ANRS 1212 Study

Impact of HSV-2 episodic therapy on HIV-1 and HSV-2 genital shedding, and ulcer healing among women in Ghana and Central African Republic: randomised controlled trial

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Background

- HIV transmission is enhanced in the presence of genital ulcer disease (GUD) *(Gray, Lancet 2001)*
- Increasing % of GUD due to HSV-2 in HIV+

Research questions

- Is HSV-2 really a cofactor of HIV transmission?
- Can HSV-2 be controlled? Will this have an impact on HIV transmission?
- By which method?
  - Prevention of GUD (role of **suppressive therapy**)
  - Treatment of GUD (role of **episodic therapy**)
  - Other (education, condoms, microbicides, vaccine?)

ANRS 1212 Trial

Multicentre, randomised, double-blind placebo-controlled trial of antiherpetic episodic treatment (acyclovir 400 mg x 3/d for 5 days) in addition to syndromic management (Ciprofloxacin + Benzathine penicillin 2.4 MU) among women with GUD in Ghana and Central African Republic

Exclusion criteria:

- indications for immediate ACV (large or chronic ulcers)
- contra-indications of ACV (pregnant, breast-feeding, renal failure, history of “allergy” to ACV)

ANRS1212: Study Outcomes

(Primary analysis group: HIV-1 +ve women with HSV-2 ulcers)

Outcomes:

1) Detection,frequency, and quantity of cervico-vaginal (CV) HIV-1 RNA* among HIV-1/HSV-2 co-infected women

2) Detection of lesional HIV-1 RNA*
   Quantity of plasma HIV-1 RNA*
   Detection,frequency and quantity of cervico-vaginal (CV) HSV-2 DNA*

3) Ulcer aetiologies (PCR) and healing rates (size)

* using real-time PCR; Methods in *Legoff J et al, J Clin Microbiol 2006;44: 423-32*

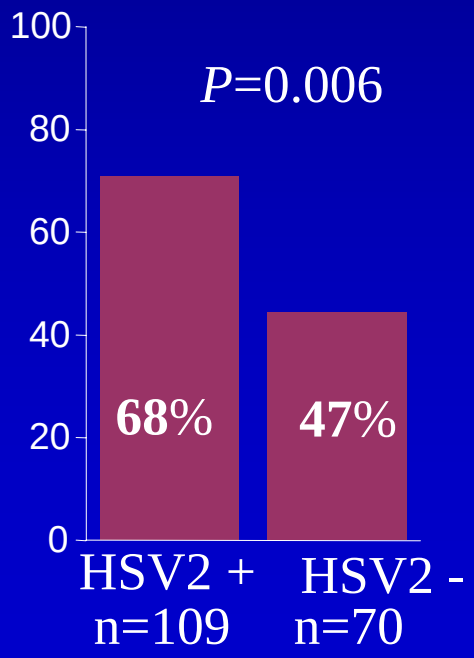
Enrollment by site: Total trial population

	Synd+Placebo n (%)	Synd+ACV n (%)
ACCRA (n=121)	60 (27%)	61 (28%)
KUMASI (n=163)	82 (37%)	81 (37%)
BANGUI (n=157)	78 (35%)	70 (36%)
Total (n=441)	220	221

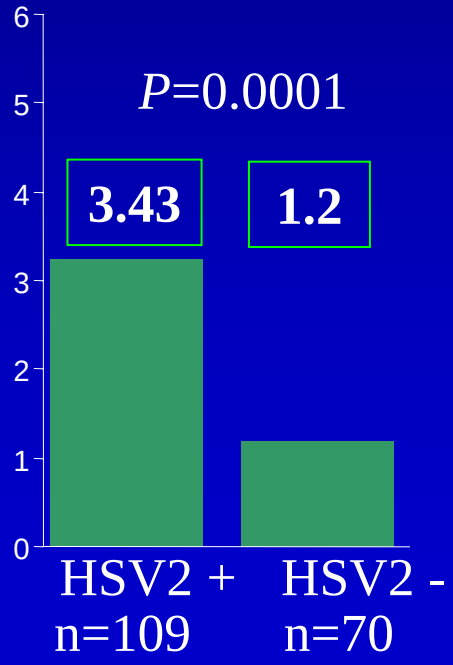
Baseline data

HSV-2 ulcers	50% (only **3%** have bacterial etiol.)
HSV-2 sero+	79%
HIV-1 sero+	47%
Dually sero+	41% (n=179)

% HIV-1 in CVL

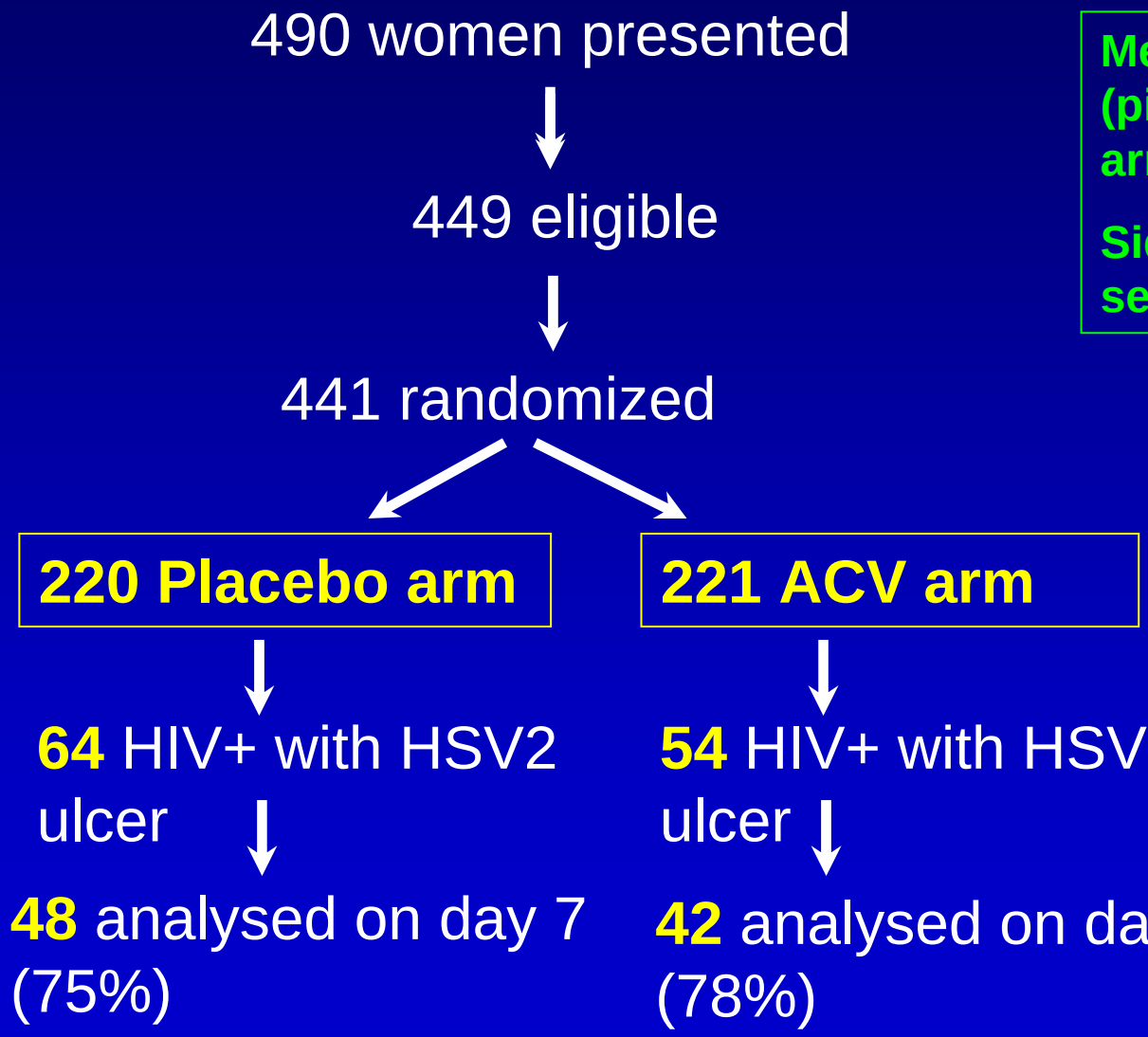


CV HIV-1 RNA (log_{10} c/mL)



Plasma HIV-1 RNA
5.13 vs. **4.64** log_{10} c/mL (*P*=0.03)

Enrolment, follow-up, compliance



Mean compliance rate (pill count) = 99% in both arms

Side effects: 8/441 (2%, severity 1 or2)

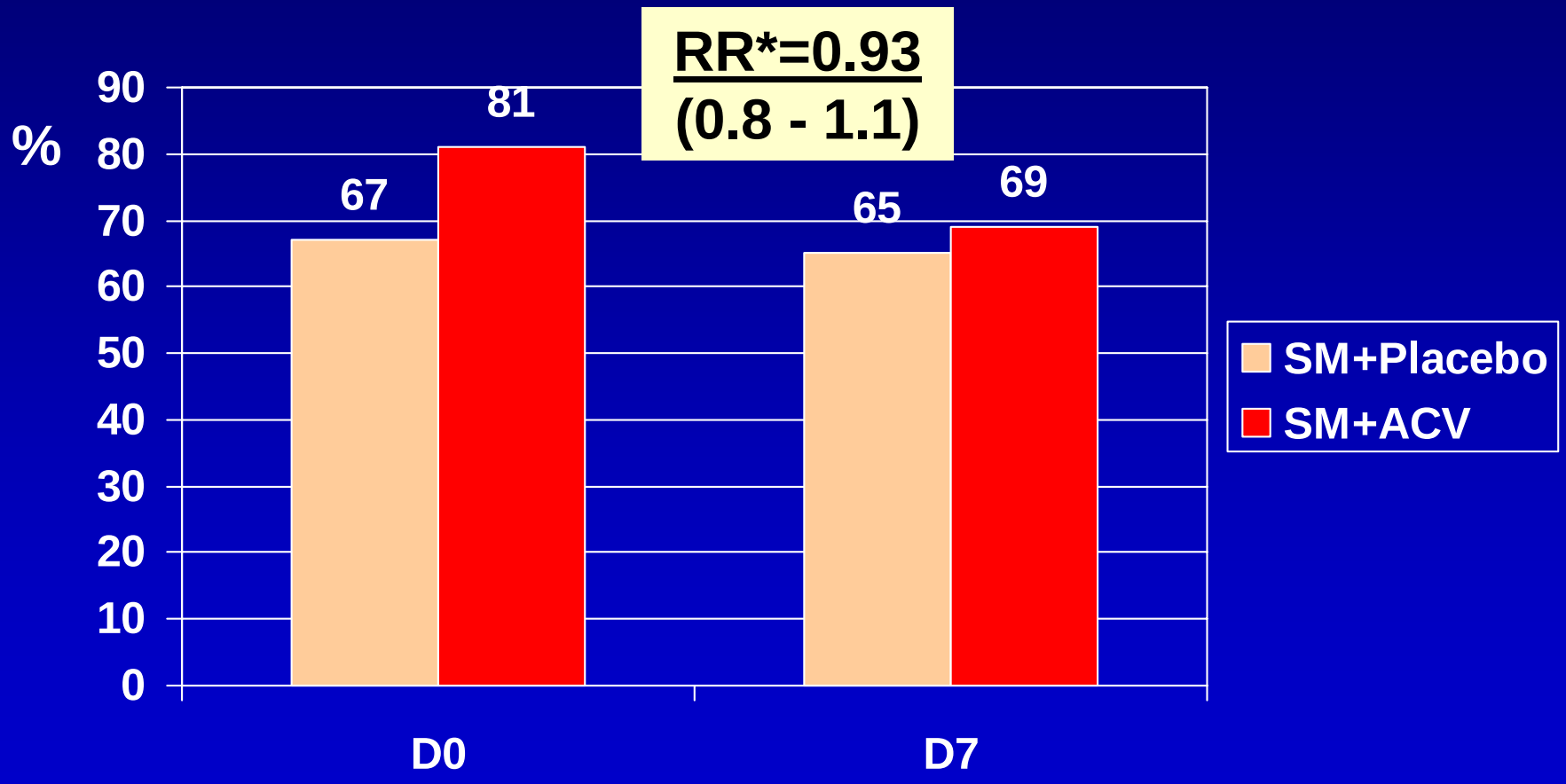
Primary analysis group:

118 HIV+ women with HSV-2 ulcer

Participants characteristics in primary analysis group (HIV+ women with HSV-2 ulcers) (N=118)

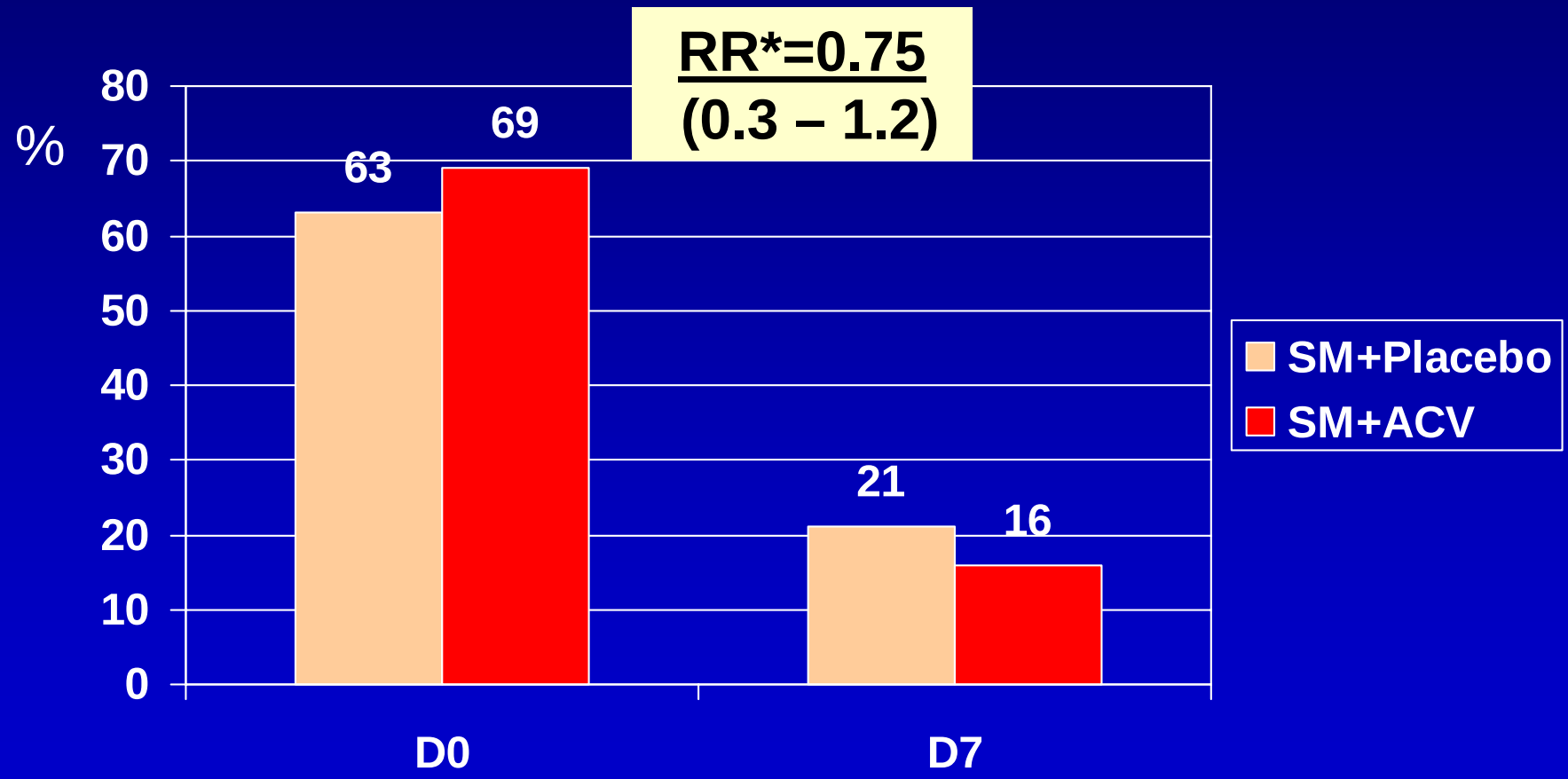
	SM+Placebo (n=64)	SM+ACV (n=54)
Mean age in years	31.4	30.8
Median CD4 count (/µL) (IQR)	188 (72-519)	194 (92-548)
Taking HAART	5 (8%)	6 (11%)
Experienced GUD last year	27 (42%)	25 (47%)
Neisseria gonorrhoeae	3 (5%)	3 (6%)
Chlamydia trachomatis	0	0
Trichomonas vaginalis	1 (2%)	1 (2%)
Serological syphilis	0	0

Impact of ACV on frequency of CV HIV-1 RNA detection at day 7 among HIV+ women with HSV-2 ulcers (N=90)



** Adjusted for site and baseline CV HIV-1 RNA*

Impact of ACV on frequency of lesional HIV-1 RNA detection at day 7 among HIV+ women with HSV-2 ulcers (N=76)



** Adjusted for site*

Impact of ACV on HIV-1 viral loads

- Little impact on mean cervico-vaginal HIV-1 RNA at day 7 (-0.11 $\log_{10}$ copies/mL, *P*=0.53)

- No impact on mean plasma HIV-1 RNA at day 14 (0.04 $\log_{10}$ copies/mL, *P*=0.76)

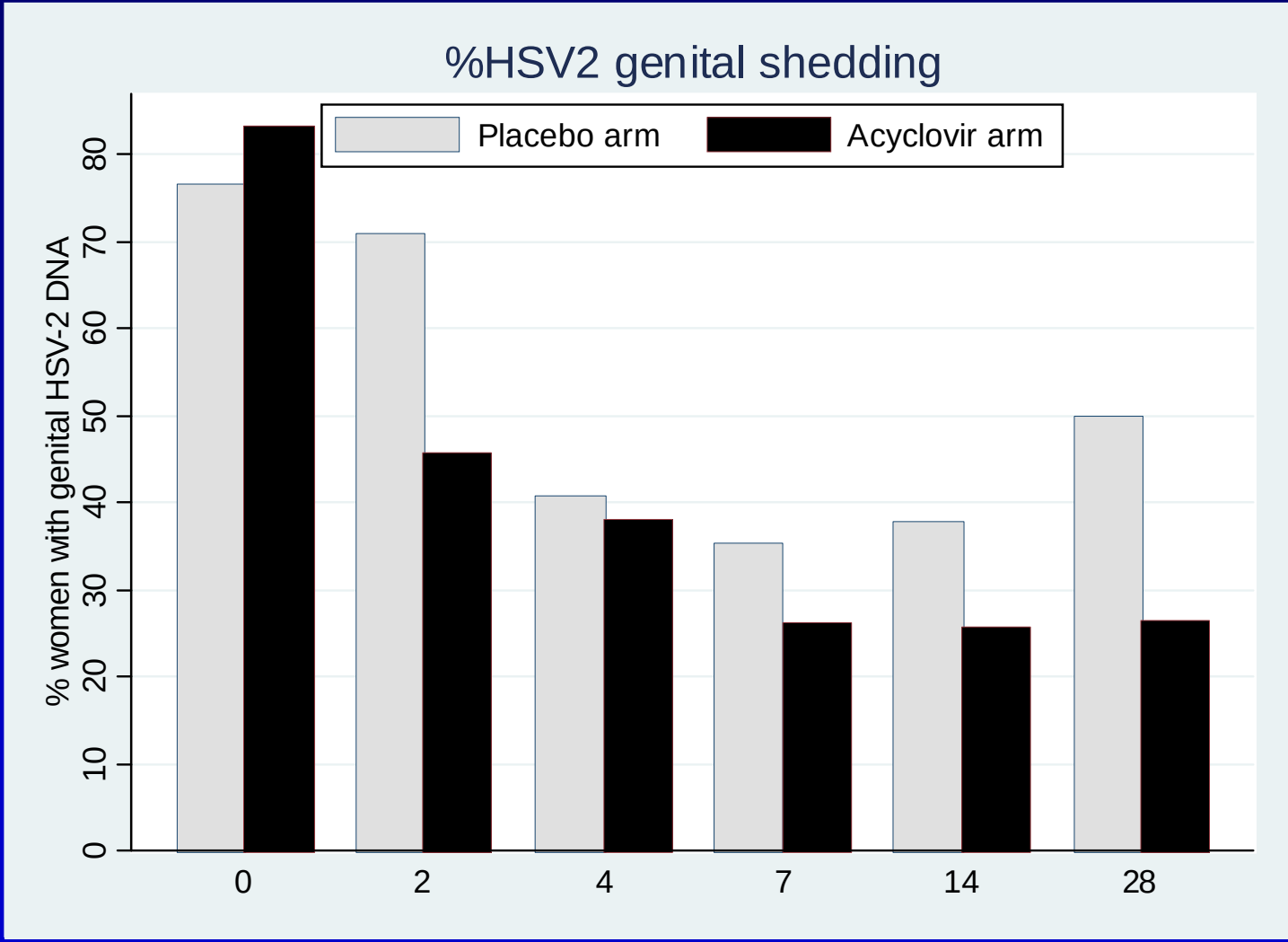
Impact of ACV on HSV-2 at day 7

- Reduction from:
  - **81%** at D0 to **26%** at day 7 in acyclovir arm,
  - **81%** at D0 to **35%** at day 7 in placebo arm

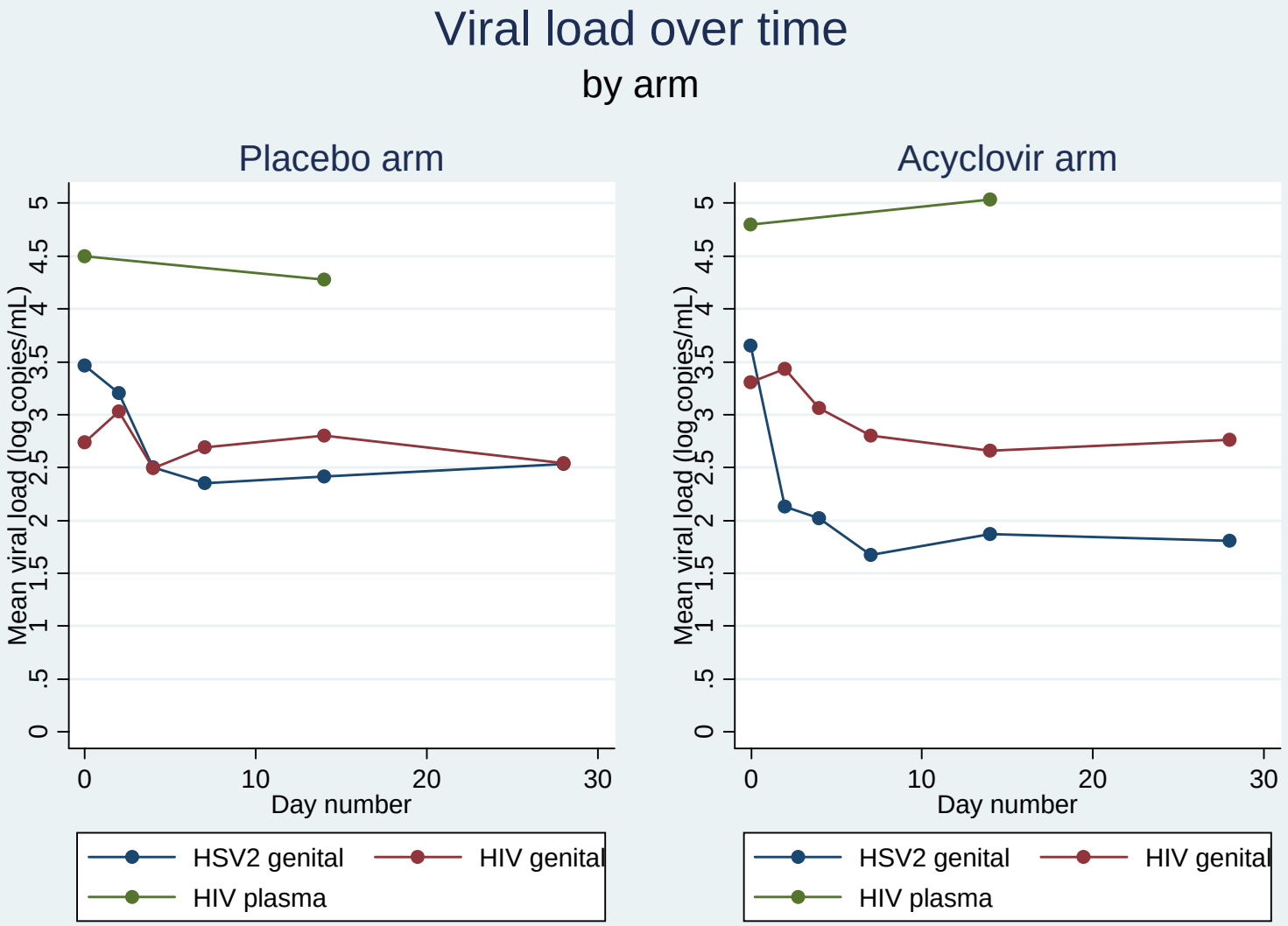
    => RR=0.73 (*P*=0.2)

- **Mean quantity HSV-2 DNA was 1.2 $\log_{10}$ copies/mL lower in acyclovir arm than placebo arm (*P*=0.004)**

Proportion of women with CV HSV-2 DNA over time in HIV+ women with HSV-2 ulcers



Mean HIV-1 and HSV-2 viral loads over time



Impact on ulcer healing at day 7 in HIV+ women with HSV-2 ulcers

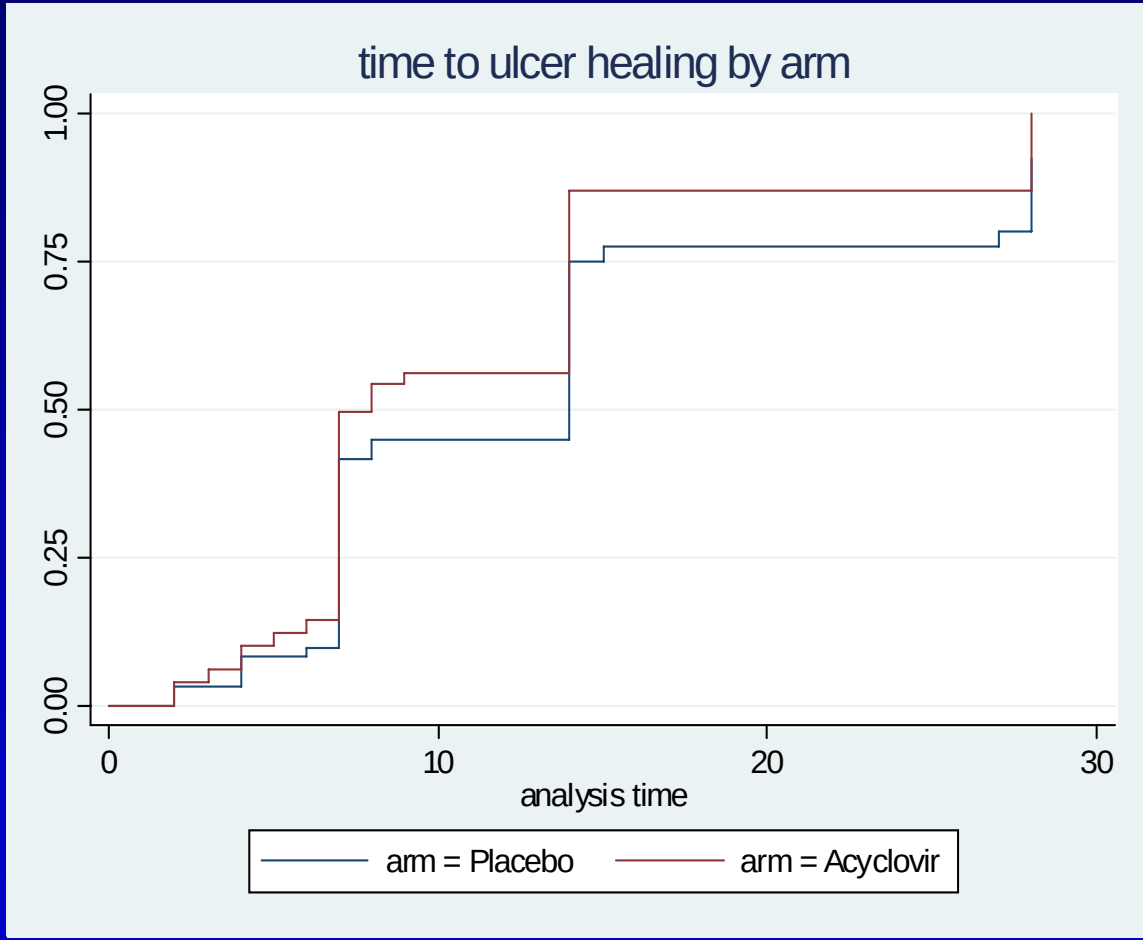
	D0		D7		Magnitude	P-value
	Plac.	ACV	Plac.	ACV		
% ulcers with >90% size reduction			44%	55%	**RR=1.23**	**0.06**
% with ulcers <10 mm^2	10%	0%	42%	58%	**RR=1.48**	**0.02**

Ulcer healing rates over time: HIV+ women with HSV-2 ulcers

Some impact of ACV among HIV+ women with HSV-2 ulcers (*P*=0.10)

No impact overall on ALL HIV+ women

Ulcers healed faster in women with higher CD4 count (*P*=0.0002)



ANRS1212: Conclusions

- **Episodic ACV has no measurable (immediate) impact on HIV-1 genital shedding**
  - Late treatment (median 7 days after ulcer first noticed by woman)
  - Insufficient duration of treatment (5 days)?
  - Insufficient dose of standard regimen?
  - Delayed effect on genital HIV load (day 28 or later)?
  - Advanced HIV disease in many women
  - Lack statistical power?
- **ACV does**:
  - Decrease frequency and quantity of CV HSV-2 DNA
  - Improve healing rates, particularly among HIV+ with low CD4
- **HSV-2 the dominant GUD aetiology**
  - Associated with high HIV-1 sero-prevalence
  - Associated with high HIV-1 viral loads (similar to levels observed in HIV-1 primary infection for PVL)

Programmatic implications

(1) Syndromic Management of GUD

- Need to remove antibiotics? **No (healing, HIV shedding)**
- Need to add ACV? **Yes** (cautiously… clin + epi impact?)

(2) Offering HIV testing to patients with GUD (+++)

- for HIV positive patients:
  - Access ARV+++
  - Explain frequent HSV reactivation
  - Possibly offer suppressive treatment
- for HIV negative patients:
  - Explain risk of HIV acquisition, reinforce prevention messages
  - HSV disease education and benefits of early Rx

Research implications

- For prevention of **HIV transmission**:
  - Await results of other trials in Malawi & South Africa
- For prevention of **HIV acquisition**:
  - High risk of HIV seroconversion (particularly PGH)
  - Should be better studied
- Relative roles of **episodic** vs. **suppressive** treatment, or **combination for HIV+ patients**?
  - Longer duration of episodic treatment?
  - Initiation of suppressive treatment
  - Operational research/trials required

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