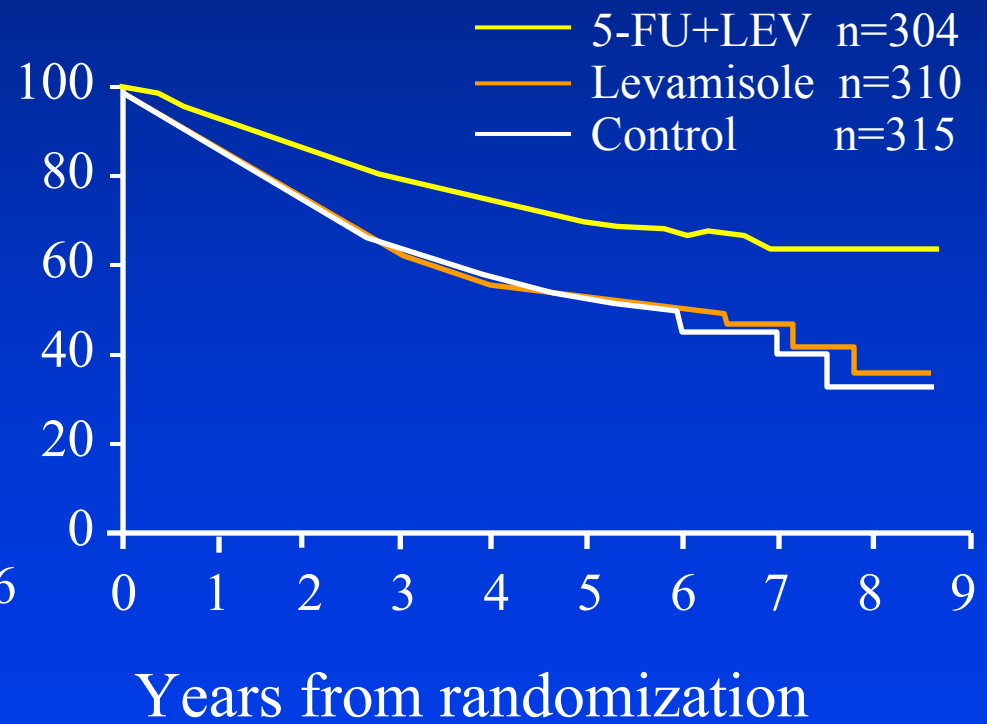
	July 1994 <u>SYNTEX #1654</u>		July 1994 <u>CPCRA #023</u>		July 1995 <u>CPCRA #023</u>	
	Rx	PLA	Rx	PLA	Rx	PLA
n	486	239	646	327	662	332
CMV (RR/2p)	76 (0.45 / 0.0001)	72	40 (0.87 / 0.60)	23	101 (0.92 / 0.60)	55
Death (RR/2p)	109 (0.71 / 0.052)	68	58 (1.27 / 0.34)	23	222 (0.83 / 0.09)	132

SURGICAL ADJUVANT THERAPY OF COLORECTAL CANCER

NCCTG Trial



Cancer Intergroup Trial



Pre-trial probability the intervention is effective is
is $\pi = 0.04$

Then,
even if $1-\alpha = 0.025$ and $1-\beta = 0.90$,

Probability a trial positive will be
a true positive is $36 / 60 = 0.60$

RESULT OF EXPERIMENT	TRUTH		
	Positive	Negative	
Positive	36	24	60
Negative	4	936	940
<hr/>			
	40	960	1000

Pre-trial probability the intervention is effective is
is $\pi = 0.60$ (when 1st trial is positive)

Then,

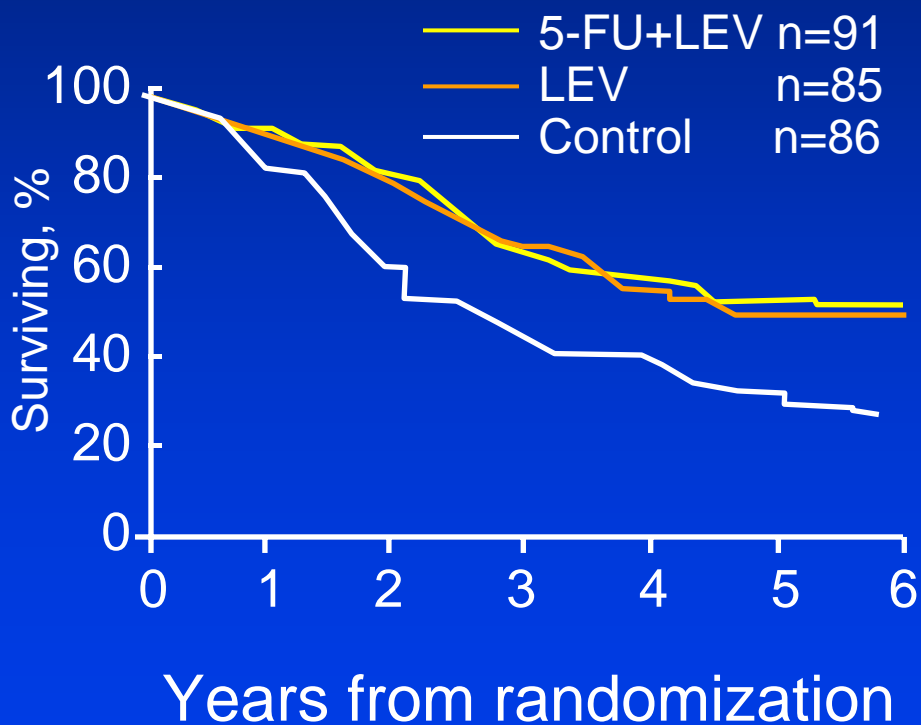
if $1\alpha = 0.025$ and $1-\beta = 0.90$,

Probability a trial positive will be
a true positive is $540 / 550 = 0.98$

RESULT OF EXPERIMENT	TRUTH		
	Positive	Negative	
Positive	540	10	550
Negative	60	390	450
<hr/>			
	600	400	1000

Surgical Adjuvant Therapy Of Colorectal Cancer

NCCTG Trial



Cancer Intergroup Trial

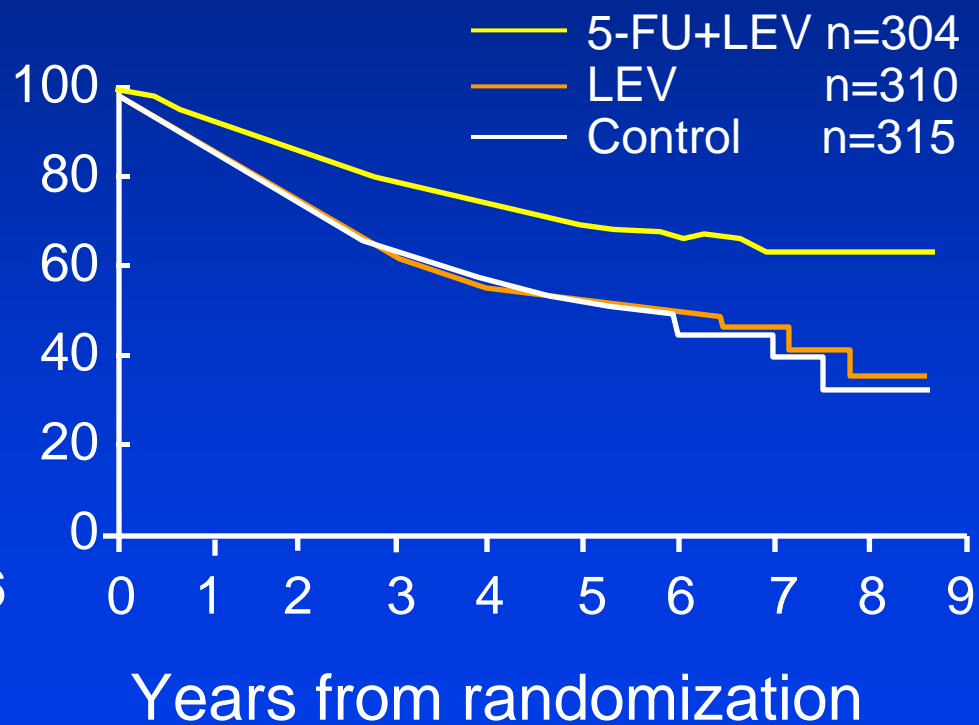
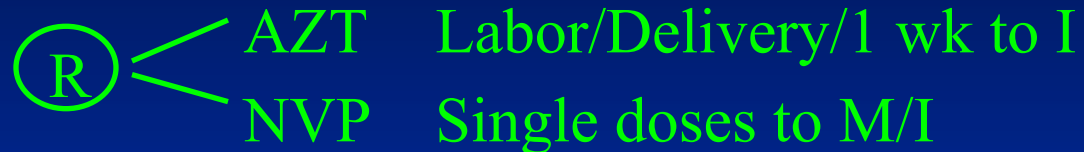


Illustration of a Single Trial with “Compelling” Results: HIVNET 012



- Results *Lancet* 1999; 354: 795-802

		<u>MCT of HIV</u>	
	<u>N</u>	<u>6-8 wks</u>	<u>14-16 wks</u>
AZT	302	59 (21.3%)	65 (25.1%)
NVP	307	35 (11.9%)	37 (13.1%)
		1p = 0.0014	1p = 0.0003

Pre-trial probability the intervention is effective is
is $\pi = 0.04$

Then,

even if $1 - \alpha = 0.0005$ and $1 - \beta = 0.90$,

Probability a trial positive will be

a true positive is $36 / 36.5 = 0.98$

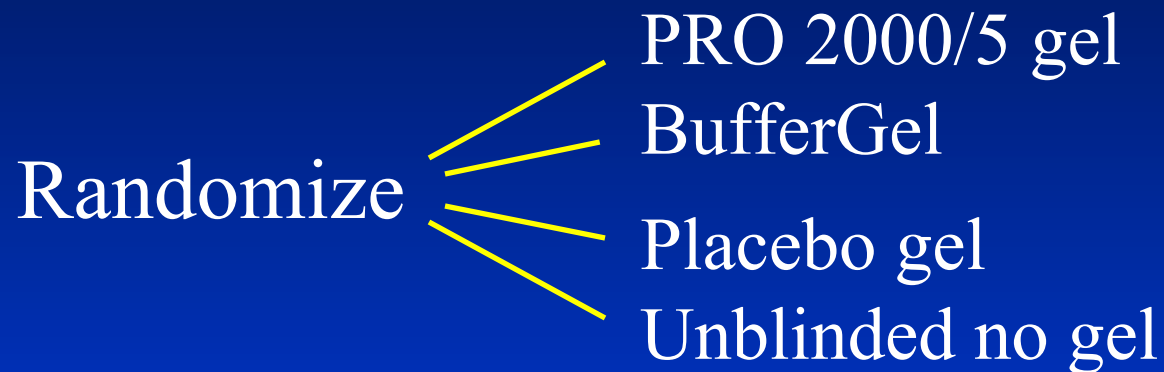
RESULT OF EXPERIMENT	TRUTH		
	Positive	Negative	
Positive	36	< 0.5	36.5
Negative	4	959.5	963.5
<hr/>			
	40	960	1000

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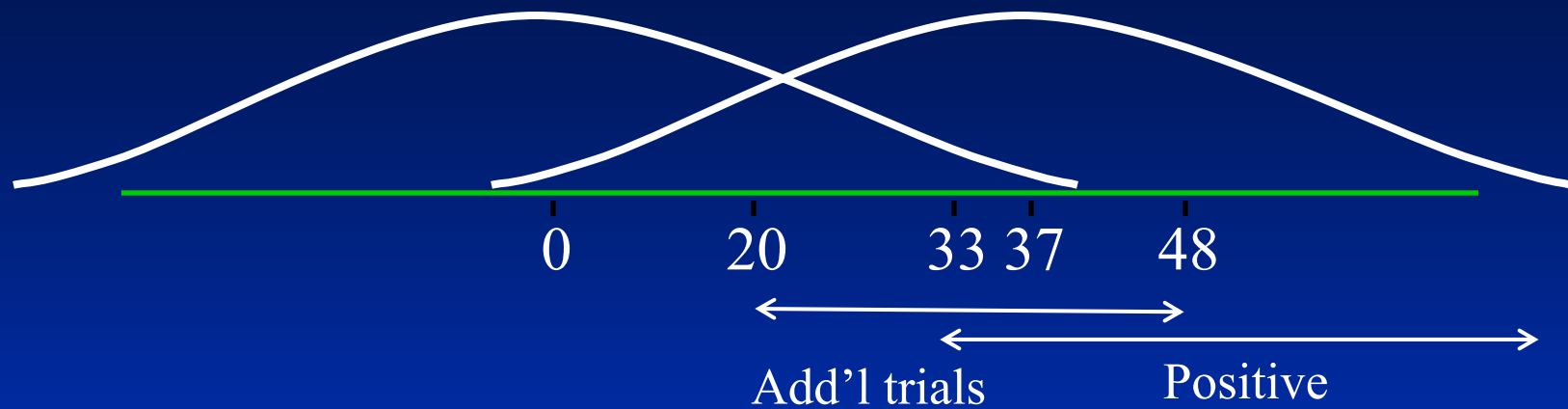
HPTN 035 Phase 2b Trial Design

Microbicides to Prevent HIV Infection

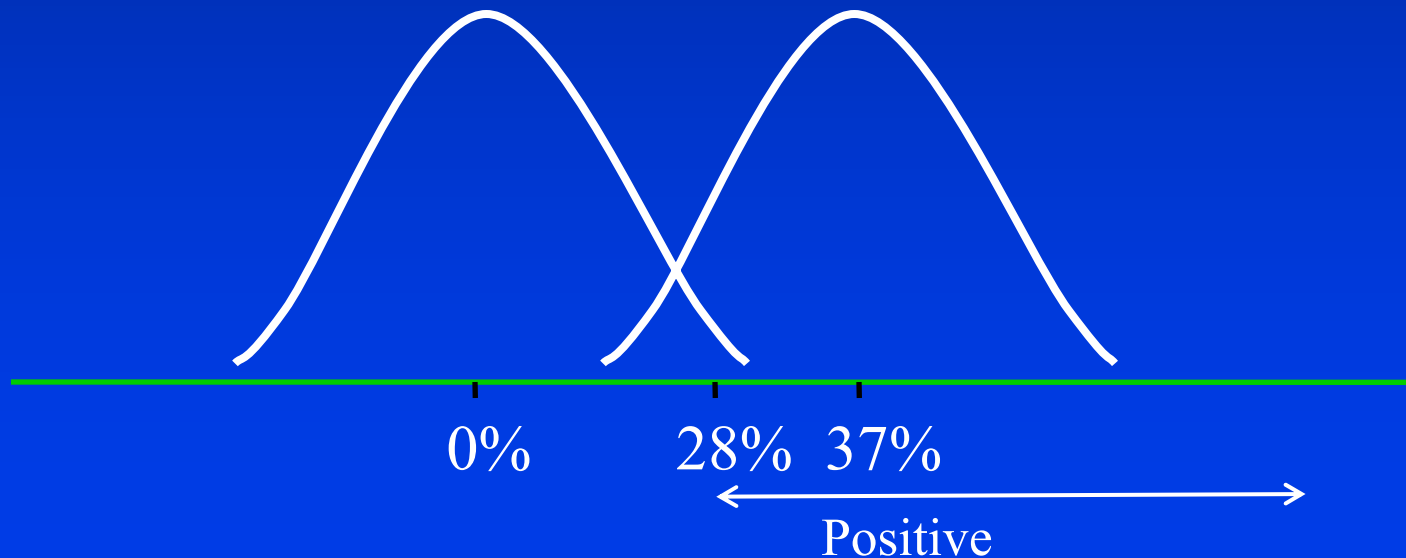


- Four-arm multi-site randomized controlled trial
- Two active arms: PRO 2000/5 Gel & BufferGel
- Two control arms: Placebo gel & Unblinded no gel
- 3100 women followed quarterly for 12-30 months

Outcome Probabilities — Phase 2b Trial Design, (L=100)



Outcome Probabilities — Phase 3 Trial Design, (L=400)

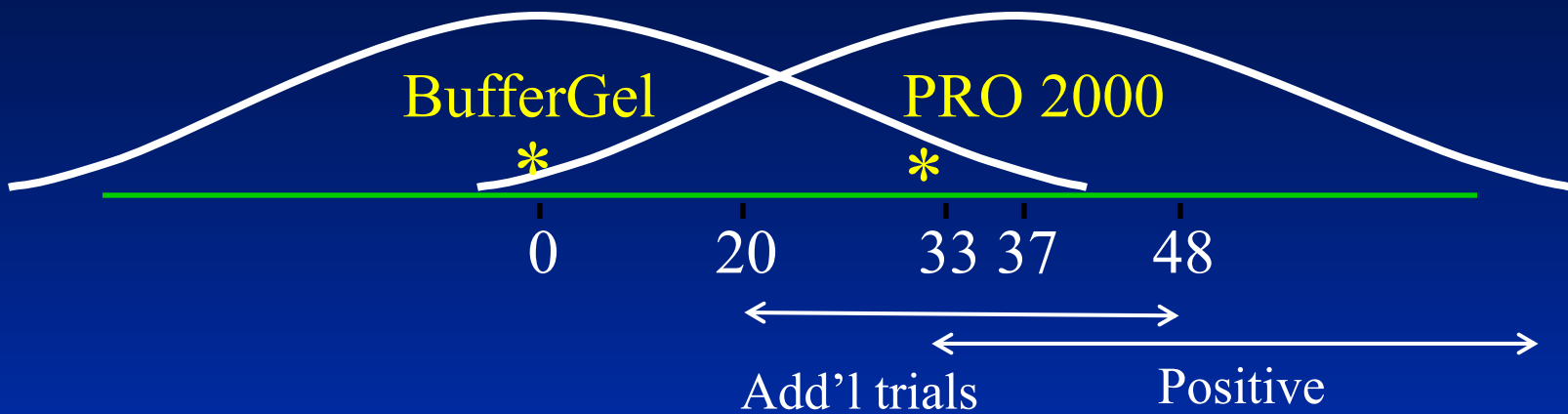


HPTN 035 Phase 2b Screening Trial

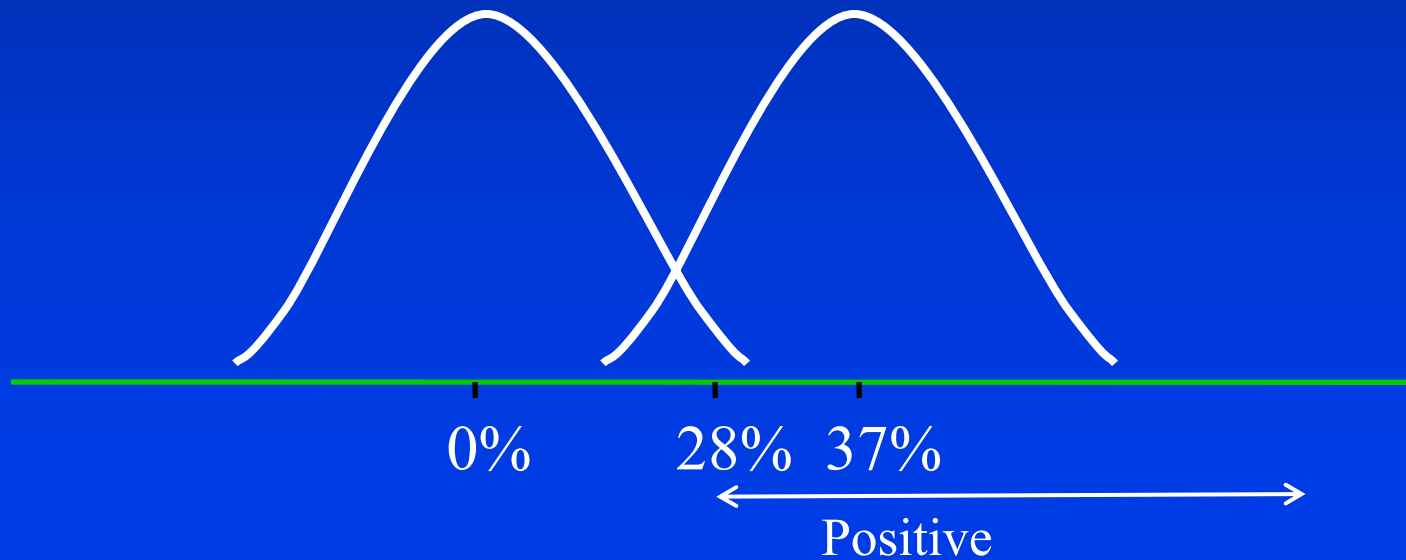
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Outcome Probabilities — Phase 2b Trial Design, (L=100)



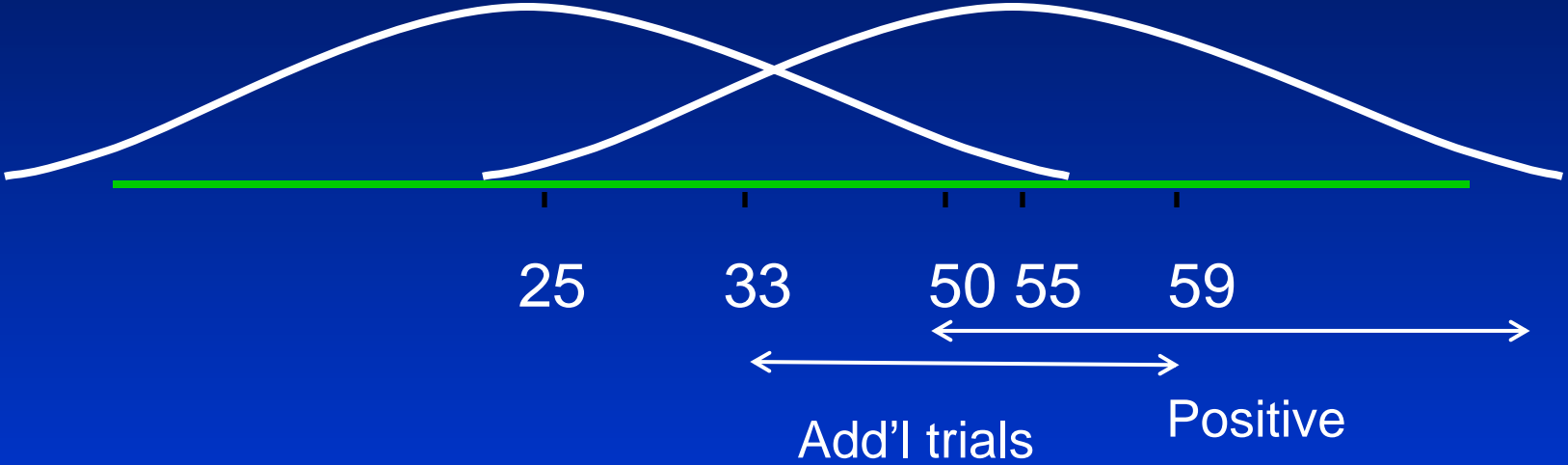
Outcome Probabilities — Phase 3 Trial Design, (L=400)



Oral Pre-Exposure Prophylaxis – Planned Trials

Sponsor	Product / Population	# Events # Arms	Phase	Power
Gates	Tenofovir/TDF/FTC/ Discordant couples	135 3	III	RR = 0.70 vs. RR = 0.40 90% power
NIH/MTN	Tenofovir/TDF/FTC/ Women	Topcl/oral 94 / 123 2 / 3	IIB	RR = 0.75 vs. RR = 0.45 Ph 2B screening trial
USAID	TDF/FTC/ High-risk women	90 2	III	RR = 0.70 vs. RR = 0.30 90% power
NIH	TDF/FTC Youth (women and MSM) 16 to 24 yrs	120 2	IIB	RR = 0.75 vs. RR = 0.40 90% power

VOICE TDF/FTC PrEP – Phase 2b Trial Design, (L=94)



Oral Pre-Exposure Prophylaxis – Planned Trials

Sponsor	Product / Population	# Events # Arms	Phase	Power
Gates	Tenofovir/TDF/FTC/ Discordant couples	135 3	III	RR = 0.70 vs. RR = 0.40 90% power
NIH/MTN	Tenofovir/TDF/FTC/ Women	Topcl/oral 94 / 123 2 / 3	IIB	RR = 0.75 vs. RR = 0.45 Ph 2B screening trial
USAID	TDF/FTC/ High-risk women	90 2	III	RR = 0.70 vs. RR = 0.30 90% power
NIH	TDF/FTC Youth (women and MSM) 16 to 24 yrs	120 2	IIB	RR = 0.75 vs. RR = 0.40 90% power

HPTN 060: Design

Youth (Women & MSM) 16-24 yrs.

Biomedical

Behavioral

	TDF/FTC	Placebo
EBI*	TDF/FTC + EBI	Placebo + EBI
SOC**	TDF/FTC + SOC	Placebo + SOC

Primary Outcome: HIV Incidence

* Enhanced Behavioral Intervention

**Standard of Care

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ACTG #076

On 17 Feb. 1994: (DMC meeting)

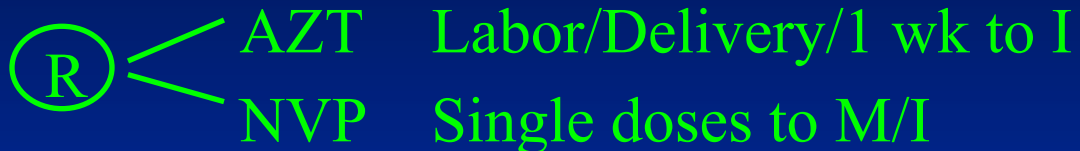
	<u>≥1 viral culture</u>	<u>≥1 culture HIV+</u>
ZDV	180	13 8.3%
Placebo	184	40 25.5%

2p<0.0001

Generalizability Issues for “076”

- Timing of initiation of antepartum care
- Levels of adherence
- Differences in viral & human populations
- Impact of breastfeeding
- Reliability of results (precision of estimates)
- Safety
 - Anemia enhanced by malaria & iron deficiencies*
- Affordability
 - + in one population \nrightarrow + in another population
 - eg + in BW #02 \nrightarrow + in Concorde

HIVNET 012



- Results

Lancet 1999; 354: 795-802

		<u>MCT of HIV</u>	
	<u>N</u>	<u>6-8 wks</u>	<u>14-16 wks</u>
AZT	302	59 (21.3%)	65 (25.1%)
NVP	307	35 (11.9%)	37 (13.1%)
		1p = 0.0014	1p = 0.0003

ACTG 316



- 2001 Results: *8th Conf on Retroviruses & OIs, Chicago, Feb '01 (Abstr LB7)*

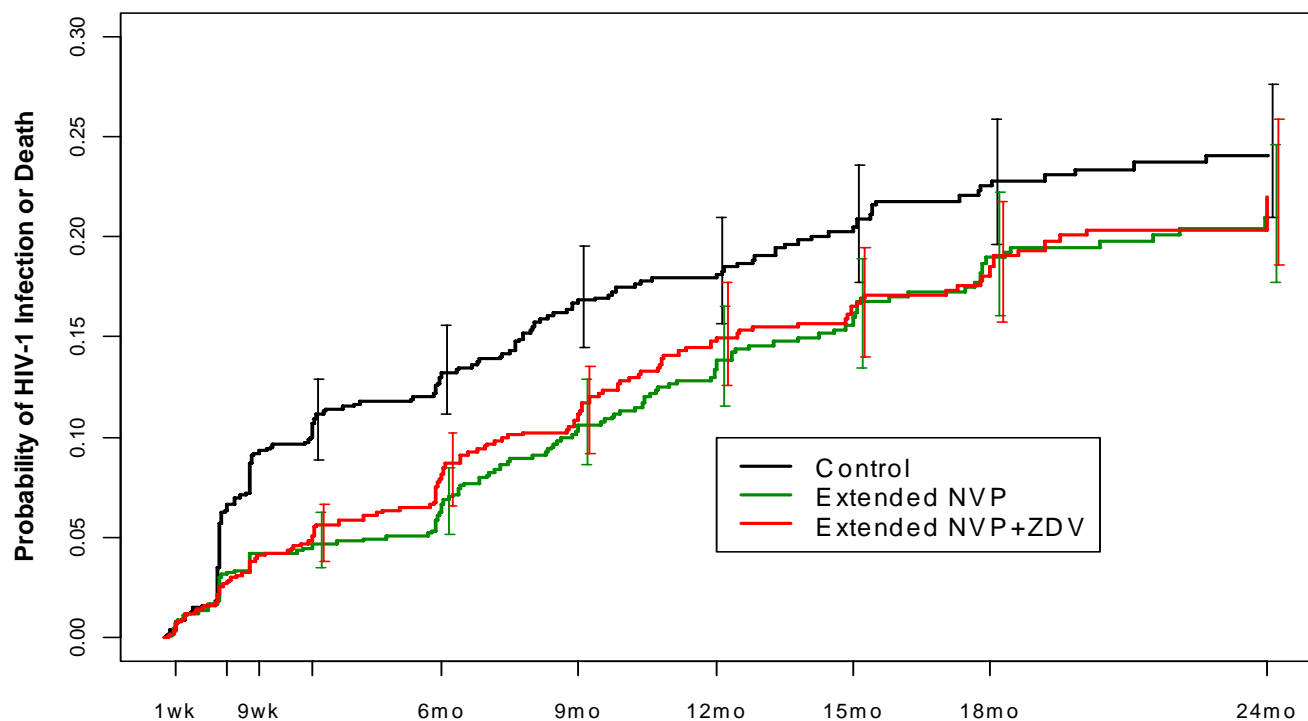
	<u>N</u>	<u>HIV Infection</u> <u>at 24 wks</u>
ART + NVP	594	9* (1.5%)
ART	580	8* (1.4%)

*9 infants antenatally infected

Results from NVP Breastfeeding Regimens

	HIV Infection			HIV-free Survival			
	6 wks.	6 mos.	18 mos.	6 wks.	6 mos.	18 mos.	
<u>HIVNET 012</u>							
sd NVP	11.8%		15.7%	12.7%		20.7%	} 10%
sc AZT	20.0%		25.8%	21.8%		30.7%	
<u>SWEN</u>							
6wk NVP	2.53%	6.91%		3.71%	8.05%		
sd NVP	5.27%	8.98%		6.81%	11.58%		
<u>PEPI</u>							
14wk NVP	1.7%	4.0%	10.1%	3.3%	6.6%	19.0%	} 3.6%
sd NVP	5.1%	10.1%	13.9%	6.7%	13.2%	22.6%	
<u>HPTN 046</u> 6 mos. NVP versus 6 wks. NVP:							
Target: 90% power for '66% ↓ of 4.2%' : 2.8% ⇒							
⇒ Stat sign: 1.7% ↓ at 6 mo. ⇒ ↓ at 6 mo : 1.0%							

Probability of HIV-1 Infection or Death in Infants Uninfected at Birth by Treatment Arm: PEPI-Malawi



Age	1 wk	6 wks	9 wks	14 wks	6 mos	9 mos	12 mos	15 mos	18 mos	24 mos
Estimates (%)										
Control	0.6	6.7	9.3	10.7	13.2	16.8	18.1	20.5	22.6	24.1
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Extended NVP+ZDV	0.5	2.8	4.1	5.1	8.2	11.2	15.0	16.5	18.6	22.0

Results from NVP Breastfeeding Regimens

	HIV Infection			HIV-free Survival			
	6 wks.	6 mos.	18 mos.	6 wks.	6 mos.	18 mos.	
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sd NVP	11.8%		15.7%	12.7%		20.7%	} 10%
sc AZT	20.0%		25.8%	21.8%		30.7%	
<u>SWEN</u>							
6wk NVP	2.53%	6.91%		3.71%	8.05%		
sd NVP	5.27%	8.98%		6.81%	11.58%		
<u>PEPI</u>							
14wk NVP	1.7%	4.0%	10.1%	3.3%	6.6%	19.0%	} 3.6%
sd NVP	5.1%	10.1%	13.9%	6.7%	13.2%	22.6%	
<u>HPTN 046</u> 6 mos. NVP versus 6 wks. NVP:							
Target: 90% power for '66% ↓ of 4.2%' : 2.8% ⇒							
⇒ Stat sign: 1.7% ↓ at 6 mo. ⇒ ↓ at 6 mo : 1.0%							

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Conclusions

Contributing Factors for Reliable Conclusions:

- Adequate and Well Controlled Trials
- Confirmatory Trials, unless single trials provide highly robust and compelling evidence
- Caution regarding extrapolating results from related clinical trials
- Need to control...
 - ~ false negative error rates PrEP: Voice vs. HARP/Young
PRO 2000
 - ~ false positive error rates Gancyclovir; HPTN 046; LEV

“It isn’t so much the things we *don’t know*
that get us in trouble.

It’s the things we *know* that aren’t so”.

—Artemus Ward (1834-1867)

