

Efficacy of HSV-2 suppressive therapy on HIV-1 shedding and plasma viral load among co-infected women receiving or not HAART in Burkina Faso (ANRS 1285 trials)

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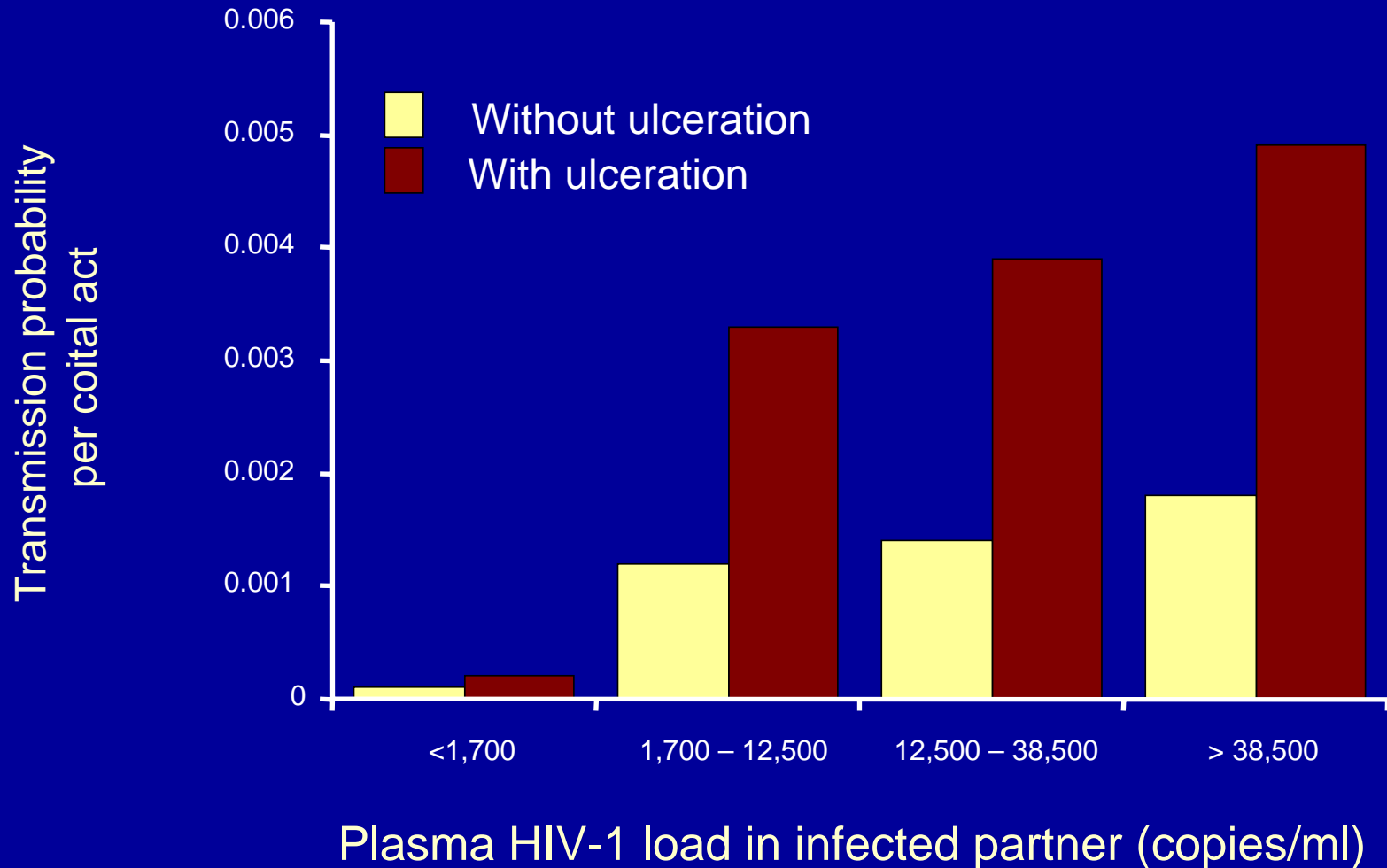
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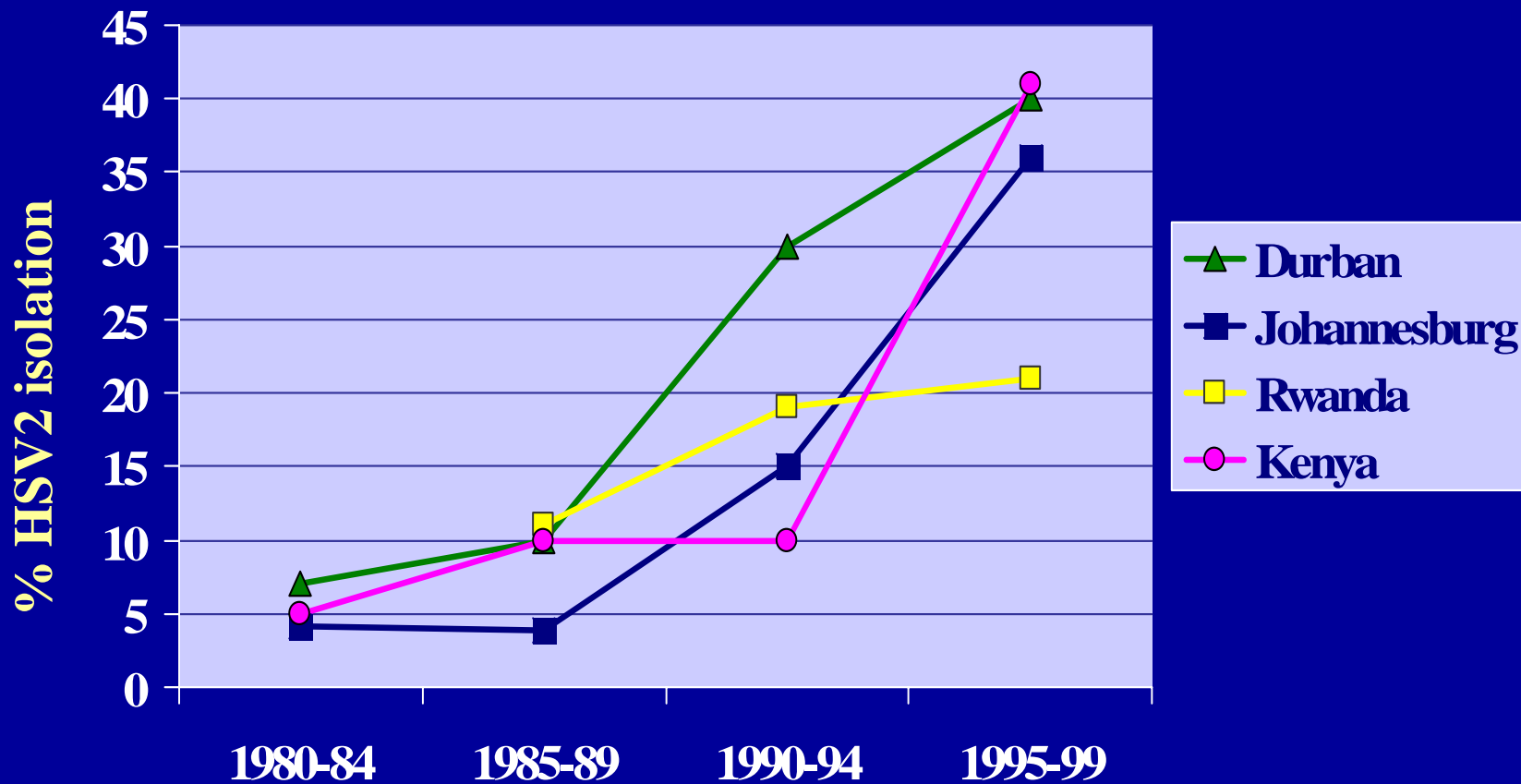
Influence of genital ulcerations

HIV-1 transmission probability per sexual intercourse in sero-discordant couples in Rakai, Uganda

(Gray RH et al., Lancet 2001)

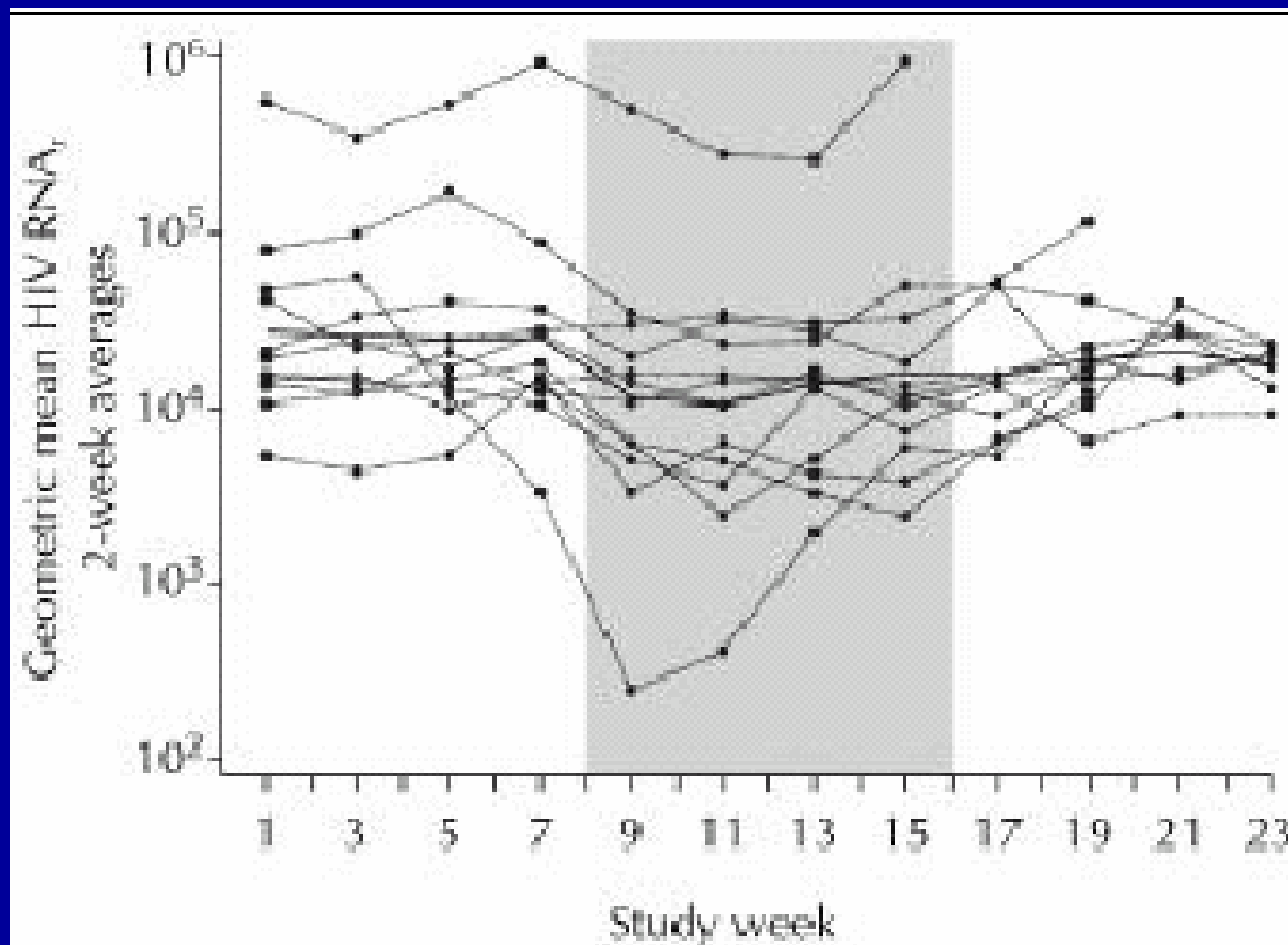


Proportion of genital herpes or HSV-2 isolation (culture/PCR) over time among GUD patients in sub-Saharan Africa settings

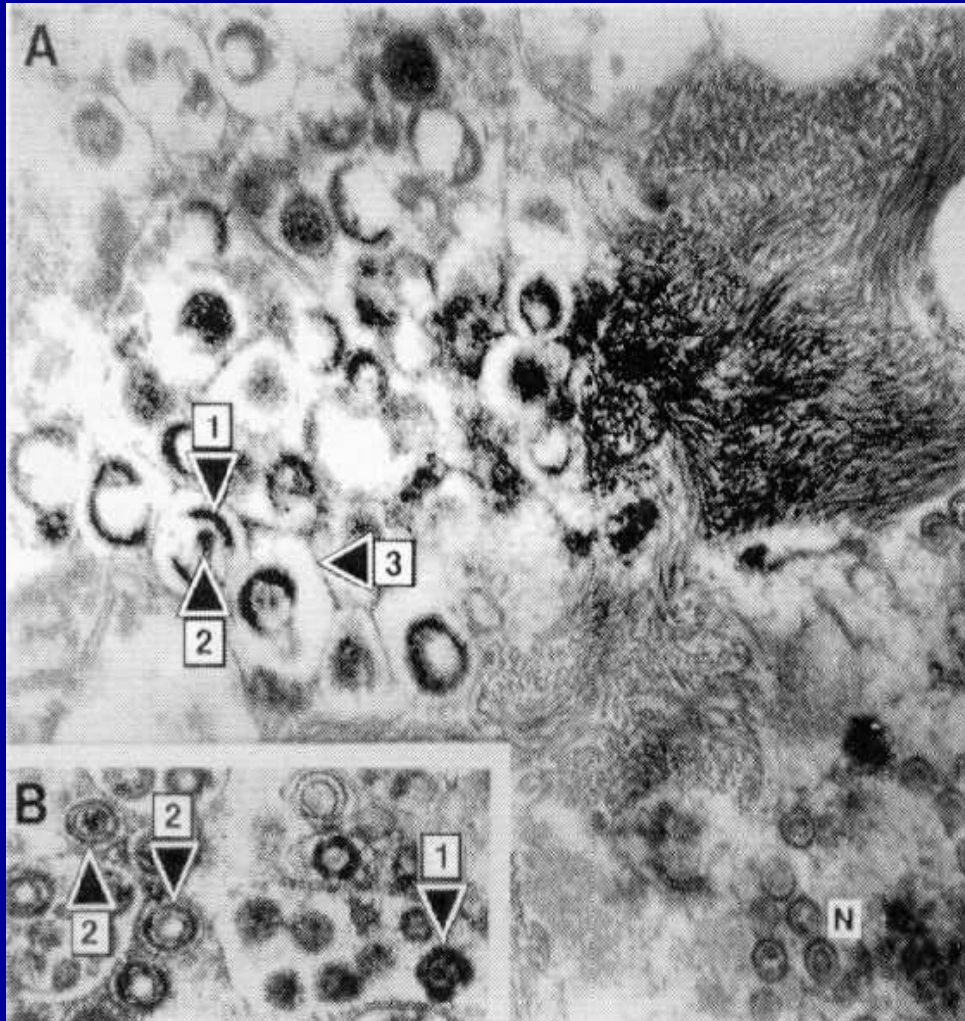


Median Plasma HIV RNA Before, During, and After Acyclovir Suppression among 12 MSM in Seattle

(Schacker et al. JID 2002)



Herpes Simplex Virus Infection Induces Replication of HIV-1



Co-infection of the same keratinocyte by HSV-1 and HSV-2 virions. Non-enveloped HSV-1 (N) in A and enveloped HSV-1 (2) in B. Atypical HIV in envelope (1), core (2) and membranes (3); typical HIV in B.

Heng et al. Lancet 1994

Design

Proof of concept double blind randomized controlled trials of daily valacyclovir 1000mg vs. placebo among co-infected women not eligible for HAART or taking HAART

Study endpoints:

- 1/ Detection and pattern of HIV-1 shedding and mean quantity of genital HIV-1 RNA
- 2/ - Mean quantity of plasma HIV-1 RNA
 - Detection and pattern of HSV-2 shedding and mean quantity of genital HSV-2 DNA
 - Occurrence of genital ulceration or vesicles

FSW cohort
(n=650)

PLWHA

Screening 1: HIV, HSV2, pregnancy
Screening 2: CD4+ count, creatinin

ANRS 1285a
(n=150)

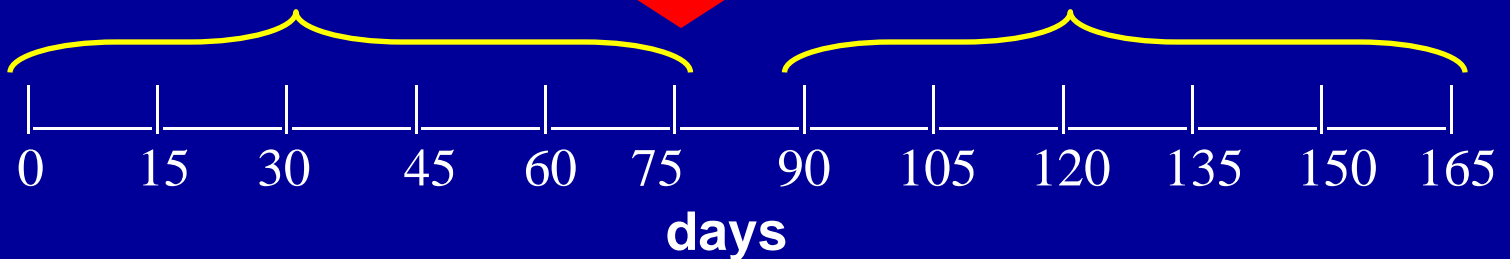
HAART

ANRS 1285b
(n=60)

P or V*

Baseline Phase

Treatment Phase

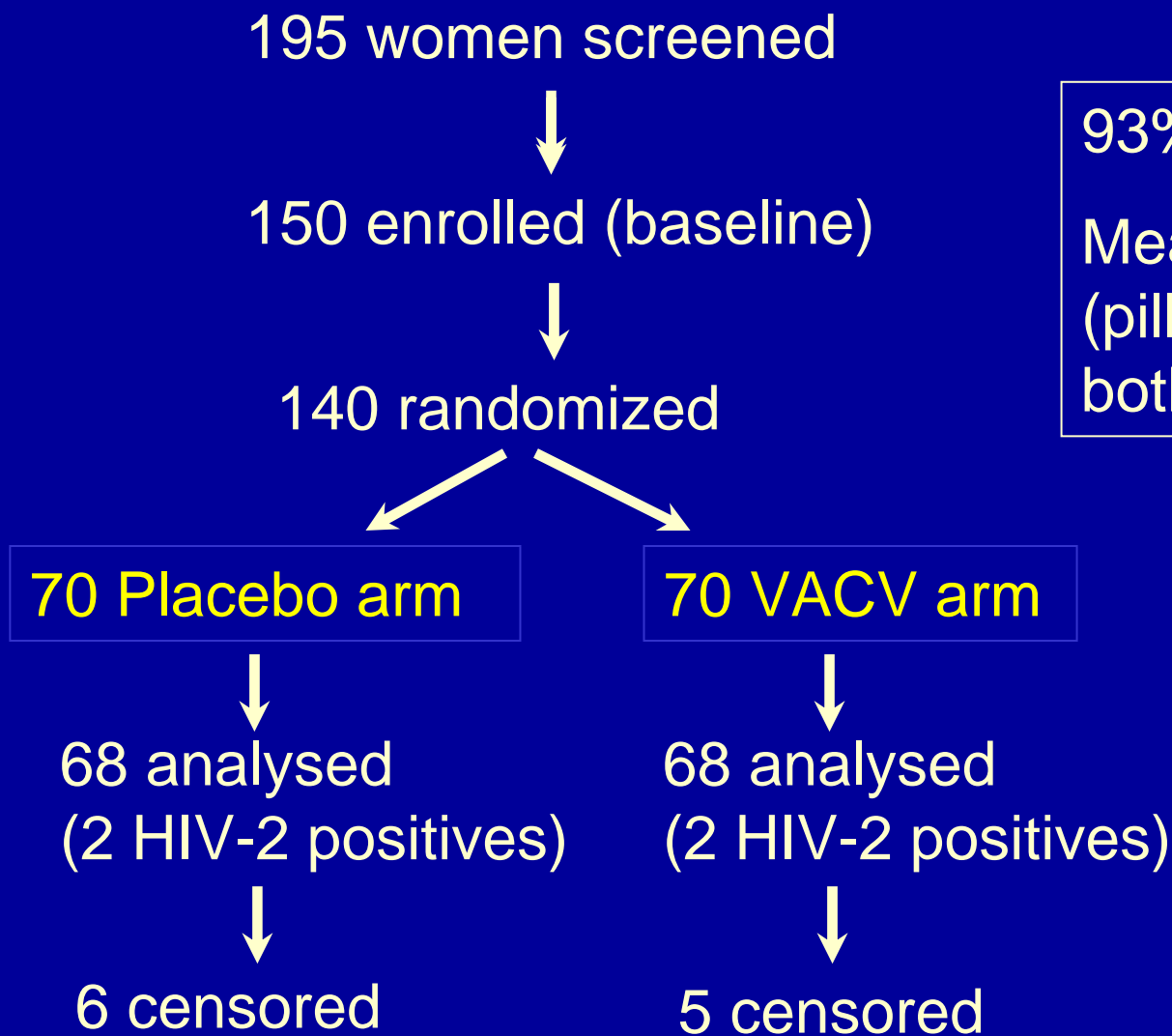


* Placebo or Valacyclovir 1000mg daily, first dose given the same day just after genital sampling

Laboratory procedures

- **Genital sample:** enriched cervico-vaginal lavage
- **HSV-2 serology**
 - Kalon test: best performance (98% specificity and 95% sensitivity, Van Dyck et al., JCM 2004)
- **Outcome measurements**
 - Real Time PCR (ABI 7000)
 - HSV-2 DNA (threshold=500 copies/mL)
 - Genital HIV-1 RNA (threshold=300 copies/mL)
 - Plasma HIV-1 RNA (threshold=350 copies/mL)
 - Technology transfer to BF, QC scheme
 - CD4 count by Facscount
 - CT by PCR & NG by culture

1285a: enrolment, follow-up, compliance



93% visits attended

Mean compliance rate
(pill count) = 97% in
both arms

1285b: enrolment, follow-up, compliance

82 women screened



61 enrolled (baseline)



60 randomized



30 Placebo arm

30 VACV arm



30 analysed



30 analysed



0 censored



2 censored

97% visits attended

Mean compliance rate
(pill count) = 99%

Median HAART duration:
19.3 wks (IQR 18-25)
(90% compliance)

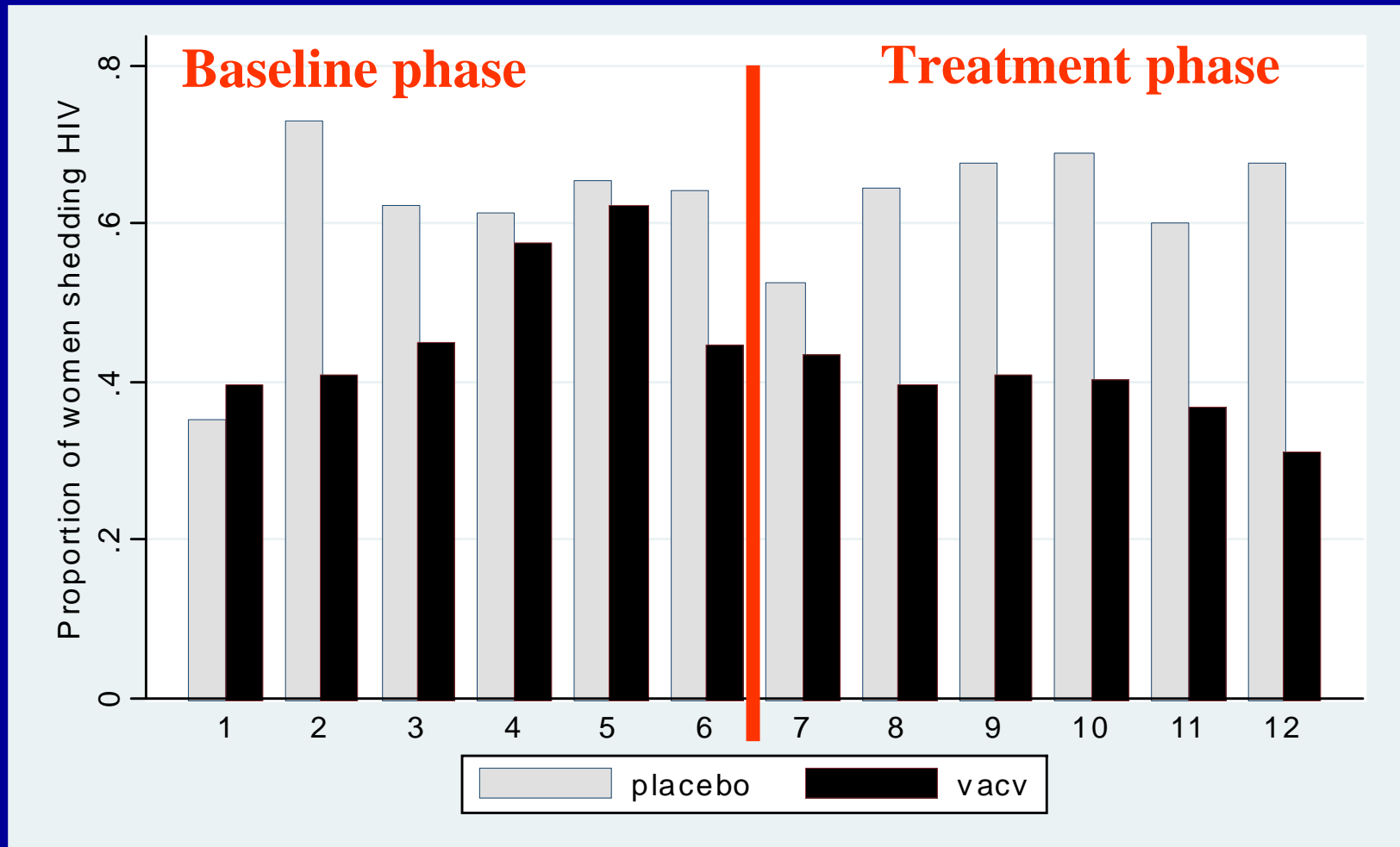
Baseline participants characteristics

1285a

	Placebo	Valacyclovir
Mean age in years (SE)	32.5 (0.89)	31.5 (0.93)
Median CD4 count (/μL) (IQR)	433 (316-621)	447 (328-655)
<i>Chlamydia trachomatis</i>	2 (2.9%)	1 (1.4%)
<i>Trichomonas vaginalis</i>	4 (5.6%)	1 (1.4%)
Serological syphilis	0	1 (1.4%)

ANRS 1285a

Proportion of women with HIV-1 genital shedding per visit per arm



Impact of VACV on detection of genital HIV-1 RNA

	ANRS 1285a (n=136)	ANRS 1285b (n=60)
% visits with HIV-1 genital shedding	OR=0.47 95%CI: 0.28-0.78 (p=0.003)	OR=1.00 95%CI: 0.39-2.56 (p=1.00)
	↓	<i>Among HIV-1 base shedders:</i> OR=0.27 95%CI: 0.07-0.99 (p=0.048)
Frequency/pattern of genital shedding (per woman analysis)	OR=0.41 95%CI: 0.21-0.80 (p=0.009)	OR=0.90 95%CI: 0.31-2.62 (p=0.85)






Impact of VACV on quantity of genital & plasma HIV-1 RNA

	ANRS 1285a (n=136)	ANRS 1285b (n=60)
Quantity of genital HIV-1 RNA	- 0.41 log ₁₀ [#] 95%CI: -0.21, -0.80 (p=0.009)	- 0.33 log ₁₀ [*] 95%CI: -0.80, 0.16 (p=0.19) <i>Among HIV-1 baseline shedders</i> -0.71 log ₁₀ [*] 95%CI: -1.27, -0.14 (p=0.013)
Quantity of plasma HIV-1 RNA	- 0.58 log ₁₀ [#] 95%CI: -0.79, -0.37 (p<0.001)	- 0.41 log ₁₀ [*] 95%CI: -1.35, 0.53 (p=0.39)

Per woman analysis (compares mean HIV-1 RNA per arm and phase)

* *Per visit analysis*, among all visits with detectable HIV-1 RNA

Impact of VACV on detection of genital HSV-2 DNA and GUD occurrence












	ANRS 1285a (n=136)	ANRS 1285b (n=60)
% visits with detectable HSV-2 DNA	OR=0.24 95%CI: 0.11, 0.51 (p<0.001) 	OR=0.37 95%CI: 0.13, 1.05 (p=0.06) 
Mean genital HSV-2 DNA (visits)	- 0.14 log ₁₀ * (p=0.77) 	- 1.18 log ₁₀ * (p=0.12) 
GUD occurrence	RR=0.16 (p=0.002) 	-

* Per visit analysis, among all visits with detectable HIV-1 RNA

Impact of VACV on HSV-2 infection (1285a)

	Baseline phase		Treatment phase		p value
	Placebo	VACV	Placebo	VACV	
GUD ≥ 1	27.9%	29.4%	27.9%	4.4%	0.002
HSV-2 shedders	45.6%	44.1%	54.4%	19.1%	<0.001
HSV-2 detected:					
No visit	54.4%	55.9%	45.6%	80.9%	<0.001
1-49% visits	38.2%	46.2%	41.3%	19.1%	
50-99% visits	7.3%	1.5%	11.7%	0	
All visits	0	0	1.5%	0	
Mean genital HSV-2 DNA	4.56 (n=50)	4.82 (n=38)	4.63 (n=68)	4.77 (n=15)	0.77

Summary Results

	1285a (N=136)	1285b (N=60)	1285b (b shedders) (N=30)
Genital HIV-1 RNA			
Frequency			
Quantity (\log_{10} copies/mL)	 - 0.41		 - 0.71
Plasma HIV-1 RNA			
Frequency			
Quantity (\log_{10} copies/mL)	 - 0.58	 - 0.41	

Rx effect increased over time: $-0.11 \log_{10}$ (CI: 0.06, 0.16)
 every 2 weeks for genital HIV-1 and **$-0.10 \log_{10}$ (CI: 0.06, 0.14)**
 for plasma HIV-1 RNA ($p < 0.001$)

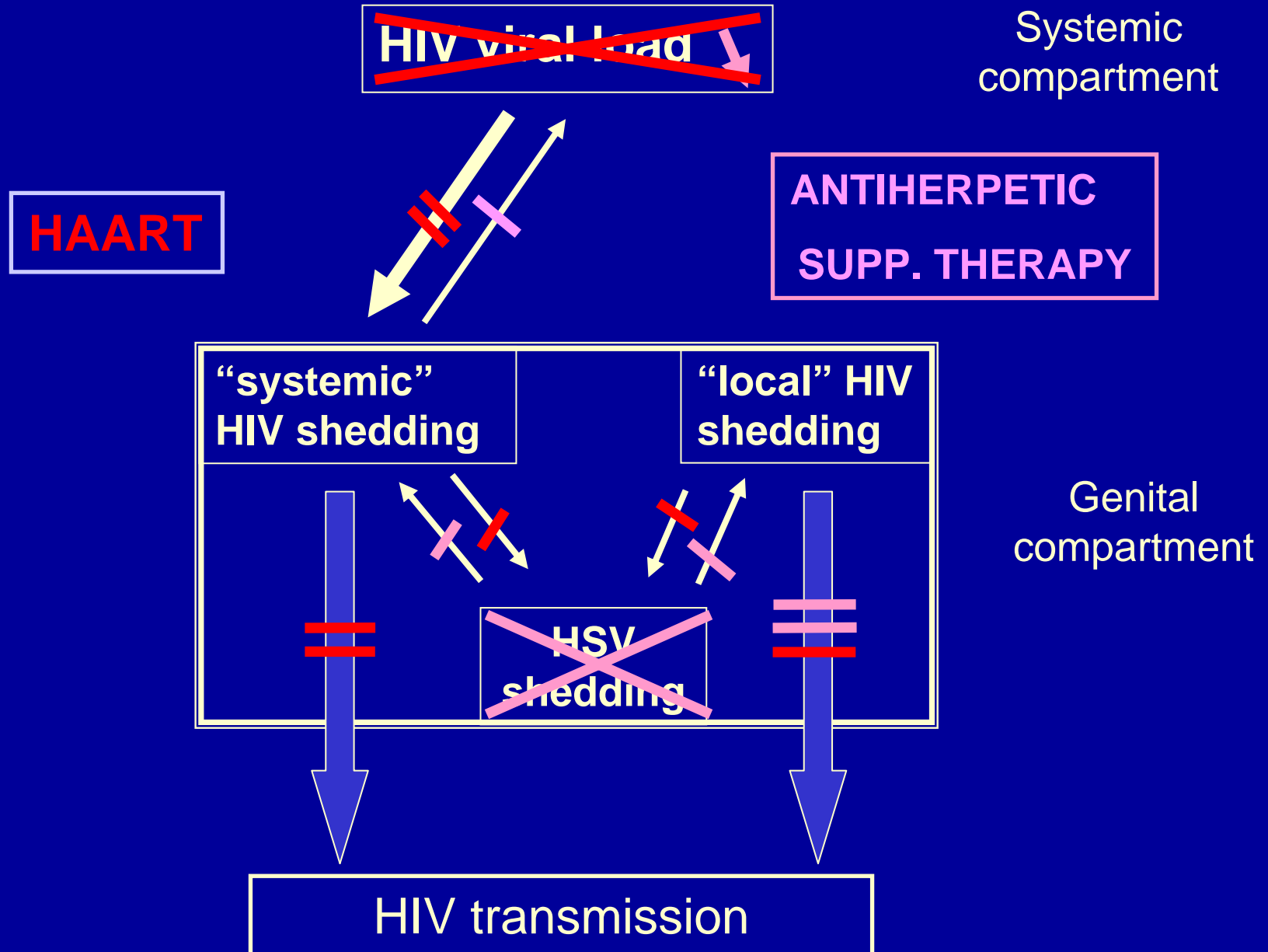
Discussion (1)

- **Causal link between HSV-2 and HIV-1 replication**
 - Proven, likely to persist while on HAART
 - Potential mechanisms for the impact of VACV on HIV-1:
 - Indirect role since ACV has no pharmacological effect on HIV-1
 - Biological explanations
 - Through impact on other latent Herpesviridae?

Discussion (2)

- **Genital compartmentalisation of HIV-1 replication**
 - 2/3 women with fully active HAART can potentially transmit HIV-1
 - Longitudinal data ++
 - Reinforce safe sex promotion among these patients
 - Poor genital penetration of d4T and EFV (Dumont et al., CROI 2006): selection of mutations?
 - VACV impacted on the genital independent HIV replication (may explain residual shedding of women on HAART)

Probable mechanisms involved



HSV suppressive therapy

- Safe, no lab monitoring required
- HSV resistance is rare, even among HIV infected individuals (<5%)
- **Potential benefits on HSV-2 infection:**
 - Prevention of clinical episodes
 - Marked reduction in HSV-2 shedding: impact on HSV-2 transmission?
 - More data required for effect of ACV with HAART
- Additional impact on other Herpes simplex viruses?

HSV suppressive therapy

Potential benefits on HIV-1 infection

- *HIV-1 transmission:*

- Impact on genital HIV-1 RNA = decreased transmission?

- *HIV-1 disease:*

- Need for clinical outcomes: does impact on PVL leads to slower CD4 decline ?
- Confirmation from other settings
- Role during HAART?

- *HIV acquisition:* ongoing effectiveness trials. Initiation during primary genital herpes?

Ongoing HSV suppressive Rx trials

HIV-1 acquisition:

- HPTN039 (University of Washington), men & women
- Mwanza (LSHTM), sex workers (ends summer 07)

HIV-1 transmission:

- Large multicentre suppressive RCT among serodisc. couples (n>3000), (Univ. of Washington)

HIV shedding & HIV plasma viral load

- South Africa: 300 women, 3 months follow-up
- Tanzania: 400 FSW, 12 months follow-up
- Peru: 20 MSM
- 'Partners in Prevention' trial

Future research...

- Extrapolation of these results to men?
- Impact of VACV on the long run before HAART, with immunological outcomes: individual benefits?
- Quantify the reduction in HIV-1 transmission
- Benefit of ACV on patients taking HAART (fully active or not)
- Cost-effectiveness and acceptability studies
- New vaccine concepts (both prophylactic and therapeutic) and develop the promising ones



Boost HSV vaccine research

Acknowledgements

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AND MANY THANKS TO ALL PARTICIPANTS