

**Impact of HSV2 Suppressive Therapy with  
Acyclovir on genital and plasma HIV-1 RNA  
in HSV-2 and HIV-1 seropositive women:  
results from randomised controlled trials**

*Sinéad Delany-Moretlwe*

*HPTN 039 WSM Retreat*

**RHRU**

Reproductive Health & HIV Research Unit  
of the University of the Witwatersrand, South Africa.



RHRU is a WHO  
Collaborating Centre

# Interactions between HSV-2 and HIV

---

- **HIV changes the natural history of HSV-2**
  - More frequent recurrences, most of which are sub-clinical  
*Augenbraun 1995, Schacker 1998*
- **HSV-2 increases risk of HIV acquisition**
  - 2-3 fold overall increased risk *Freeman 2005, Wald 2004*
- **HSV-2 increases risk of HIV transmission**
  - 5-fold increase in per-contact risk due to GUD (Rakai) *Gray 2001*
- **HSV-2 associated with HIV disease progression**
  - 0.5 log ↑ plasma HIV viral load (set-point) in early HIV *Gray 2004*

# Outline

---

- Interactions between HSV-2 and HIV-1
- Design and results of South African trial
- Comparison with other trial results
- Conclusions

# South African trial

---

A proof-of-concept, randomised, double-blind, placebo-controlled trial of daily acyclovir 400mg BD vs. placebo for 3 months among co-infected women not requiring HAART

## Inclusion:

- HIV seropositive, WHO Stage I/II AND CD4 count > 250 cells/mm<sup>3</sup>
- HSV-2 seropositive (Focus HerpeSelect  $\geq$  3.5, Kalon for equivocals)

## Exclusion:

- Known contra-indications to ACV
  - renal failure, pregnant, hypersensitivity
- Not willing to give consent/adhere to study procedures
- Would benefit from treatment
  - chronic ulcer > 30 days, > 6 recurrences/year; on suppressive therapy already

# Clinical and laboratory procedures

## Screening:

- Clinical staging (WHO classification)
- **Blood:** HIV rapid test, HSV-2, CD4 count
- **Urine:** pregnancy, protein <3+

Refer CD4  
count < 250 for  
HAART

## Enrolment I/II (D0, D7):

- **CVL:** HIV-1 RNA Roche Amplicor; RT-PCR HSV-2 DNA
- **Blood:** HIV viral load; RPR/TPHA, storage
- **Genital swabs:** NG/CT PCR, TV, BV, yeast; GUD swab

**RANDOMISATION** at 2<sup>nd</sup> enrolment visit

## Follow-up (Month 1, 2, 3 and final):

- same investigations as enrolment
- dispense study drug; counseling, condom distribution

**Main outcome: Month 3**

# Trial outcomes and analysis

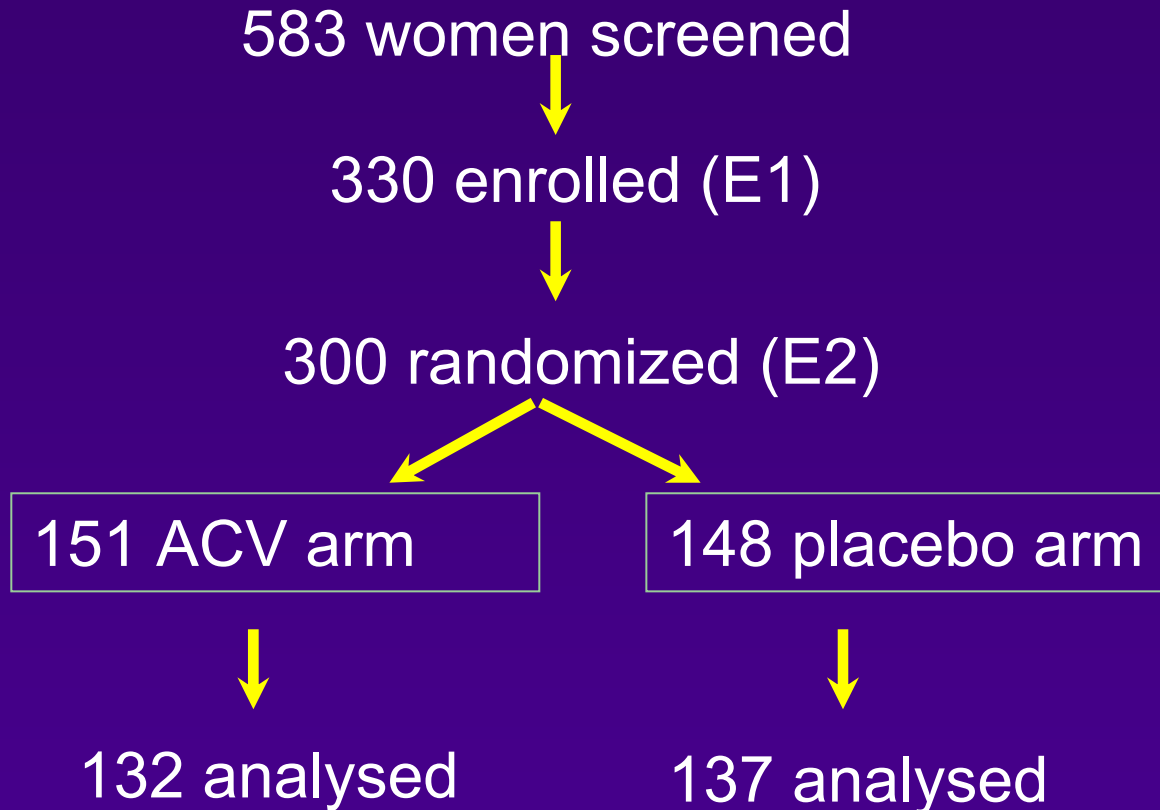
---

- 1/ Detection and quantity of **genital HIV-1 RNA** at M3
- 2/ Quantity of **plasma HIV-1 RNA** and **CD4 count** at M3;  
Detection, quantity of **genital HSV-2 DNA** and  
Frequency of **GUD**;  
Treatment adherence.

## Statistical analyses:

- Intent-to-treat (ITT) using binomial and linear regression models;
- Summary and repeated measures used when including all visits;
- Predefined sub-groups

# Screening, enrolment, and follow-up



*17 lost to follow up at M3  
2 HIV results not available  
1 on ARV at E2*

*11 lost to follow up at M3*

91% visits attended

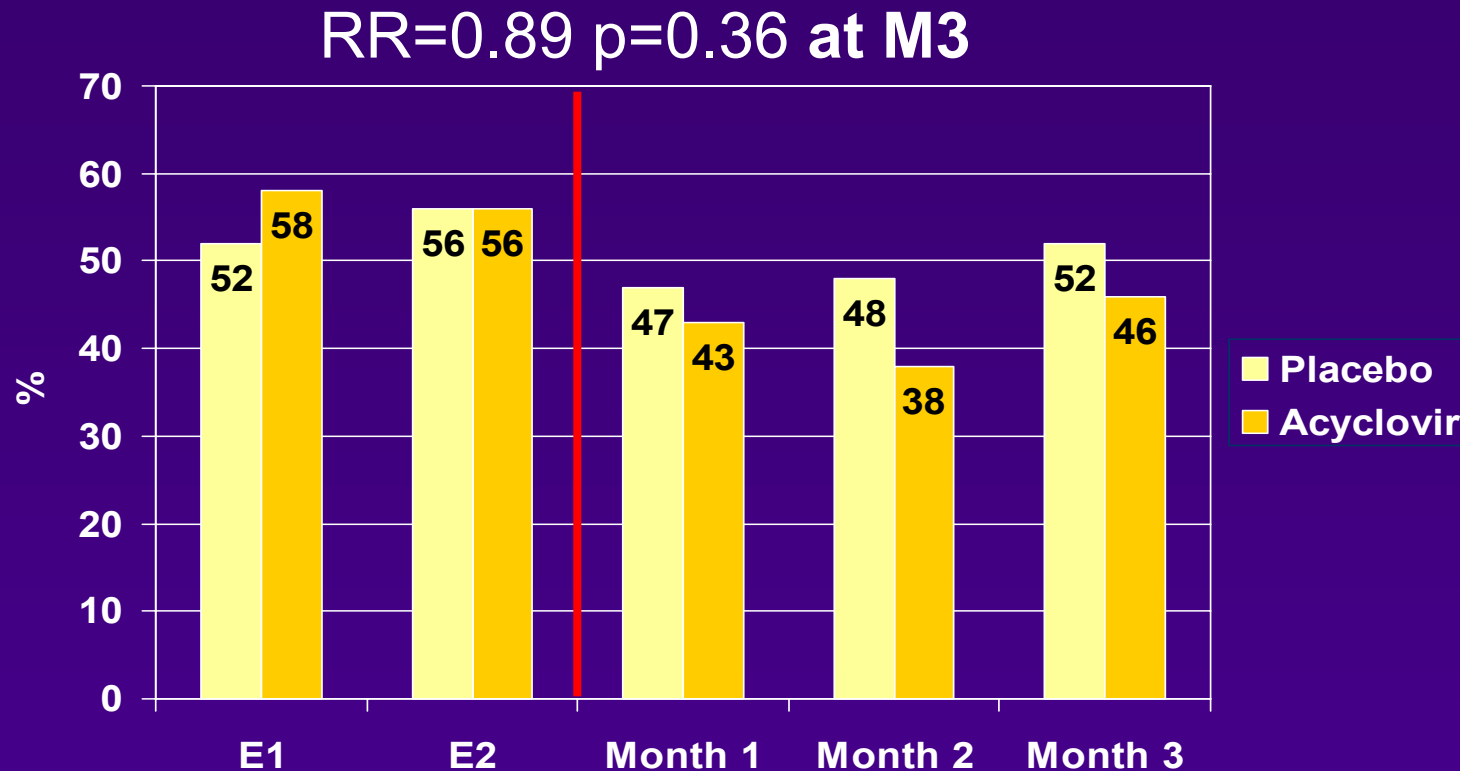
Mean adherence rate  
(pill count) = 95%  
both arms

No SAE related to  
study drug

# Baseline characteristics

	<b>ACV (n=151)</b>	<b>Placebo (n=148)</b>
Mean age (yrs) (sd)	31.8 (7.0)	32.1 (7.6)
Median yrs since HIV diagnosis (IQR)	1.0 (0.1-3.1)	1.2 (0.2-3.6)
Median CD4 count (cells/mm <sup>3</sup> ) (IQR)	446 (337-615)	500 (369-731)
Mean plasma HIV (log <sub>10</sub> /ml) (sd)	4.1 (0.9)	4.1 (0.8)
Genital HIV-1 RNA detected	107 (71%)	94 (64%)
Genital HSV-2 DNA detected	61 (40%)	70 (47%)
<i>Neisseria gonorrhoeae</i>	7 (5%)	4 (3%)
<i>Chlamydia trachomatis</i>	8 (5%)	10 (7%)
<i>Trichomonas vaginalis</i>	18 (12%)	22 (15%)

# Impact of ACV on genital HIV-1 at M3



- Persistent shedders at baseline **RR=0.76 (95%CI 0.62 to 0.94)** vs. intermittent shedders **RR=1.1 (95% CI 0.66 to 1.80)** (p-value test for interaction=0.20)
- No difference in mean quantity HIV-1 RNA = **0.12 log<sub>10</sub>copies/ml** (95% CI -0.13 to 0.39 log<sub>10</sub>copies/ml p=0.346)

# Impact of ACV on pattern of genital HIV-1 shedding (summary measures n=288)

	ACV n=146	Placebo n=142
Women with genital HIV-1 detected at:		
No visit	45 (31%)	40 (28%)
0% <visits <50%	34 (23%)	24 (17%)
50% ≤ visits <100%	34 (23%)	36 (25%)
All visits (100%)	33 (23%)	42 (30%)

**Adjusted OR = 0.56; 95% CI, 0.36 to 0.87; p=0.01**

# Impact of ACV on plasma HIV-1

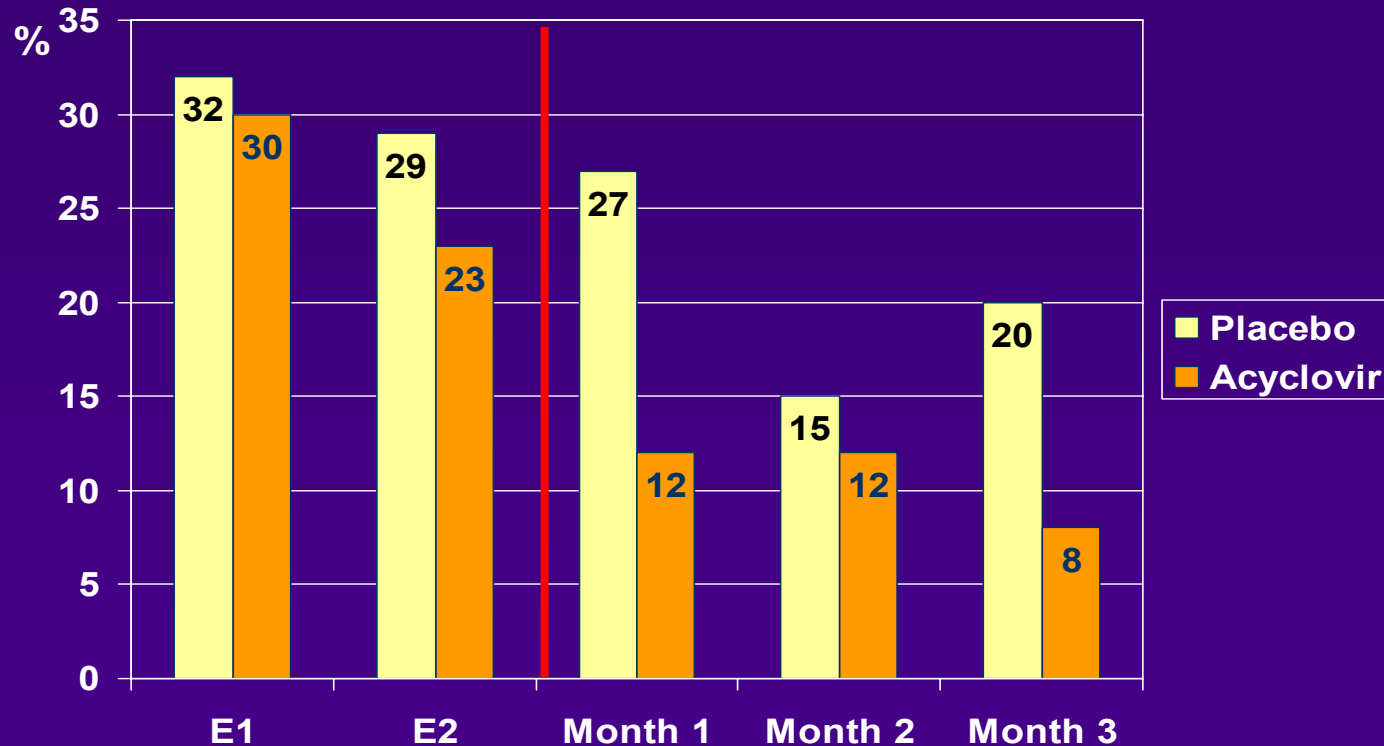
	ACV N=132	Placebo N=137	Effect	p-value
<b>Plasma HIV-1 RNA at Month 3</b>				
Mean quantity (log <sub>10</sub> copies/mL)	3.67	3.92	↓0.37*	0.001

- Difference in CD4 count 1.0%\* (95% CI 0.9 to 1.1 p=0.71)

\*Adjusted for baseline values

# Impact of ACV on genital HSV-2

RR=0.36 p=0.002 at M3



- Reduction in proportion of women who experienced  $\geq 1$  ulcer episode  
RR=0.42 (95% CI 0.18-0.72 p=0.013)
  - 50% swabs HSV-2 positive; 1 H.ducreyi and HSV-2, 0 T.pallidum, 0 HSV-1

# Comparisons with other trials

	<b>Burkina Faso ANRS 1265a</b>	<b>South Africa</b>	<b>CDC Thai</b>
<b>Design</b>	RCT Val 1G	RCT ACV 400 mg BD	RCT cross-over ACV 800 mg BD
<b>Population</b>	142 HSV-2/HIV+ Not on HAART	299 HSV-2/HIV+ CD4>250	62 HSV-2/HIV+ CD4>200
<b>Duration of follow-up</b>	6 visits over 3 months	4 visits over 3 months	3 visits over 1 month
<b>Main outcome measure</b>	Genital HIV-1 over all visits (Qual./quant.)	Genital HIV-1 at month 3 (Qual./quant.)	Genital HIV-1 RNA (Quant. only)

Source: Nagot, NEJM 2007; Dunne, CROI 2007

# Comparisons with other trials

	<b>Burkina Faso ANRS 1265a</b>	<b>South Africa (all visits)</b>	<b>CDC Thai</b>
<b>Genital HIV-1 Detected <math>\geq 1</math></b>	RR=0.86 (0.73-1.02)	RR=0.96 (0.82-1.11)	
<b>Frequency</b>	OR=0.41 (0.21-0.80)	OR=0.56 (0.36-0.88)	
<b>Quantity</b>	-0.29 (-0.44 to -0.15)	-0.18 (-0.32 to -0.02)	Mean diff 0.44 log <sub>10</sub> /ml
<b>Plasma HIV-1</b>	-0.53 (-0.72 to -0.35)	-0.27 (-0.32 to -0.02)	

- All 3 trials observed reductions in HSV-2 DNA detection

Source: Nagot, NEJM 2007; Dunne, CROI 2007

# Summary & potential implications (1)

---

- **Impact of ACV on genital HIV-1 RNA**

- Weak evidence for overall effect on detection at least once
- Strong evidence for reduction in frequency of shedding
- Linked to decrease in plasma viral load?
- Need results from ongoing trials to confirm impact on HIV transmission
- *Ultimately need effective HSV-2 vaccines for lasting form of HIV prevention*

# Summary & potential implications (2)

---

- **Impact of ACV on plasma HIV-1 RNA ( $\downarrow 0.37 \log_{10}$  copies/mL)**
  - Reduction equivalent to  $\geq 43\%$  reduction in plasma viral load
  - No direct anti-viral effect of ACV on HIV-1
  - HSV-2 suppressive therapy prevents HSV-2 reactivations responsible for increased HIV-1 replication
  - Possible impact on other latent *Herpesviridae*?
  - Need trials with longer follow up to assess impact on CD4
- **Conclusion**
  - Results consistent with other trials
  - Differences may be due to populations, intervention or measurement of outcome

# Acknowledgements

---

- Participants, Community Advisory Board, and PLWHA organisations in greater Johannesburg, South Africa
- Reproductive Health & HIV Research Unit, South Africa: H Rees, N Mlaba, G Akpomiemie, J Arjun, BB Nkosi, C Dube, T Mashapa, T Pather, K Thobega, M Likhoeli, P Masuku, D Mbatha, D Ncube, S Sigasa, G Tshabalala, Z Mchunu, K Machete & staff of Esselen St Clinic
- Dept. Hematology & Molecular Medicine, Wits University, South Africa: W Stevens, A Capovilla, K Hira, I Doddameade, C Ingram, G Napier, W Le Roux
- London School of Hygiene & Tropical Medicine, UK: P Mayaud, T Clayton, H Weiss, C Watts, D Mabey
- INSERM U734, France: L Belec, J LeGoff, M Lecerf
- Data Monitoring Committee: A Nunn (chair), R Jewkes, A Puren
- *Funded by research grants from the Wellcome Trust, the National Research Foundation of South Africa, and DFID Research Programme Consortium on Reproductive Health & HIV*