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# Les stratégies d'interruption chez les patients traités lors de la primo-infection à VIH

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# Les essais d'immuno-intervention au cours et au décours de la primo-infection à VIH

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## ◆ Objectifs

- Améliorer la qualité du contrôle de la réplication virale par le système immunitaire de l'organisme infecté (towards an altered setpoint)

## ◆ Moyens

- Vaccination (**QUEST**, **PRIMOVAC**)
- Activation de cellules quiescentes par IL-2 (**PRIMOVAC**)
- Interruptions séquentielles de traitement (**PRIMSTOP**)
- Administration d'IF- $\alpha$  (**PRIMOIFERON**, **INTERPRIM**)
- Ciclosporine A

Evaluation of two therapeutic HIV vaccination regimens in HAART-treated primary HIV infection subjects following analytical treatment interruption: a randomised, placebo-controlled study



**Kinloch-de Loes S, Perrin L, Hoen B, Lampe FC, Phillips AN, Goh L, Tsoukas C, Sonnerborg A, Autran B, Andersson J, El Habib R, Theofan G, Carter N, Cooper DA**

**On behalf of the Core Group for the QUEST Study**

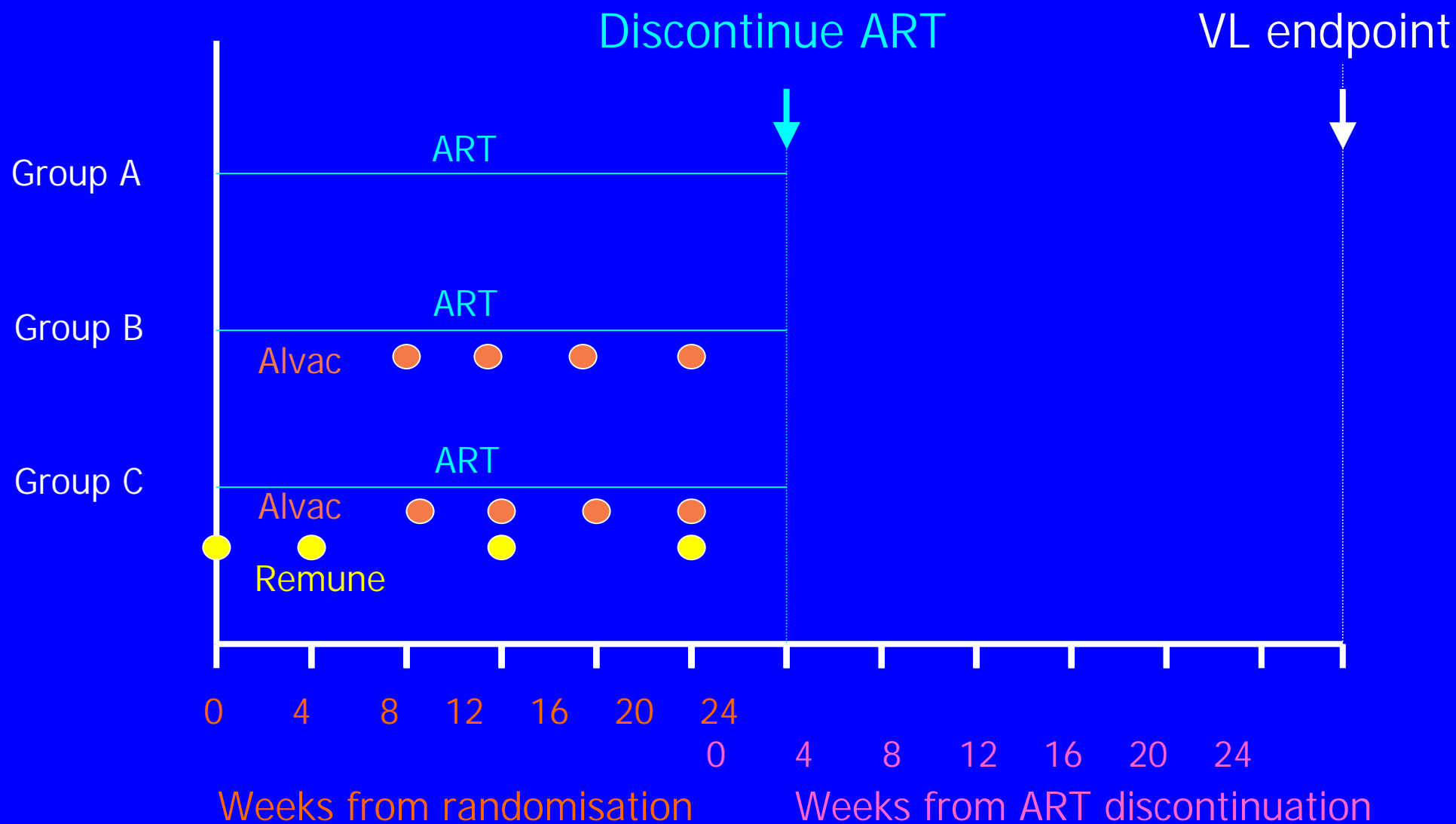
# Study Design

- ◆ Randomised, double-blind, placebo-controlled trial among PHI subjects ( $\leq 3$  bands on WB) on ART  $\geq 72$  weeks with VL  $< 50$ c/mL to one of 3 arms:
- ◆ Group A: ART alone
- ◆ Group B: ART + ALVAC vCP1452
- ◆ Group C: ART + ALVAC vcP1452 + Remune<sup>TM</sup>

# HIV Vaccines

- ◆ ALVAC vCP1452: canarypox-based vaccine with HIV-1 inserted genes env, gag, synthetic polypeptide encompassing the known human CTL epitopes from the nef and pol gene products. Inserted vaccinia virus E3L and K3L coding sequences (Aventis Pasteur)
- ◆ Remune™: inactivated, envelope-depleted (gp 120) HIV-1 virus delivered in Incomplete Freund's Adjuvant (IFA) (Immune Response Corporation)
- ◆ Placebo: ALVAC vCP 1452 placebo – IFA

# Study design



# Endpoints

## Primary endpoint:

- ◆ VL  $\leq$  1000 c/mL at 24 weeks post-stopping ART  
(ITT-restart ART/missing VL = failure)

## Additional endpoints:

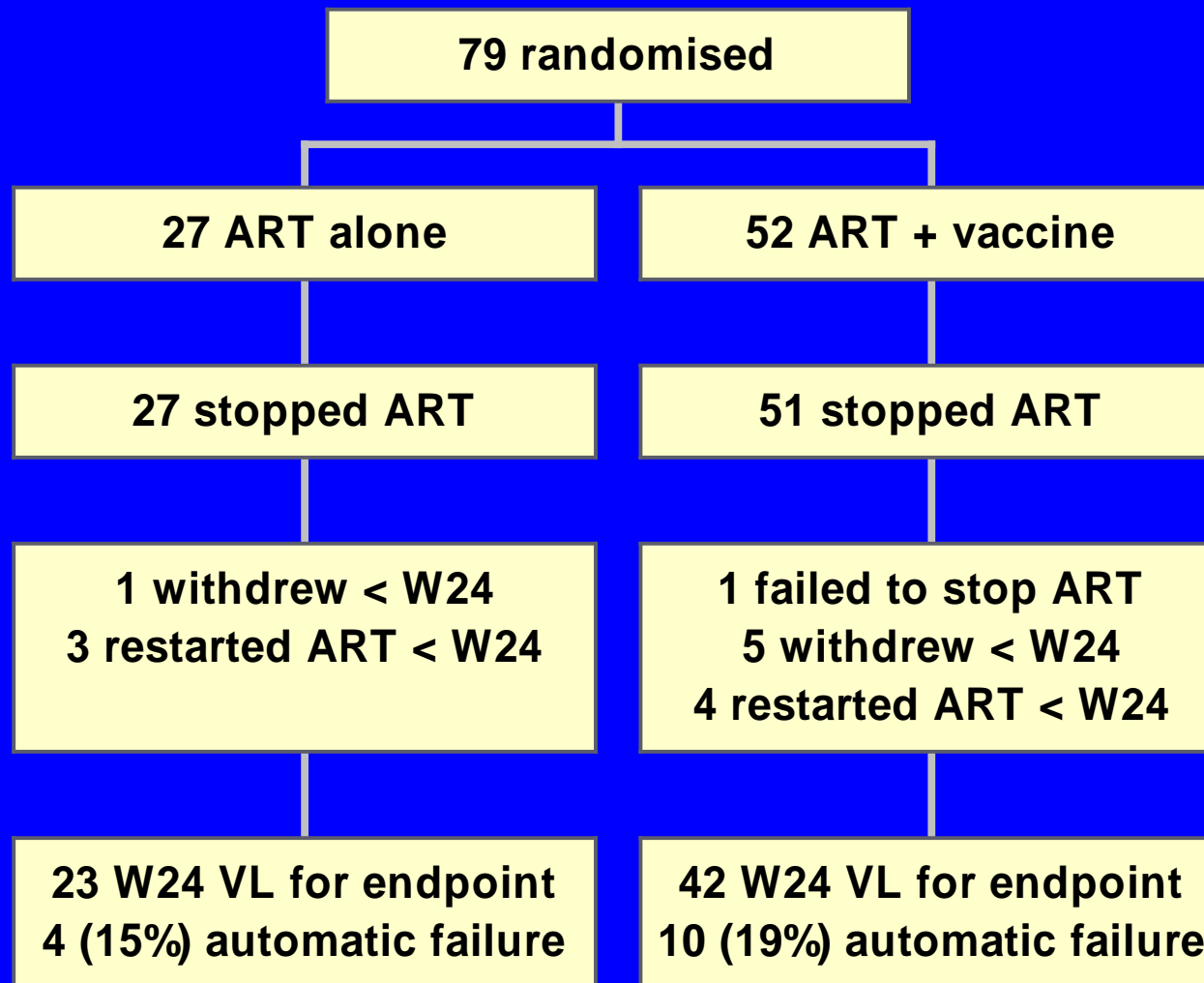
- ◆ VL  $\leq$  400 c/mL throughout 24 weeks post-stopping ART  
(ITT-restart ART/missing VL = failure)
- ◆ Time to reaching  $>$  1000 c/mL after stopping ART (restart = failure)

# Subject characteristics at baseline

	ART alone (Group A)	ART+Vaccine (Groups B/C)
N	27	52
Male sex, n (%)	24 (88.9)	48 (92.3)
White, n (%)	27 (100)	50 (96.2)
Homosexual, n (%)	20 (74.1)	37 (71.2)
Age in years, median	37.4	36.6
Years ART, median [range]	2.1 [1.5, 5.1]	2.1 [1.4, 5.3]
CD4/mm <sup>3</sup> , median [range]	719 [327, 1172]	795 [396, 1451]
Viral load ≤50 c/mL, n (%)	26 (96.3)	49 (94.2)



# Subject follow-up and adherence to protocol



# End of immunisation characteristics

	ART alone (Group A)	ART+Vaccine (Groups B/C)	P value
N	27	52	
CD4 count, median [range] cells/mm <sup>3</sup>	735 [517, 1216]	795 [303, 1657]	0.36
VL ≤50 c/mL, n (%)	27 (100.0)	48 (92.3)	0.36
Response to p24 (CD4 ELISPOT), median [range] SFC/10 <sup>6</sup> PBMC	0 [0, 410] n=18	180 [0, 2000] n=32	0.006*
Response to gag (CD8 ELISPOT), median [range] SFC/10 <sup>6</sup> PBMC	0 [0, 230] n=18	275 [0, 4255] n=34	0.002*

\*Mann-Whitney test

Primary endpoint:

$VL \leq 1000$  c/mL W24 post-stopping ART

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ART alone (n=27)	ART + Vaccine (n=52)	Difference (95% CI)	P value
6 (22.2%)	8 (15.4%)	-6.8% (-23.5, 11.7)	0.54*

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\*Fisher's exact test

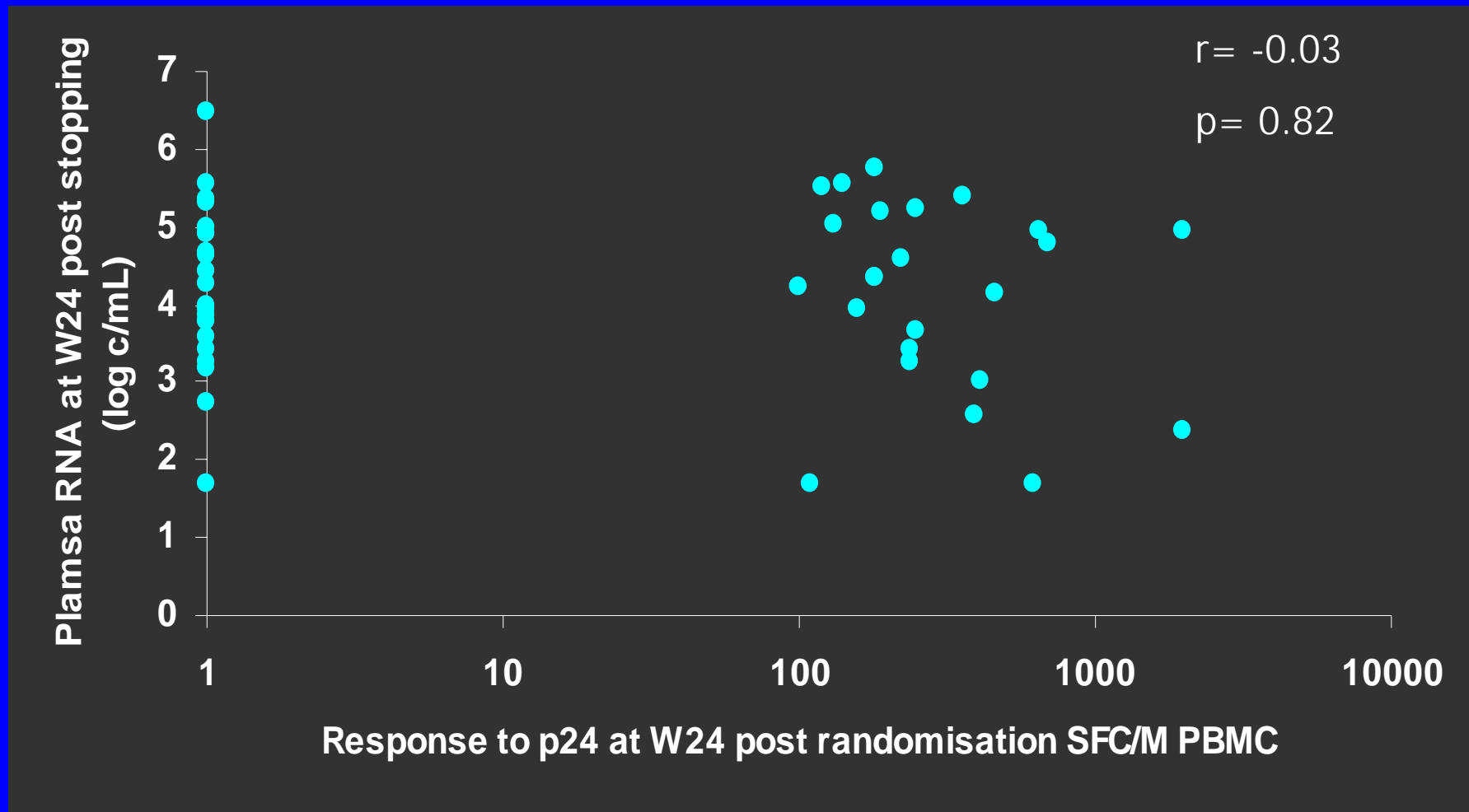
## Other endpoints

	ART alone (n=27)	ART + Vaccine (n=52)	Difference (95% CI)	P value
$\leq 400$ c/mL until W24	2 (7.4%)	1 (1.9%)	-5.5% (-16.0, 5.1)	0.22*
Median no. days to VL >1000 c/mL	28	29	HR=1.0 (0.6, 1.6)	0.99 **

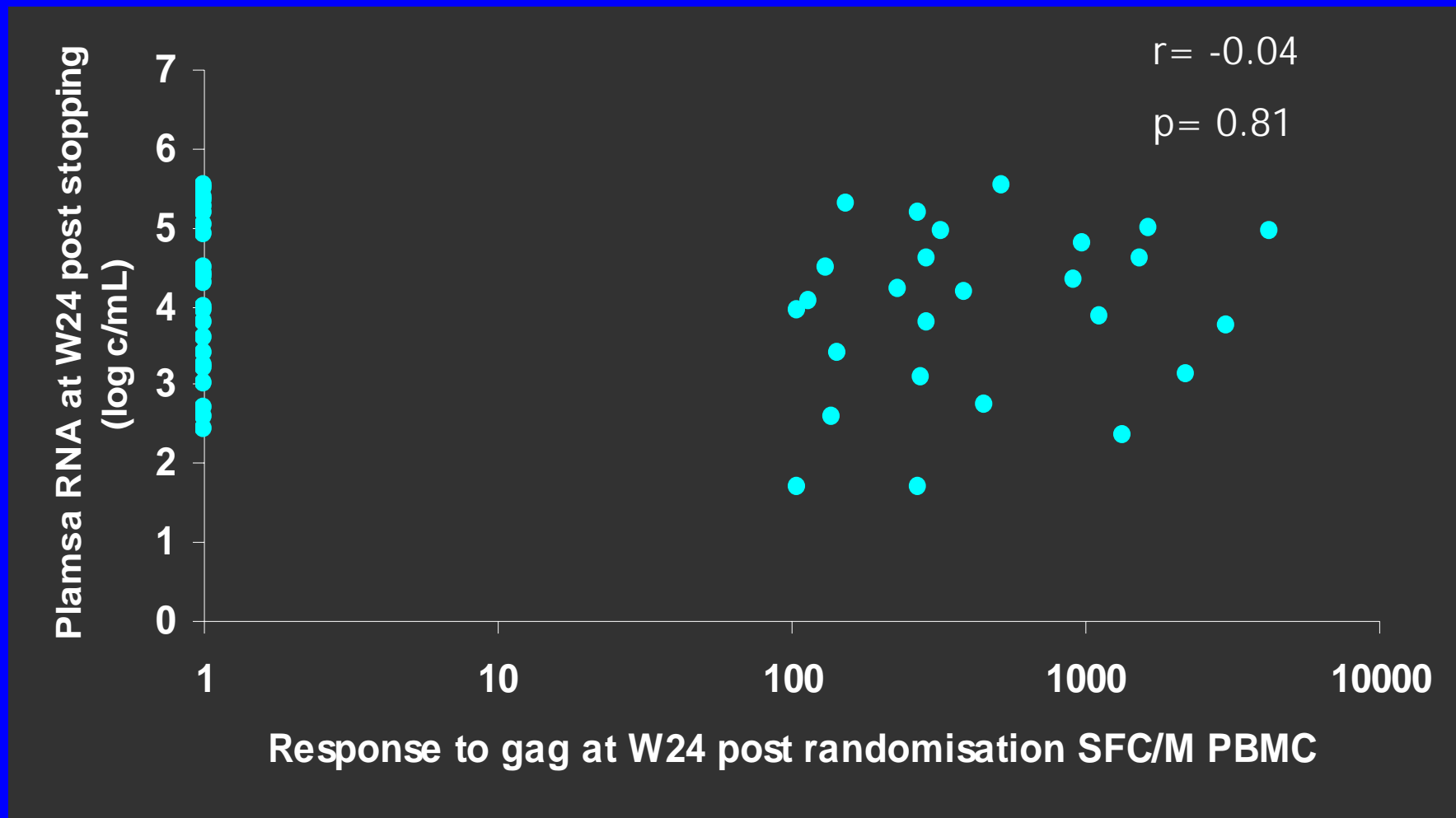
\* Fisher's exact

\*\* Log-rank

# CD4 ELISPOT response (end of immunisation) in relation to VL (W24 post-stopping)



# CD8 ELISPOT response (end of immunisation) in relation to VL (W24 post-stopping)



## Summary & Conclusions

- ◆ First international randomised, controlled trial of HIV therapeutic immunisation in PHI followed by interruption of treatment. No major safety concerns
- ◆ No evidence of superiority of vaccine intervention over ART alone in promoting control of VL 24 weeks post-ART discontinuation in ART-treated PHI subjects
- ◆ Immunogenicity of vaccines did not translate into an increased rate of VL control 24 weeks post-ART discontinuation in vaccine versus ART alone arms

HIV Immune and Virological Responses following the Administration  
of IL-2 either alone or combined  
to ALVAC-HIV 1433 and HIV Lipopeptides (LIPO-6T)  
in Patients Treated Early with HAART during Primary Infection:  
the ANRS 095 (PRIMOVAC) Randomized Study

C. Goujard<sup>1</sup>, F. Marcellin<sup>2</sup>, H. Chavez<sup>1</sup>, V. Meiffredy<sup>2</sup>, C. Rouzioux<sup>3</sup>, A. Venet<sup>4</sup>,  
Y. Lévy<sup>5</sup>, Y. Taoufik<sup>1</sup>, P. de Truchis<sup>6</sup>, P. Morlat<sup>7</sup>, R. El Habib<sup>8</sup>, V. Mazarin<sup>8</sup>,  
J.F. Delfraissy<sup>1</sup>, J.P. Abouker<sup>2</sup> and the ANRS 095 Study Group

<sup>1</sup>Hosp. Bicêtre, Le Kremlin-Bicêtre; <sup>2</sup>INSERM SC10, Villejuif; <sup>3</sup>Hosp. Necker, Paris;

<sup>4</sup> Faculty of Medicine, Le Kremlin-Bicêtre; <sup>5</sup> Hosp. Henri Mondor, Créteil;

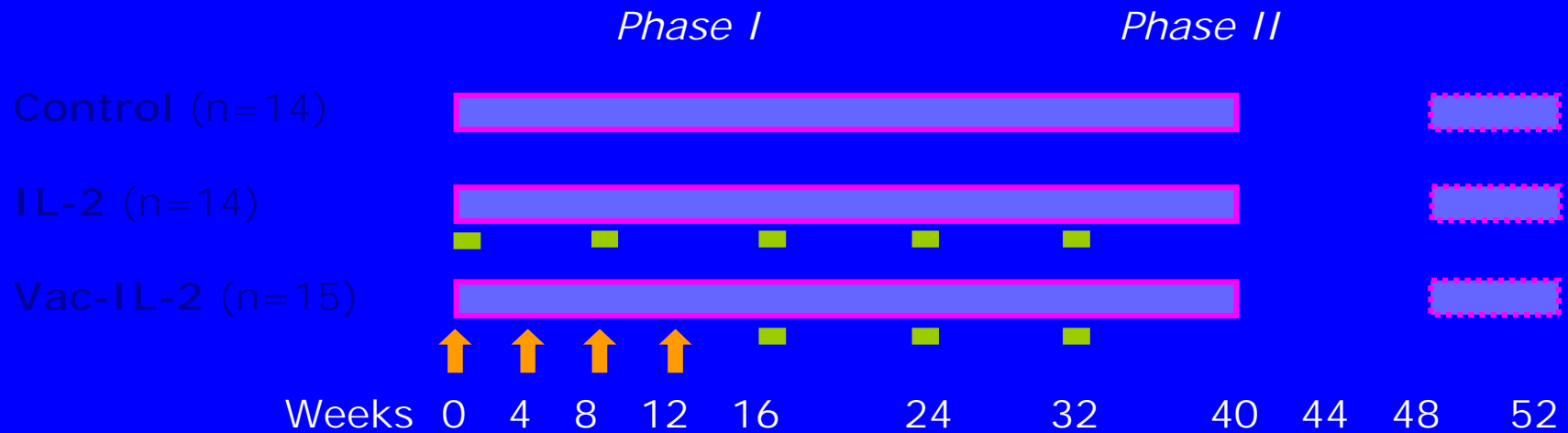
<sup>6</sup> Hosp. R. Poincaré, Garches; <sup>7</sup> Hosp. Saint André, Bordeaux; <sup>8</sup> Aventis Pasteur, Lyon - France



# Patients and design

43 HIV-1 infected adult patients treated early during primary infection

randomized to 3 arms:



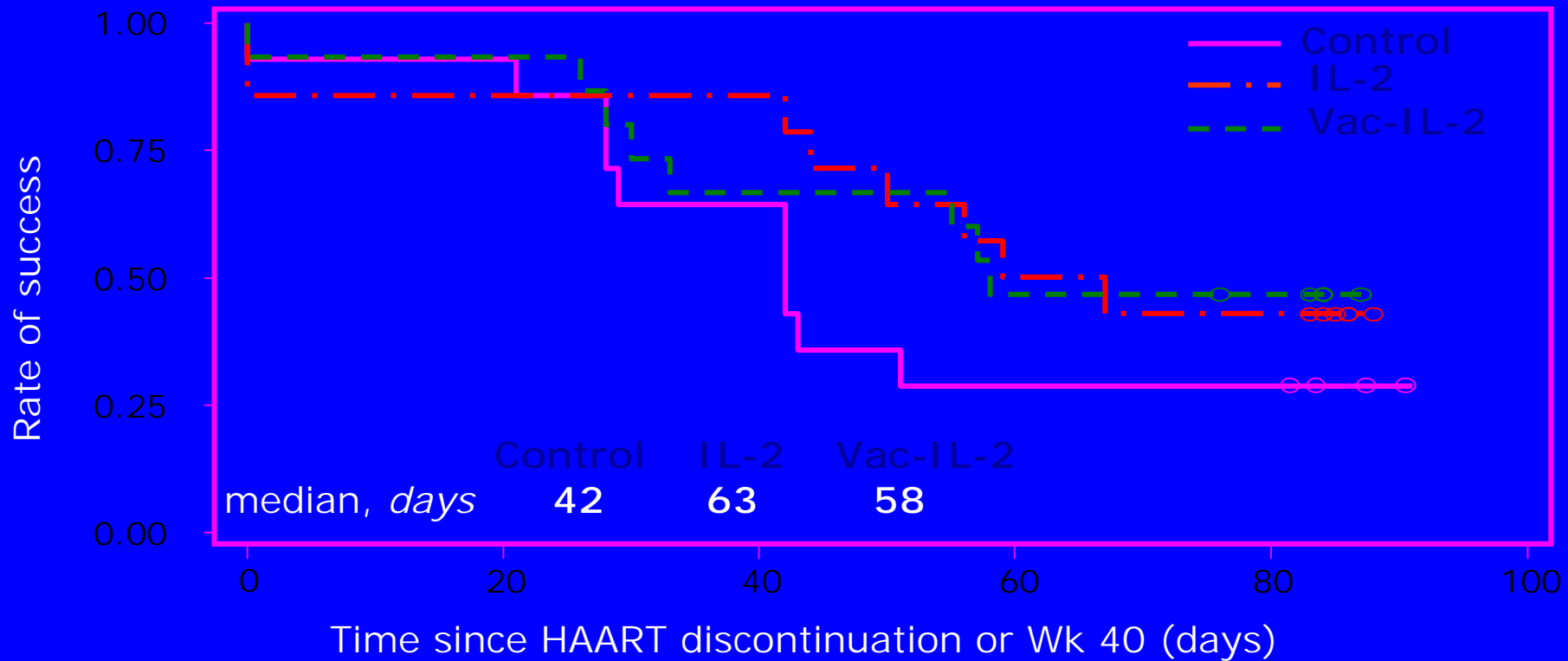
- HAART (red bar) (dashed red bar) reinitiation)
- ALVAC-HIV 1433+LIPO-6T (green arrow)
- SC IL-2 4.5 MIU bid for 5 days (blue square)

HAART stopped at Wk 40 if HIV RNA < 50 cp/ml

Re-initiated if:

- HIV RNA > 50 000 cp/ml after Wk 44
- HIV RNA > 10 000 cp/ml after Wk 48

# Time to virological failure\*



P-value (log-rank test)  
(a) Control vs IL-2  
(b) Control vs Vac-IL-2

(a) .11 (b) .13

\* First HIV RNA >50 000 cp/ml after Wk 44  
or >10 000 cp/ml after Wk 48

## HIV RNA and CD4 characteristics after HAART discontinuation

median (range)	Control n=13	IL-2 n=12	Vac-IL-2 n=14	P-value <sup>1</sup>	
				(a)	(b)
Time to first HIV RNA value >50cp/ml, <i>days</i>	21 (7; 82)	19.5 (0; 58)	16.5 (8; 84)	.21	.49
Maximum HIV RNA slope <i>log<sub>10</sub> cp/ml/day</i>	0.19 (0; 0.30)	0.20 (0.08; 0.37)	0.20 (0; 0.40)	.23	.35
HIV RNA peak value <i>log<sub>10</sub> cp/ml</i>	4.80 (<1.70; 5.98)	4.49 (2.70; 5.88)	4.56 (<1.70; 6.05)	.14	.26
Time to HIV RNA peak value <i>days</i>	42 (21; 82)	39 (14; 86)	36 (26; 84)	.21	.28
HIV RNA decay before HAART re-initiation or Wk 52 <i>log<sub>10</sub> cp/ml/day</i>	-0.01 (-0.16; 0)	-0.01 (-0.04; 0)	-0.03 (-0.13; 0)	.16	.48
Nadir CD4 cell count <i>cells/mm<sup>3</sup></i>	680 (361; 1188)	979 (330; 1642)	890 (501; 1501)	.04	.08

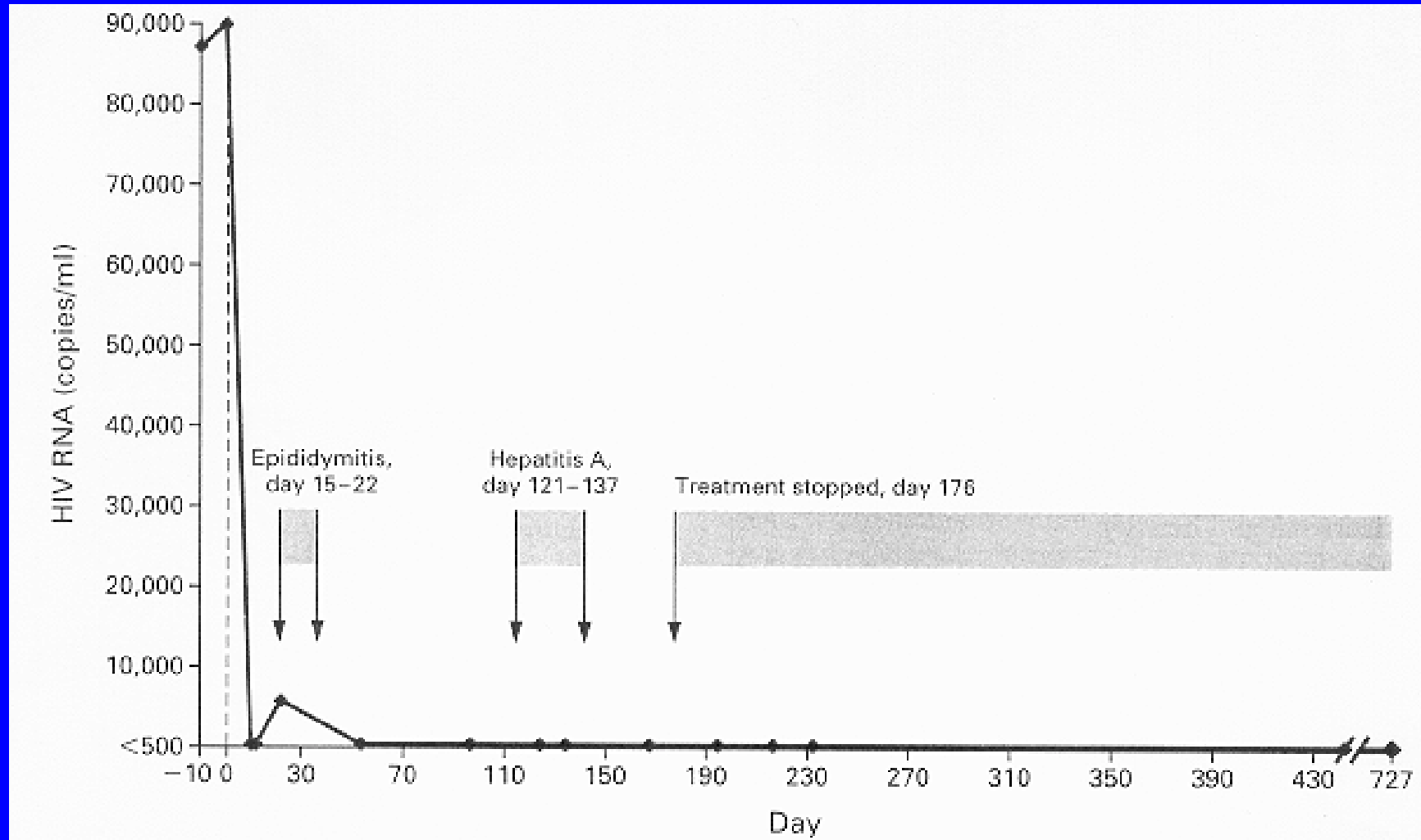
<sup>1</sup>Wilcoxon rank-sum test or log-rank test (for time variables)

(a) Control vs IL-2

(b) Control vs Vac-IL-2

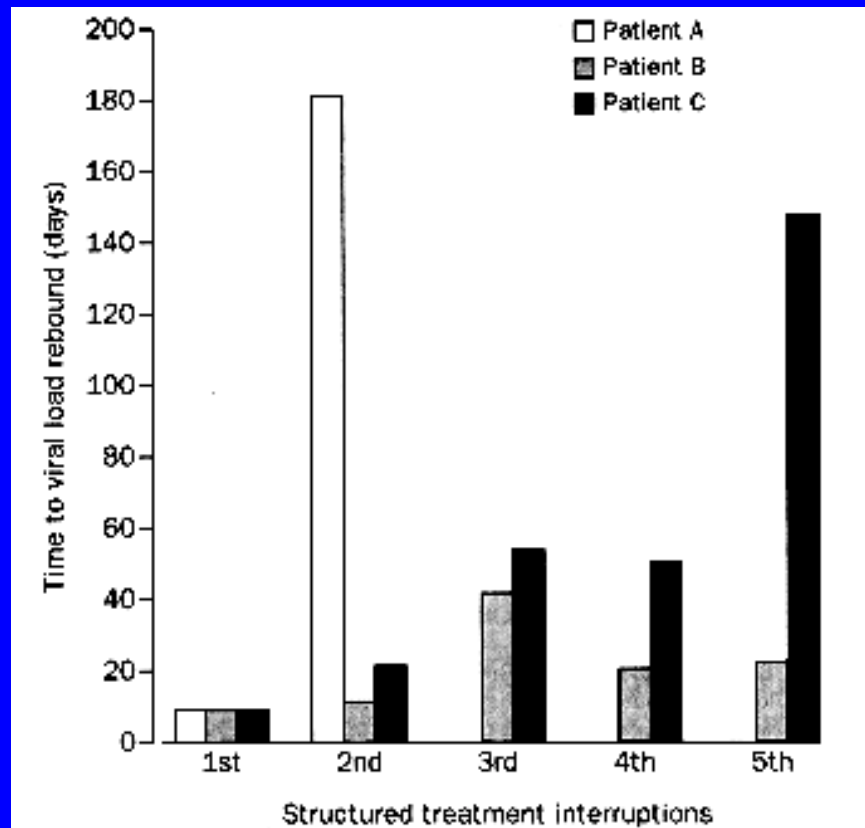
# Control of HIV despite the discontinuation of ART

*J Lisziewicz, N Engl J Med 1999;340:1683*



# Structured treatment interruptions to control HIV-1 infection

*Lori et al. Lancet 2000;355:287-8.*



	Rebound rate (log/day)	Change in viral load (copies/mL)*	Change in CD4-cell count (/ $\mu$ L)*
<b>Patient A</b>			
2nd interruption	0.027	6870	182
<b>Patient B</b>			
2nd interruption	0.118	1098†	96
3rd interruption	0.127	11 637	-78
4th interruption	0.267	13 926	38
5th interruption	0.293	8124	-225
<b>Patient C</b>			
2nd interruption	0.284	5805	-97
3rd interruption	0.097	8199	21
4th interruption	0.070	9907	-42
5th interruption	0.036	5831	30

# Immune control of HIV-1 after early treatment of acute infection

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## ◆ Protocole des interruptions

- 8 malades mis sous HAART au moment de la PIS, pendant 1 à 3 ans, CVP indétectable
- Reprise de traitement si :
  - » CVP > 5000 c/ml sur 3 prélèvements hebdomadaires successifs
  - » CVP > 50000 c/ml sur un prélèvement

## ◆ Résultats

- Rebond et stimulation de la réponse CD8 chez tous les patients
- Contrôle spontané de la CVP < 5000 copies chez 3 patients
- Reprise Trt et nouvelle interruption chez les 5 autres patients
- 5 patients restent sans Trt après une médiane de 6 mois.

# Limited Durability of Immune Control following Treated Acute HIV Infection

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- ◆ 14 patients received HAART at the time of PHI and were followed up for a median of 5.3 years and had up to 4STIs.
- ◆ **Results**
  - Recurrence of viremia in all patients. However PVL < 5000 copies/ml in:
    - » 11/14 patients at 90 days
    - » 3/14 patients at 720 days
  - CD8 T cell response increased in breadth and magnitude but magnitude of response was not predictive of virologic control.
- ◆ **Conclusions**
  - Despite initial control of viremia, durable immune control in persons following treated acute infection occurs infrequently.
  - Loss of viremia control occurred despite increase of the magnitude of HIV-specific CD8 T-cell responses during the first STI.

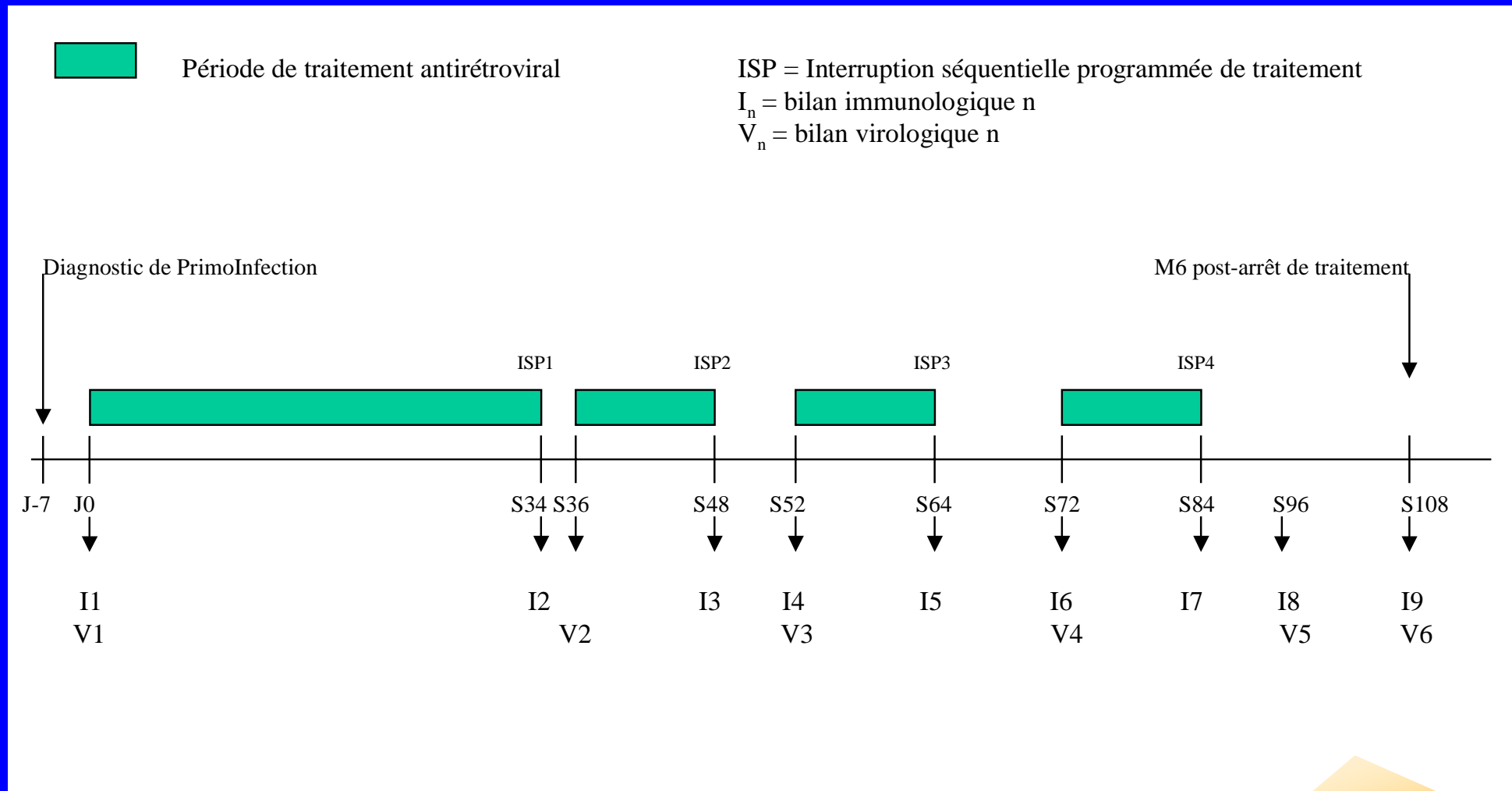
Structured Treatment Interruptions in  
Primary HIV Infection:  
Final Results of the Multicenter Prospective PRIMSTOP  
(ANRS 100) Pilot Trial

B. Hoen, I. Fournier, I. Charreau, C. Lacabartz,  
M. Burgard, C. Arvieux, E. Bouvet, F. Pariente,  
J.P. Aboulker, A. Venet, C. Rouzioux, F. Raffi,  
and the Primstop study group.

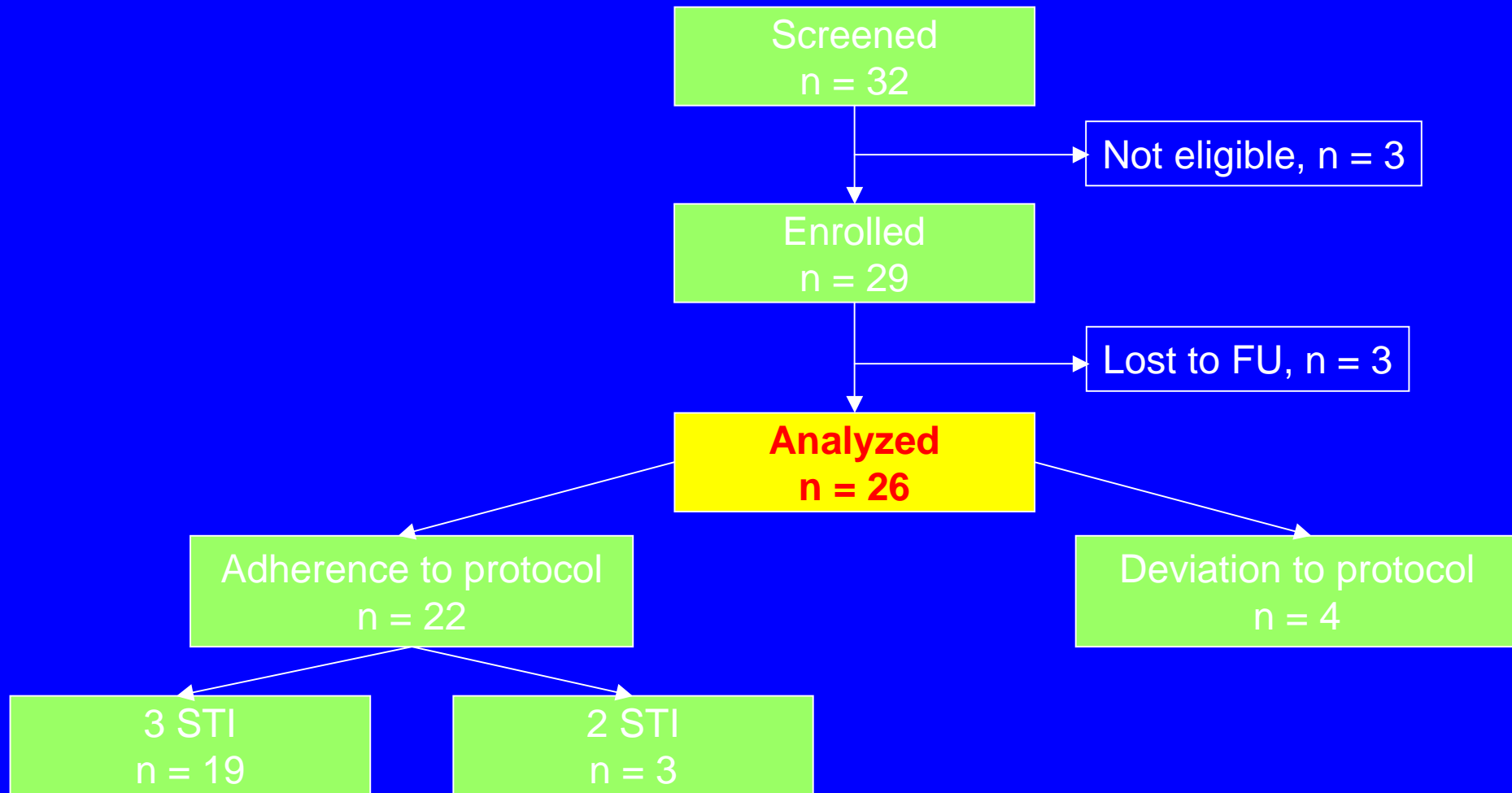




# Schéma de l'essai PRIMSTOP (ANRS 100)



# Disposition of patients



# Virologic success

Endpoint	Rate (%)	Exact binomial 95% CI
<b>PVL <math>\leq</math> 50 c/ml throughout W84-W108*</b>	<b>1/26 3.9%</b>	<b>0.1 – 19.6</b>
PVL $\leq$ 400 c/ml throughout W84-W108	3/26 11.5%	2.5 – 30.2
PVL $\leq$ 1000 c/ml throughout W84-W108	5/26 19.2%	6.6 – 39.4
PVL $\leq$ 1000 c/ml by W108	7/26 26.9%	11.6 – 47.8

\*: primary endpoint

# Predictors of virologic success (PVL $\leq$ 1000 copies/ml by W108)

	Success (n=7)	Failure (n=19)	HR [95% CI] Univariate LR analysis
Age (years)	29	33	0.96 [0.97 – 1.06]
<b>Sex (F vs. M)</b>	<b>4 vs. 3</b>	<b>1 vs. 18</b>	<b>24.0 [1.95 – 295]*</b>
WB (<4 vs. $\geq$ 4 bands)	4 vs. 3	7 vs. 12	0.44 [0.108 – 1.81]
CD4 (n/mm <sup>3</sup> ) @ BL	633	499	1.00 [0.55 – 1.81]
PVL (log c/ml) @ BL	4.86	5.28	0.60 [0.25 – 1.45]
HIV-DNA (log c/Mc) @ BL	2.90	3.00	0.48 [0.06 – 4.50]
HIV-DNA (log c/Mc) @ W84	1.95	2.00	0.73 [0.07 – 6.50]
W84 throughout HAART, y vs. n	2 vs. 5	8 vs. 11	0.55 [0.108 – 3.60]

\*: p<0.05, only significant predictor of virologic success

# Neither baseline nor W84 specific anti-HIV immune responses predict virologic success

	Success (n = 7)	Failure (n =19)	P value*
CD8 T cell IFN $\gamma$ response (Elispot) (SFC/10 <sup>6</sup> PBMC, m $\pm$ SD)			
- Baseline	1156 $\pm$ 994	2039 $\pm$ 3106	>0.99
- W84	943 $\pm$ 1453	2543 $\pm$ 2641	0.07
CD4 T cell proliferative response (Stimulation Index, m $\pm$ SD)			
- Baseline	10.8 $\pm$ 19.6	3.1 $\pm$ 0.6	0.20
- W84	4.7 $\pm$ 3.3	5.1 $\pm$ 3.8	0.90
CD4 T cell IFN $\gamma$ response (Elispot) (SFC/10 <sup>6</sup> PBMC, m $\pm$ SD)			
- Baseline	<50	54 $\pm$ 115	0.39
- W84	142 $\pm$ 173	126 $\pm$ 121	0.82

\*: Mann-Whitney U test

# Resistance studies:

## PI resistance acquisition in 3 cases

	W0	post-
<b>◆ Resistance to NRTI</b>		
<b>W84</b>		
– 184V/I	1	0
– 215Y/F/C	3	2
<b>◆ Resistance to NNRTI</b>		
– 188C/H/L/I	1	0
<b>◆ Resistance to PI</b>		
– 30N	1	1
– 82A/F/S/T	2	2
– 88S/D	1	1
<b>90M</b>	<b>0</b>	<b>3*</b>

\*: resistance first detected at W72, W46, W34

# Avantages/inconvénients d'un trt ARV au cours de la PIV

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## Avantages

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Atténuation du syndrome de PIV

Préservation de la réponse  
immunes CD4 anti-VIH

Moindre transmission du VIH

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Opportunité de STI

Abaissement du "setpoint" viral

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Démonstré

Conjecture

Adapté de Kassutto & Rosenberg, CID 2004;38:1452



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## Avantages

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immunes CD4 anti-VIH

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## Inconvénients

Bénéfices long terme non établis

Toxicité et risques long terme,  
possiblement méconnus

Limitation des option Rx futures

Risque de sélection de résistance

Impact sur la qualité de vie

Coût

Démontré

Conjecture

Adapté de Kassutto & Rosenberg, CID 2004;38:1452

## En conclusion...

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- ◆ Les primo-infections symptomatiques sont suivies d'une évolution plus rapide vers le SIDA (en histoire naturelle)
- ◆ Un traitement antirétroviral puissant initié au moment de la primo-infection permet
  - de modifier favorablement cette histoire naturelle.
  - de mieux préserver les réponses immunes anti-VIH
- ◆ Il n'existe cependant pas de preuve de la supériorité d'un traitement précoce sur un traitement différé
- ◆ Les immuno-interventions en cours de (et avant arrêt du) traitement antirétroviral ont un impact limité.

## ... to treat or not to treat?

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- ◆ La balance pour/contre penche plutôt pour
- ◆ Décision au cas par cas, en tenant compte de :
  - Manifestations cliniques
  - Adhésion du patient
- ◆ Si un traitement est envisagé :
  - trt ARV puissant
  - plutôt dans une perspective de durée limitée à quelques mois
  - dans le cadre d'un essai thérapeutique