Herpes simplex virus type-2 (HSV-2) suppressive therapy to reduce genital and plasma HIV-1 RNA: overview of ANRS1285 trials, potential mechanisms and future interventions

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HSV-2 – HIV-1: Double Trouble

- HSV-2 facilitates HIV-1 acquisition *(Freeman E et al. AIDS 2006)*
- >80% of HIV-1 infected individuals are co-infected with HSV-2 in Africa
- HIV alters the natural history of HSV-2
- HSV-2 may potentially increase HIV-1 transmissibility through increased shedding

=> RCTs required to demonstrate a causal role of HSV-2 on HIV-1 replication and transmissibility, at all stages of HIV disease, incl. HAART

Design & Study Outcomes

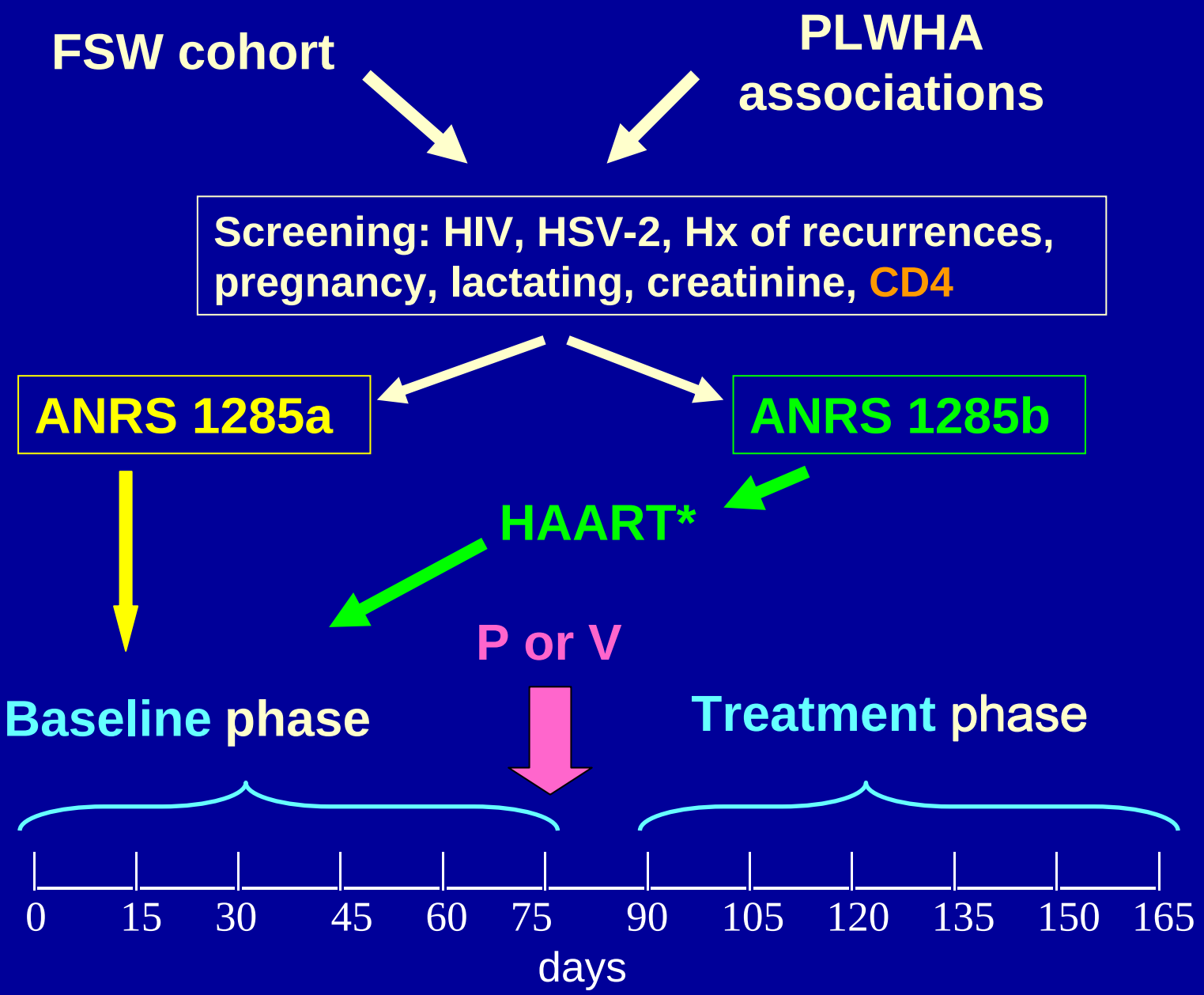
Proof-of-concept double-blind randomized trials of daily valacyclovir 500mg BD for 3mo. vs. Placebo among dually HIV-1 / HSV-2 sero+ women, either not eligible for HAART (ANRS 1285a), or taking HAART for >4 mo. (ANRS 1285b)

Study Outcomes:

1. Detection, frequency & quantity of cervico-vaginal (CV) HIV-1 RNA
2. Quantity of plasma HIV-1 RNA
   Detection, frequency & quantity of CV HSV-2 DNA
   Occurrence of genital ulcerations
3. Compliance and side effects rates

Laboratory Methods

- Serologies: HIV-1, HSV-2 (Kalon® gG2), syphilis
- HIV plasma viral load (real time PCR) - monthly
- CD4 cell count by FACSCAN – once/phase
- Standardised enriched cervico-vaginal lavage (eCVL) *(Nagot N et al, JAIDS 2005)* - bi-weekly
- HIV-1 RNA and HSV-2 DNA quantitated by real-time PCR, using external standards for QC (ANRS HIV, HSV 1/2 Clear QC)



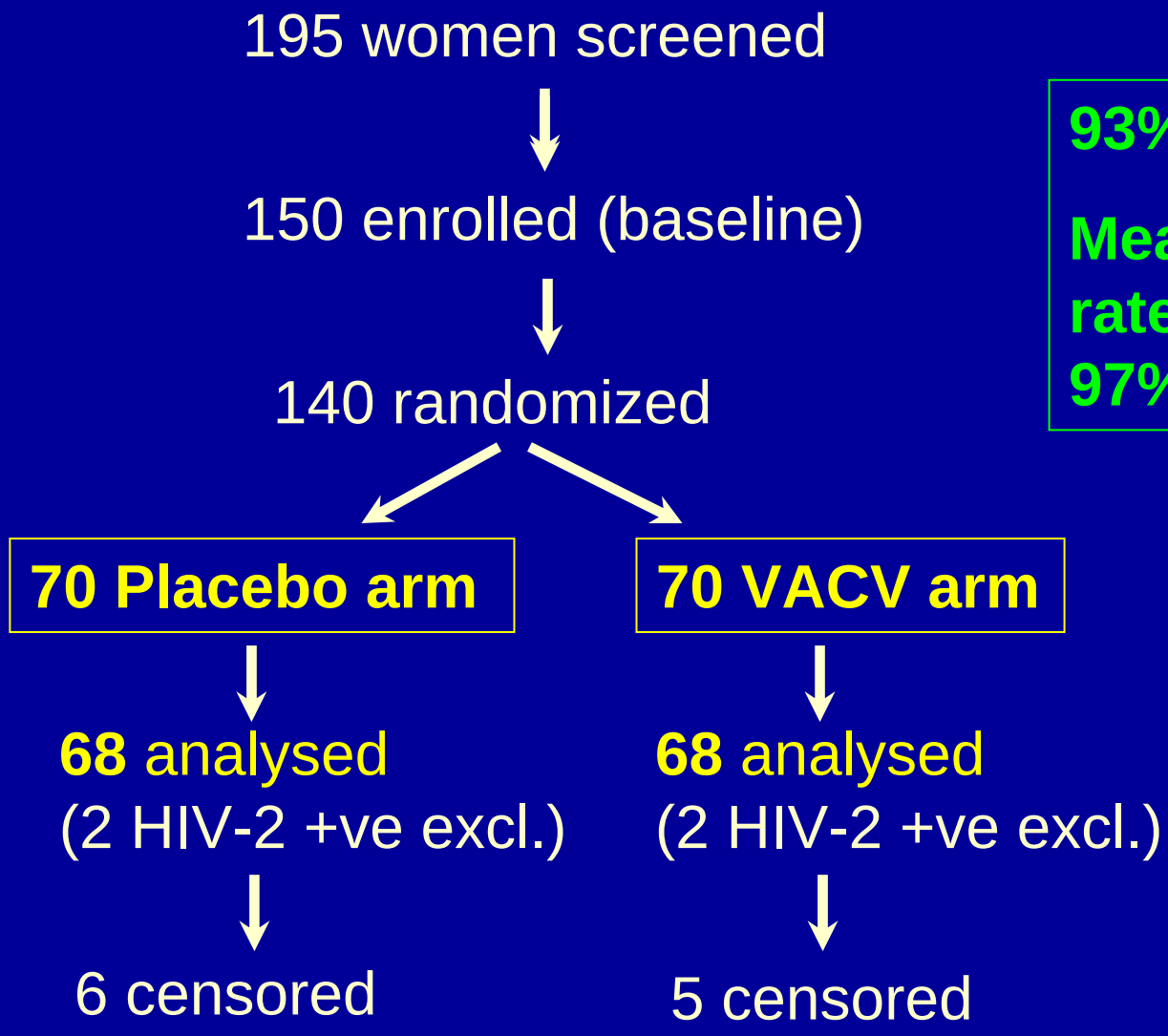
** First line: AZT or stavudine [d4T] + lamivudine [3TC] + efavirenz [EZV]*

Statistical Methods

- Modified Intention to Treat approach (censoring incident pregnancy)

- Summary measure (per woman) analysis
  - Quantitative outcomes: linear regression
  - Qualitative outcomes: (ordered) logistic regression
- Repeated measures analysis (per visit) analysis
  - Random effects models
- Pre-specified subgroup analyses (1285b)
  - Women shedding HIV-1 at least once over the baseline phase

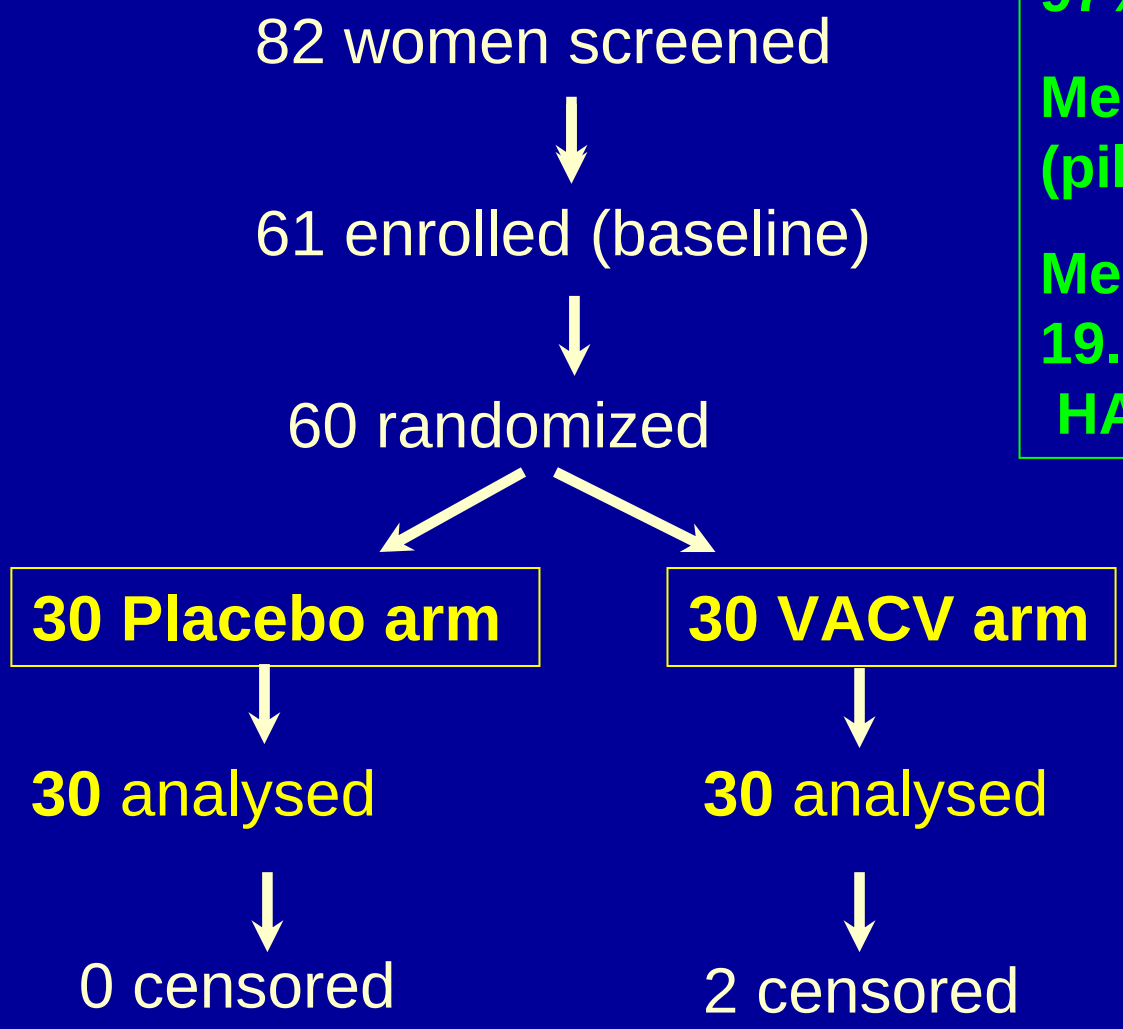
ANRS 1285a:
Enrolment, follow-up, compliance



93% visits attended

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

ANRS 1285b:
Enrolment, follow-up, compliance



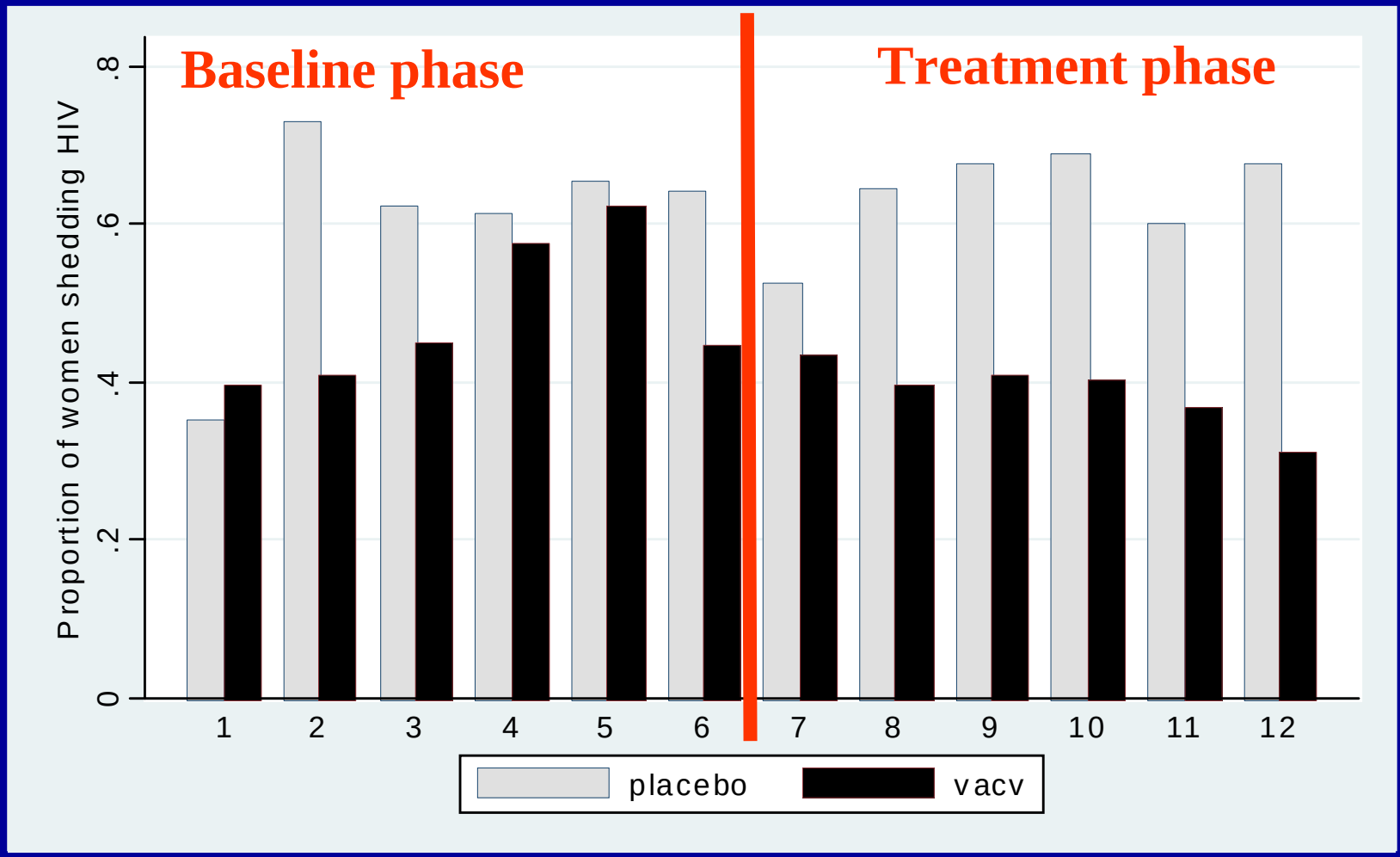
97% visits attended

Mean compliance rate (pill count) = 99%

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

ANRS 1285a (non-HAART)

Proportion of women with detectable genital HIV-1 RNA by visit, treatment arm and study phase



Summary Results: Impact on HIV-1

	1285a (N=136)	1285b (N=60)	1285b (base. shed.) (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**	↔

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) every month for plasma HIV-1 RNA ($p<0.001$)

Impact of VACV on HSV-2 and ulcers

- Women not taking HAART (1285a):
  - Reduction of genital HSV-2 by 65% (54% to 19% of visits)
  - Reduction of occurrence of ulcers by 84% (30% to 4.4% of visits)
- Women on HAART (1285b):
  - Very little HSV-2 shedding, but further reduced by 70%
  - No ulcer occurrence in both arms

Discussion (1)

- **First RCT to demonstrate causal relationship between HSV-2 and HIV-1 replication**
  - Effect still persists while on HAART (1285b, baseline shedders).
  - Potential mechanisms:
    - no direct antiretroviral effect of VACV
    - known biological interactions (afflux of CD4+; HSV proteins transactivate HIV tat or LTR) – role of lesions?
    - impact on other *Herpesviridae* (HSV-1, CMV, EBV HHV-6)?
- **Impact on genital HIV-1 RNA and plasma HIV-1 RNA**
  - Sufficient impact to reduce HIV-1 transmission?

    => Await results of ongoing trials among sero-discordant couples (C. Celum)
  - Could virological impact at systemic level be translated into impact on CD4?

    ⇒Specific trials needed? Operational research?

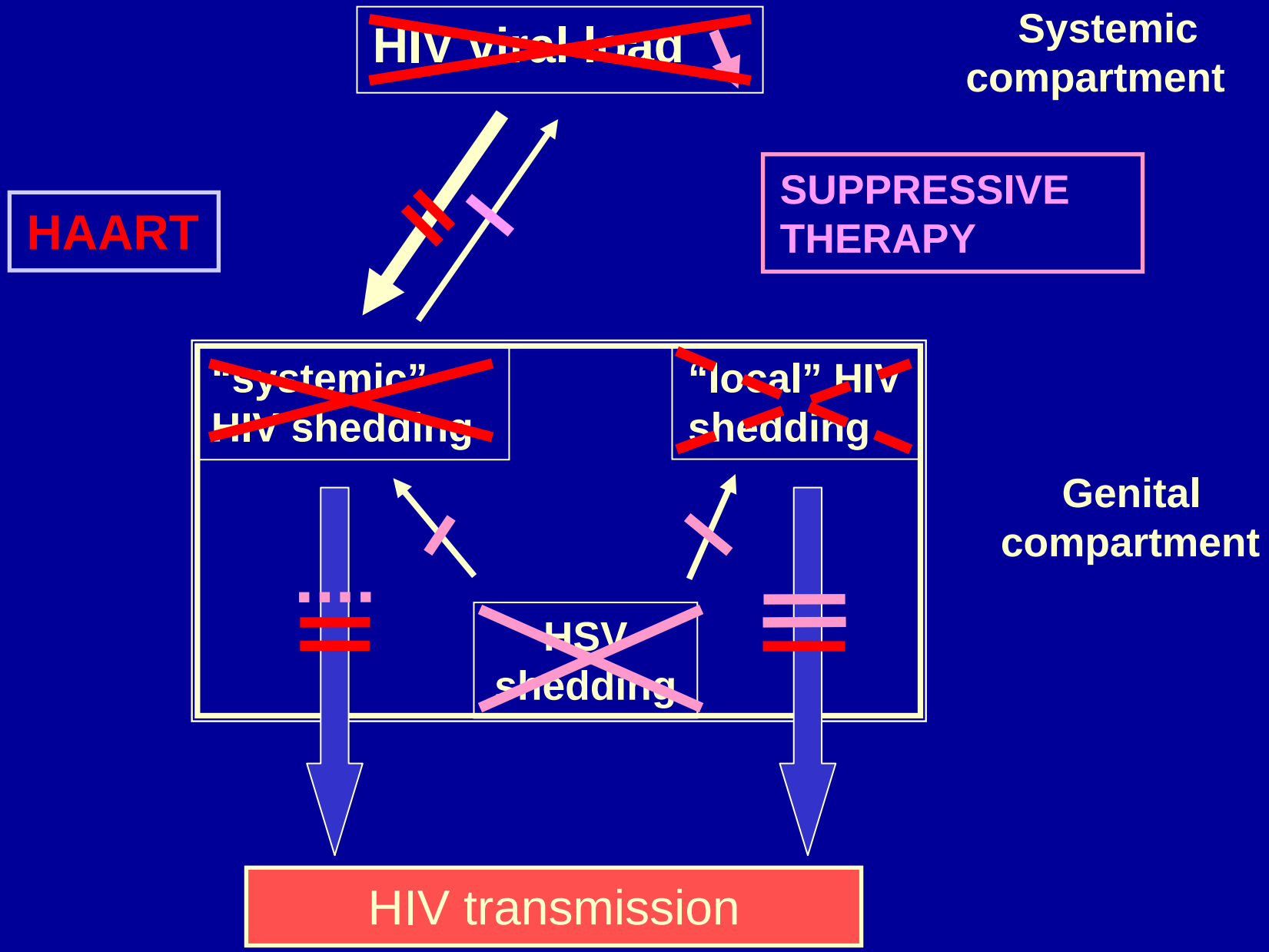
Discussion (2)

- **Genital compartmentalisation of HIV-1 replication**
  - Suggested by results of ANRS1285b
  - Two-thirds of women with fully active HAART shed HIV at some point and could potentially transmit HIV-1

    => safe sex promotion to be emphasized
  - Poor genital penetration of d4T and EFV (*Dumont et al., CROI 2006*)

    => selection (and transmission?) of HIV mutants?

Possible mechanisms of action



HSV suppressive therapy: Important Remaining Questions

1) Is it safe and practical to use?

• few side effects, no lab monitoring required, resistance is rare (<5% in HIV+), good compliance possible

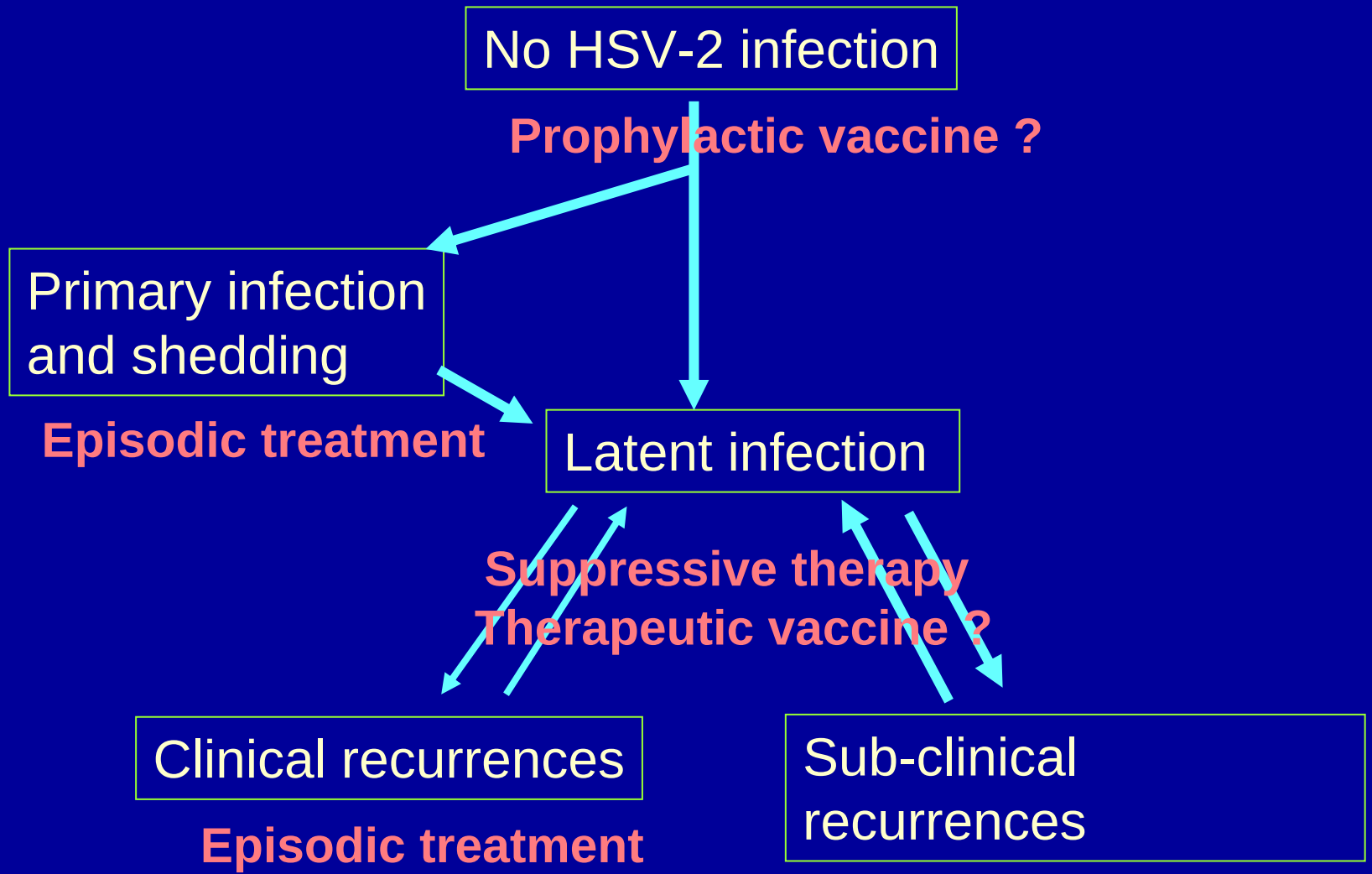
2) What will be the potential benefits?

• on HSV-2: clinical episodes, shedding, HSV transmission?
• on other Herpesviridae? (co-morbidity)
• on HIV transmission? disease progression? acquisition?

3) In which populations should it be offered?

• High-risk groups?
• Sero-discordant couples?
• In HIV+: before HAART? during HAART?

HSV-2 potential control tools



For More Information

- ANRS Symposium, Tues 15/08, 18:00, Skills Building Room #3

- ANRS 1285a: CROI Feb 2006 (Nagot N et al, Abs# 33LB)
- ANRS 1285b: Poster TuPE0402 (Nagot N et al) and *AIDS* 2006 (in press)