

HIV-1 virological remission for more than 12 years after interruption of early initiated antiretroviral therapy in a perinatally-infected child

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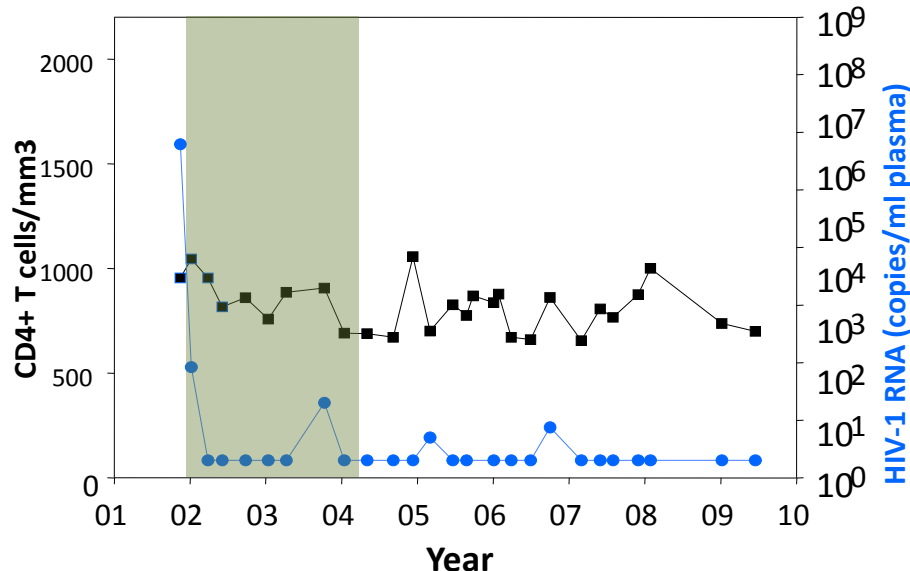
Institut Pasteur

HIV remission: examples are available



HIV remission should allow patients to durably discontinue therapeutic intervention, without (i) developing HIV-associated morbidities, (ii) showing decline of clinical parameters or progression to disease, (iii) while maintaining viremia at the lowest levels to avoid enhancing risk of transmission of infection.

Post-treatment controllers (PTC)

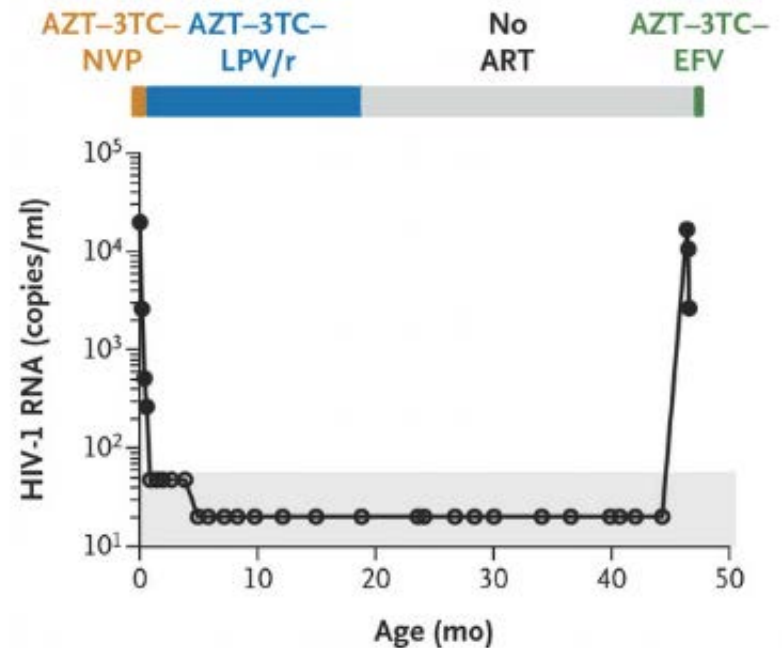


ANRS VISCONTI. 14 patients

Therapy started within 10 weeks following Primary Infection (median 39 days p.i.)

Saez-Cirion et al PLoS Path 2013

Mississippi Baby



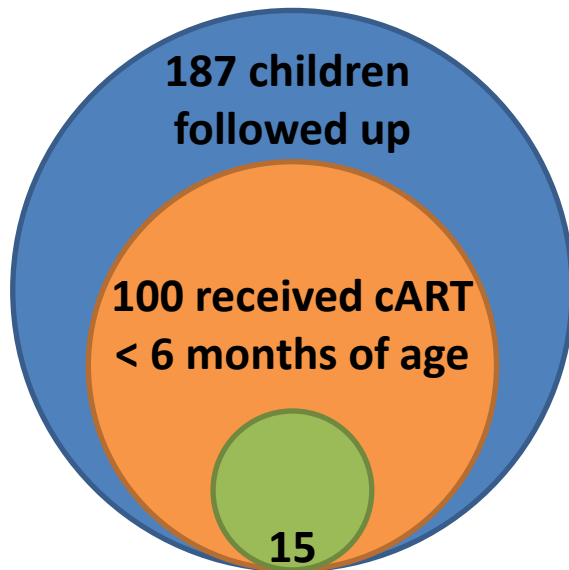
Therapy started within hours of birth

Persaud et al NEJM 2015

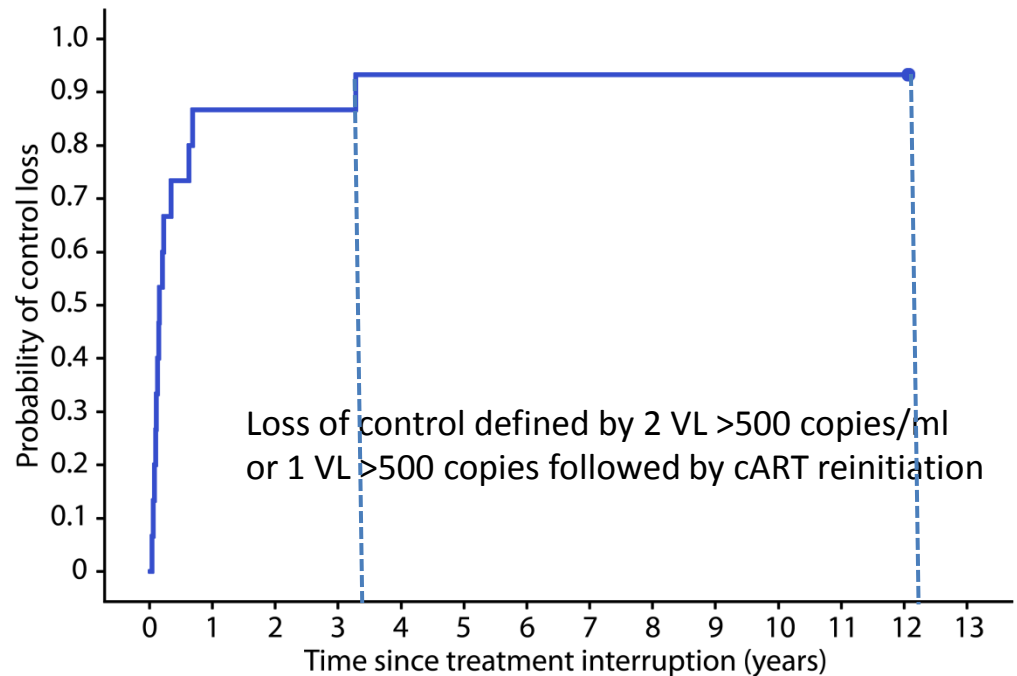
ANRS CO10 EPF paediatric cohort of HIV-1 infected children

One of the oldest ANRS cohorts. Monitoring over 10000 mother-infant couples
Since 1986: inclusion and follow up since birth of 579 HIV-1 infected children

Since 1996



15 interrupted treatment while their VL < 500 copies



Probability to still control infection 2 years after treatment interruption: 0.13 [0.02 - 0.35]

13 patients lost control before 12 months
1 patient controlled for >3 years
1 patient still controls infection (>12 years)

Duration on cART before interruption:
33 months IQR [24-74]

A paediatric case of durable remission of HIV-1 infection

Delivery at 37 weeks + 5 days of gestation

At delivery, the mother:

- treated with zalcitabine (ddC) (since 13 weeks of gestation)
- Plasma VL: 4.63×10^6 HIV-1 RNA copies/mL
- CD4+ T-cell count: $81/\text{mm}^3$
- CD4/CD8 ratio = 0.16

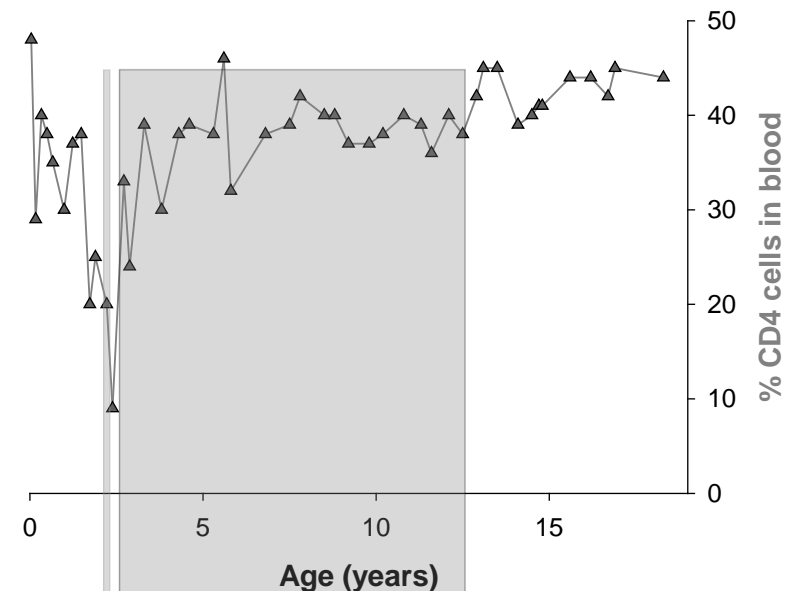
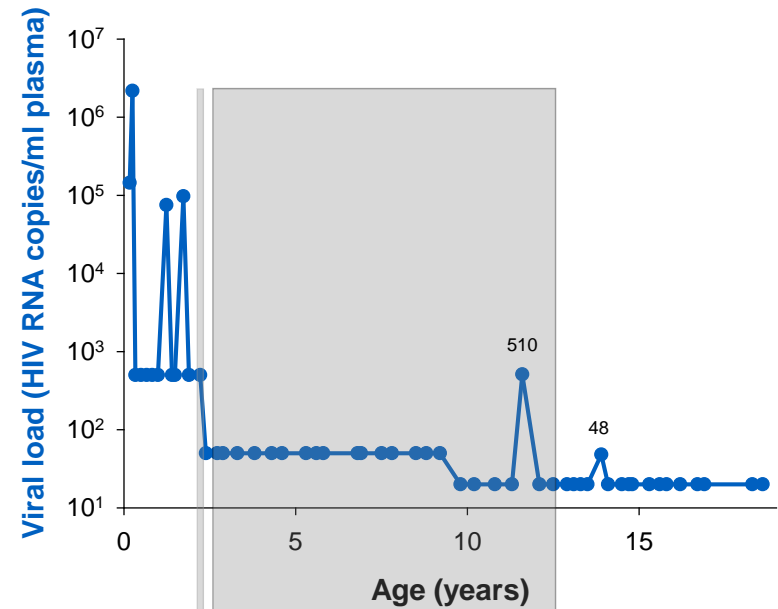
The baby:

- ZDV prophylactic treatment started at birth
- RNA viral load undetectable at day 3
- DNA viral load undetectable at days 3 and 14, detected at week 4.

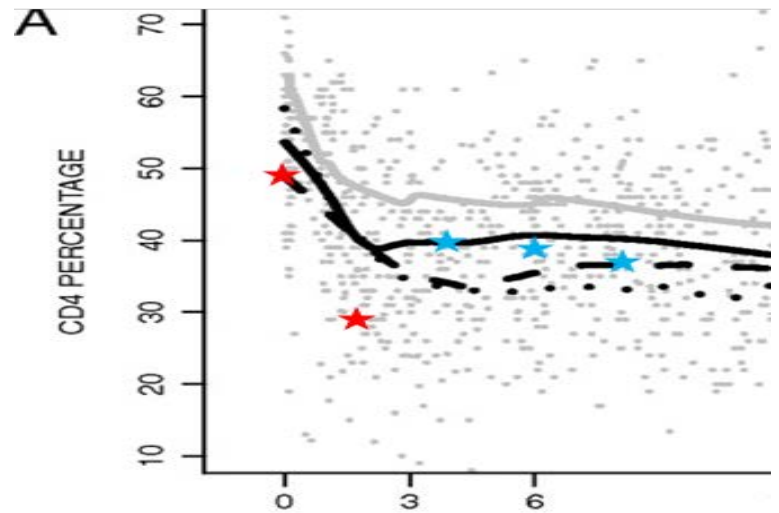
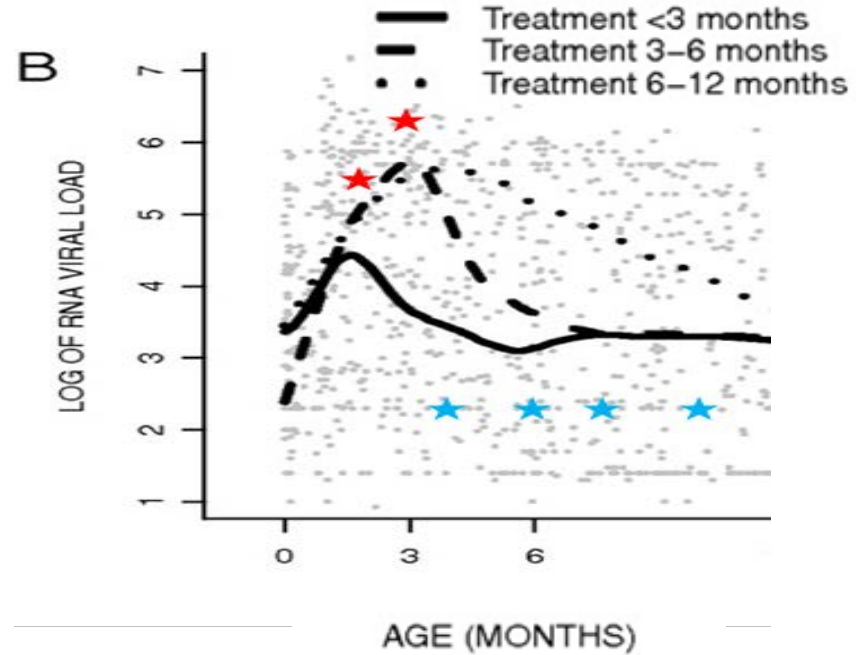
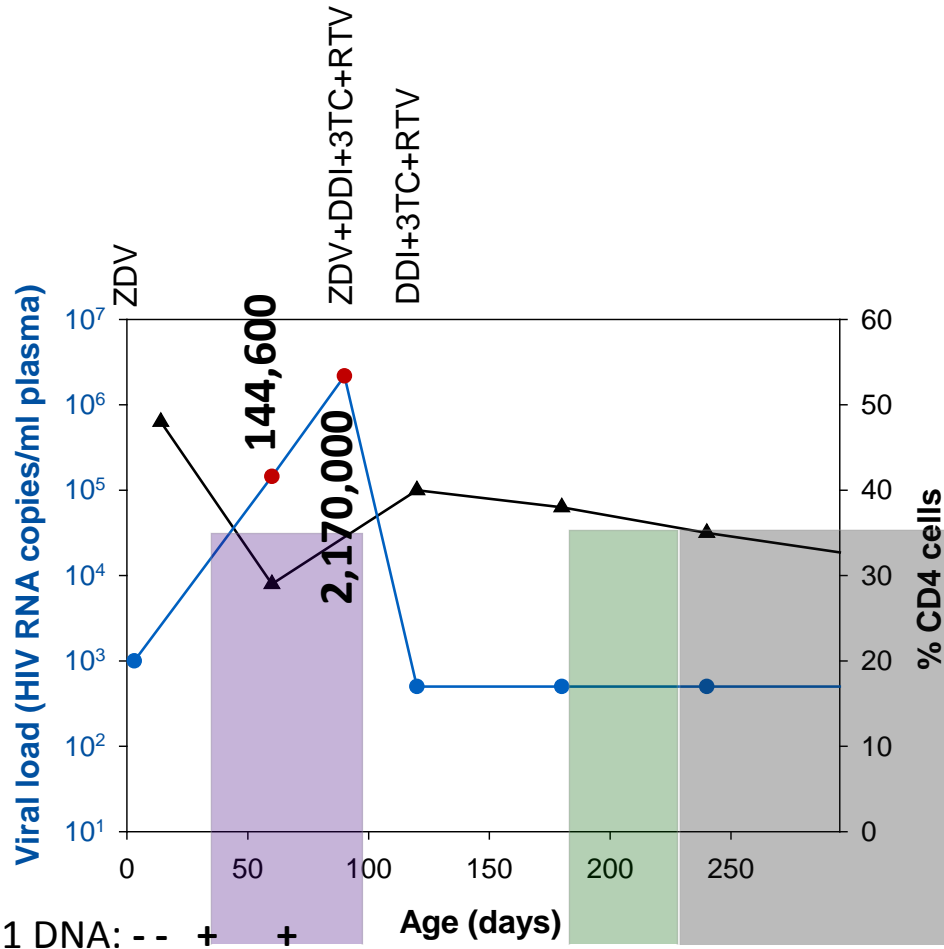
-ZDV interrupted at week 6.

-VL increased sharply : 2.17×10^6 HIV-1 RNA copies/mL at month 3 → initiation of cART (ZDV, ddi, 3TC, RTV)

-Loss for follow up between 5.8 and 6.8y, VL undetectable when she returns despite treatment interrupted a few months earlier

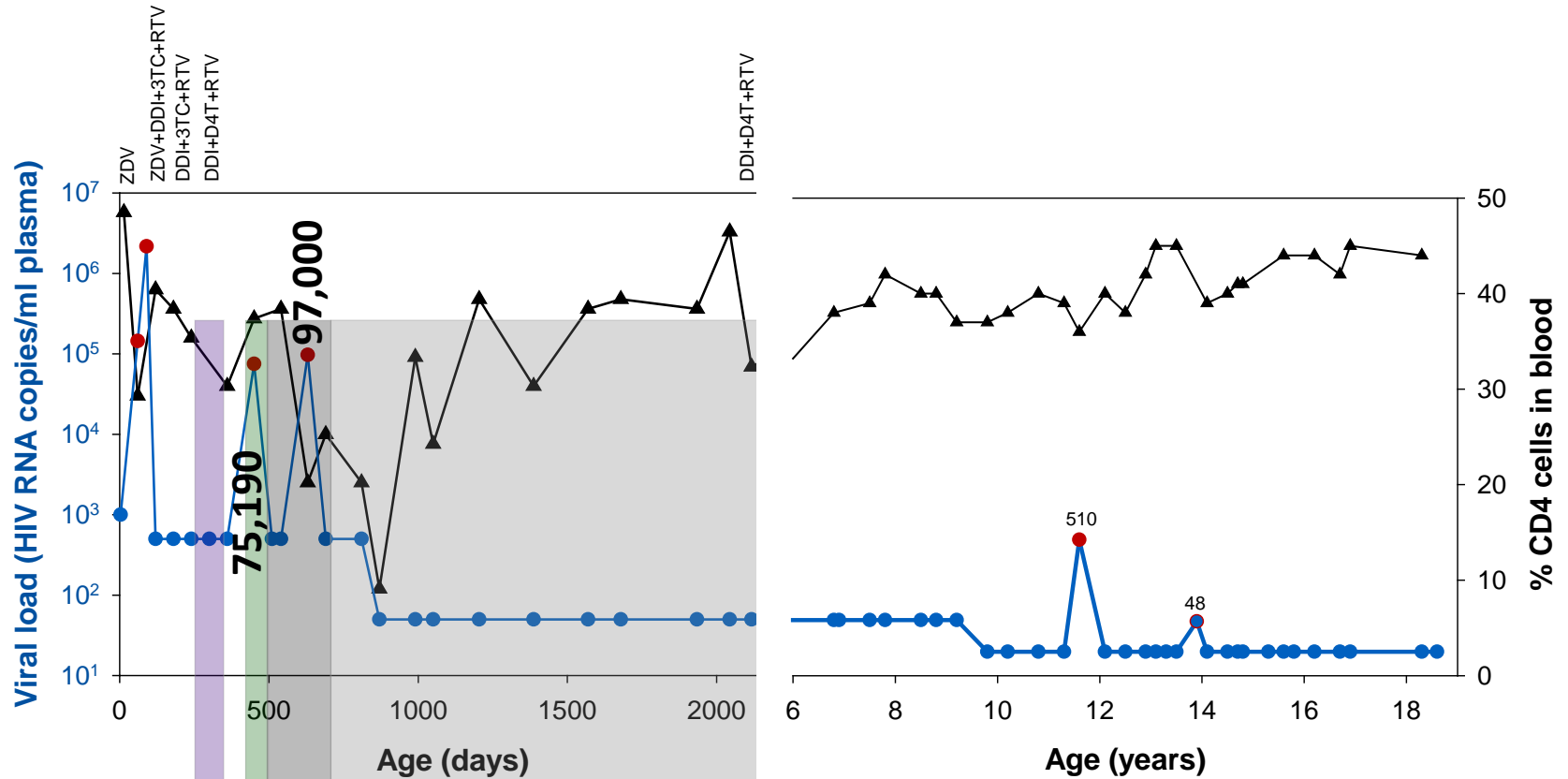


Focus on the Early phase of infection



Adapted from Dolfus et al CID 2010

Complete follow up



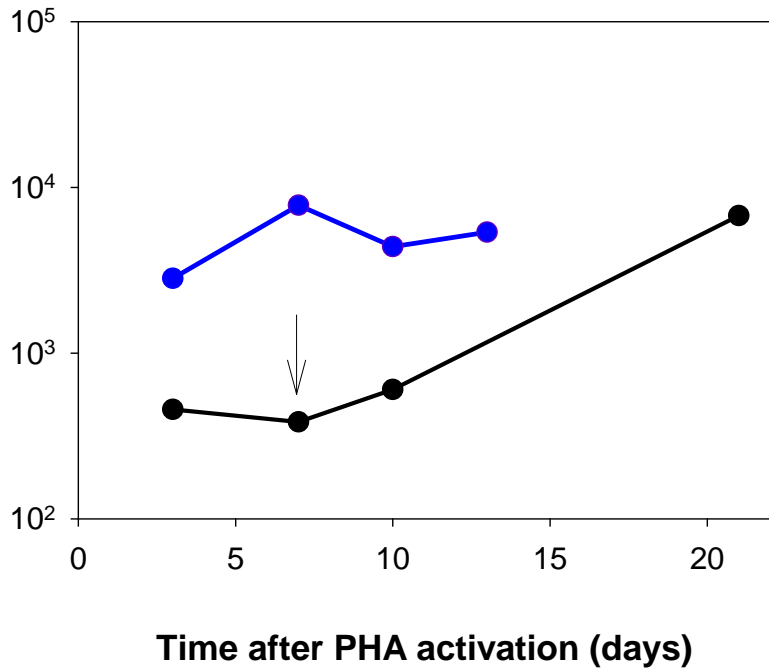
HIV-1 RNA: <9 copies/ml of plasma 2013
 <4 copies/ml of plasma 2014
 <7 copies/ml of plasma 2015

HIV-1 DNA: 2.1-2.5 log copies/10⁶ PBMC between 2013-2015

2015 negative antiretrovirals in plasma
 (by liquid chromatography coupled with tandem mass spectrometry)

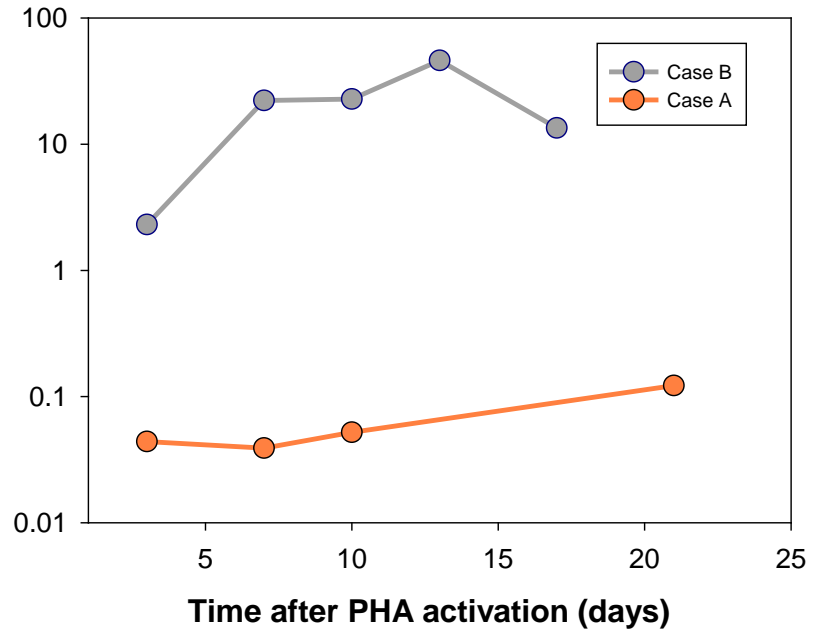
Detection of low levels of replicating virus after in vitro stimulation of purified CD4+ T cells

HIV-1 RNA in culture supernatants (copies/ml)

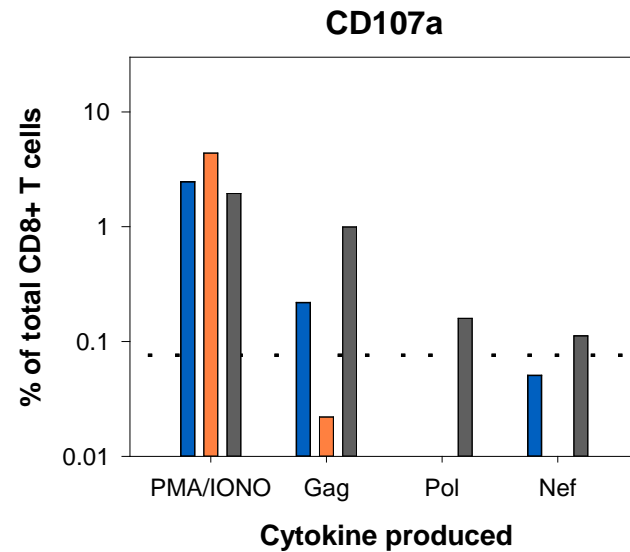
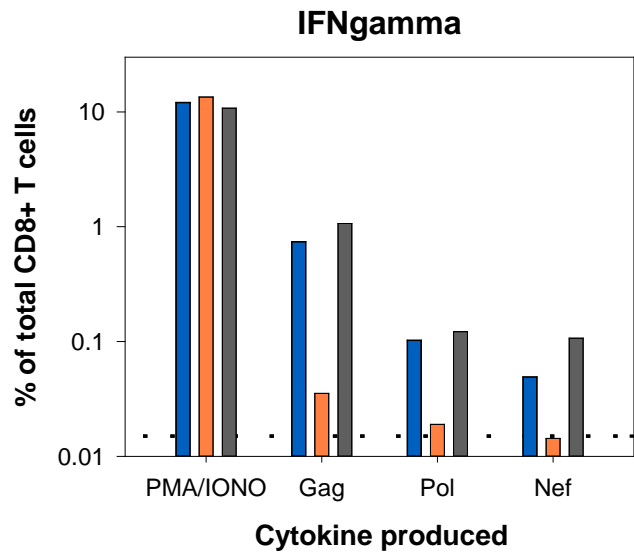
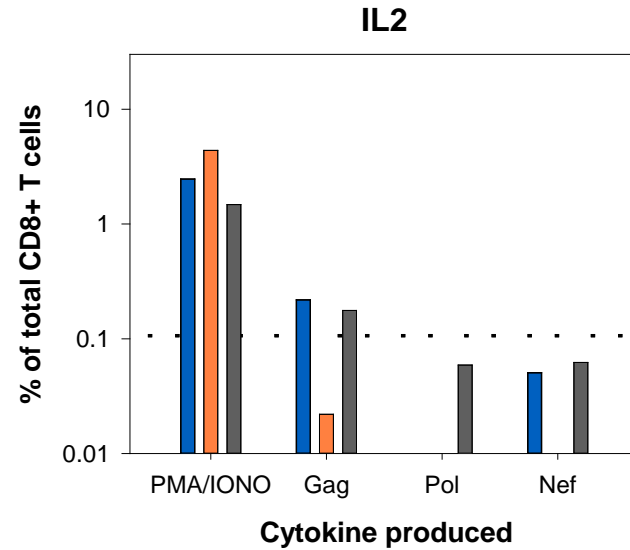
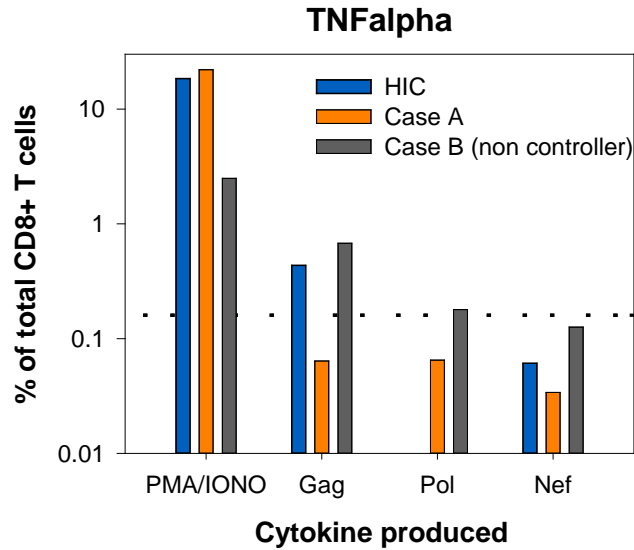


HIV-1 p24 in culture supernatants (pg/ml)

HIV-1 p24 in culture supernatants (ng/ml)

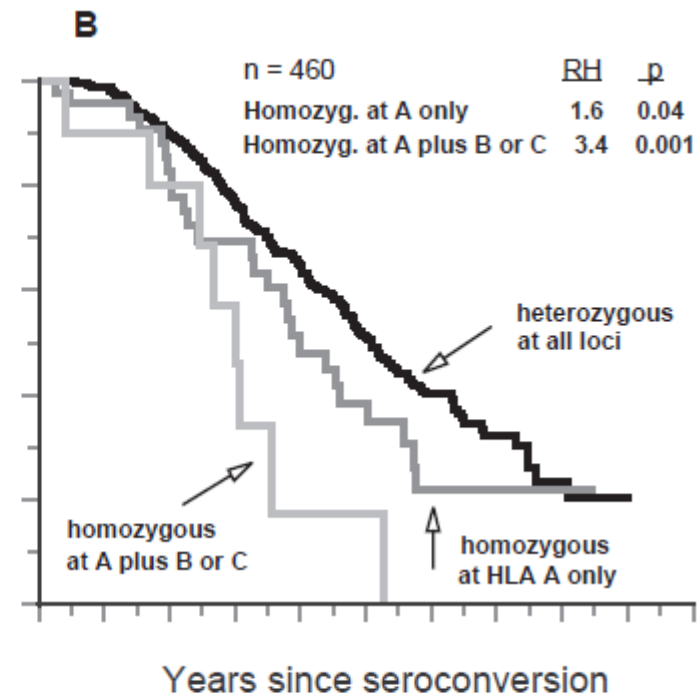
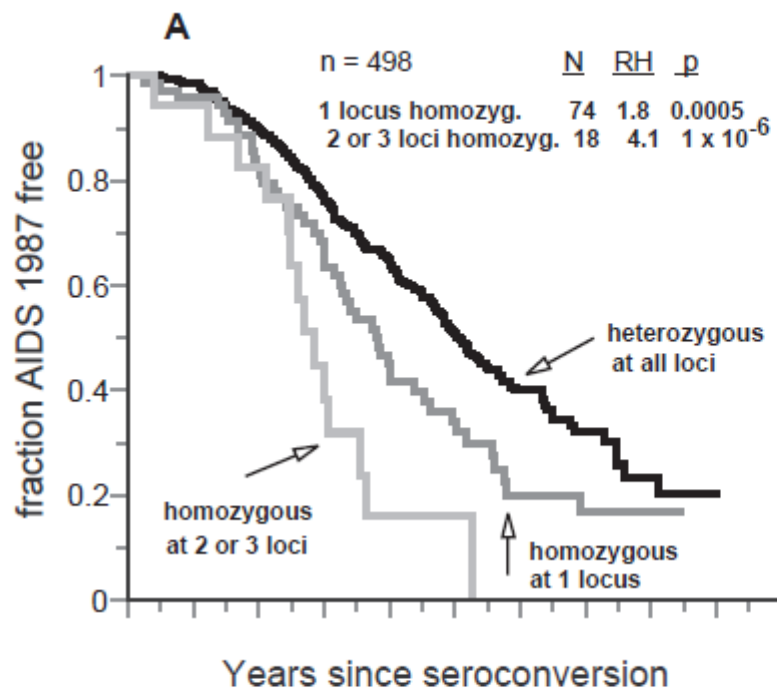


Weak HIV-specific T cell responses during period of control



HLA background not favourable for control of infection

| HLA A | HLA B | HLA C | HLA DRB1 | HLA DQB1 |
|-------|-------|-------|----------|----------|
| 2301 | 1503 | 0201 | 1101 | 0602 |
| - | 4101 | 0802 | - | - |



Non-favourable HLAs are also found in adults in remission of HIV-1 infection

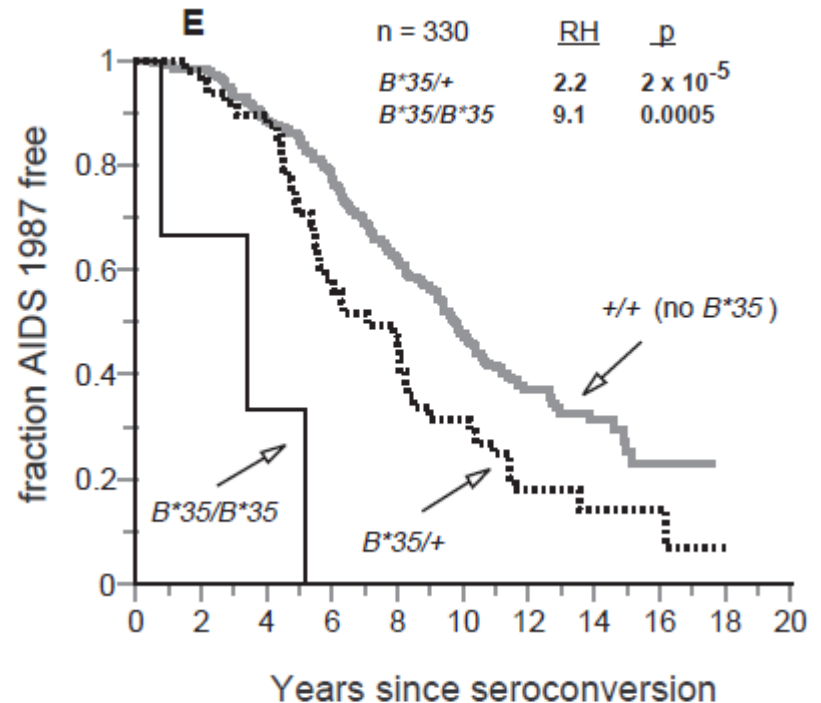
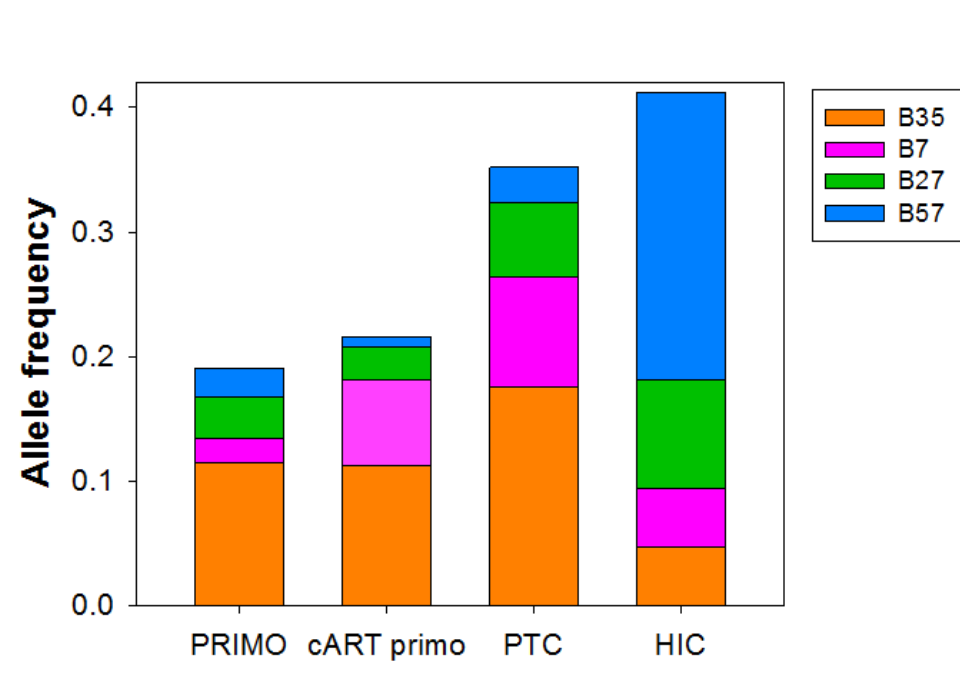
Helene Mens, Hillerød Hospital, Denmark

C09 PHI 08-96 Rx [08-96 → 4-98]

C21 PHI 01-99 Rx [01-99 → to 03-01]

C25 PHI 05-00 Rx [08-00 → 08-04]

| HLA*A | HLA*A | HLA*B | HLA*B | HLA*C | HLA*C | |
|-------|-------|-------|-------|-------|-------|--|
| 0201 | - | 4002 | - | 0202 | - | |
| 0101 | 0201 | 3501 | - | 0401 | - | |
| 02 | - | 07 | 27 | 01 | 07 | |



Carrington et al Science 1999

Conclusions

Long-term (>12 years) virological remission of HIV-1 infection has been observed in a perinatally-infected girl

HIV-1 remission occurred after interruption of antiretroviral treatment initiated early after birth

During her early life the absence of efficient antiretroviral treatment was accompanied by rebound of viremia

HIV-1 DNA is consistently detected in circulating CD4+ T cells and some viral replication can be induced in vitro, however viremia is undetectable (<4 copies in some analysis)

Similarly to what has been observed in the adults in the ANRS VISCONTI study, this girl does not have favourable HLA background

Understanding the ability to durably contain HIV replication may guide new strategies towards HIV remission

Acknowledgements

Thanks to patients and physicians who participate to our studies



Institut Pasteur



HIPer
HIV, Inflammation
and Persistence

HIV inflammation and persistence
Michaela Müller-Trutwin

Mechanisms of control of HIV/SIV infection



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Annie
Caroline

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Christine Rouzioux
Véronique Avettand-Fenoel
Adeline Mélard

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Hillerød Hospital, Denmark

Helene Mens

Hôpital Bichat

Diane Descamps
Gilles Peytavin



**ANRS CO10
EPF Paediatric cohort**



**ANRS
iVISCONTI**

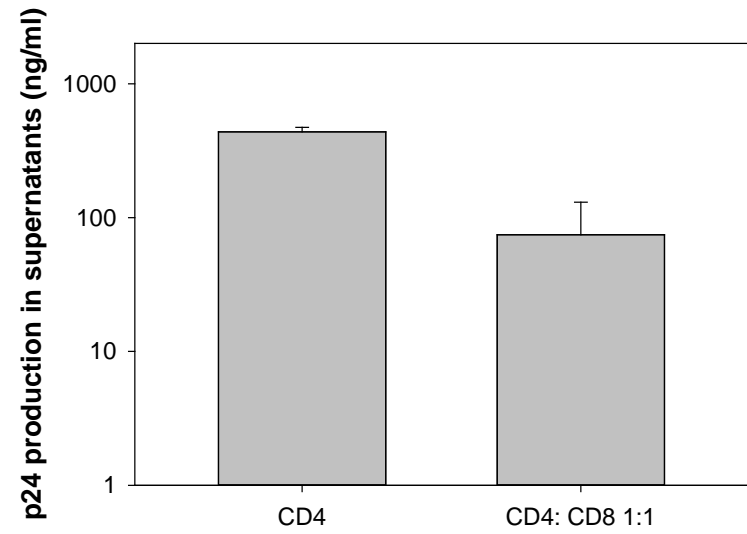
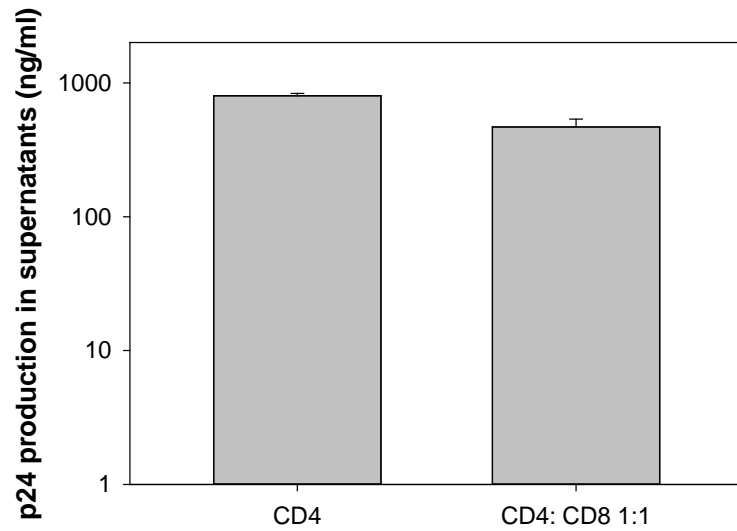


**ANRS CO21
CODEX**



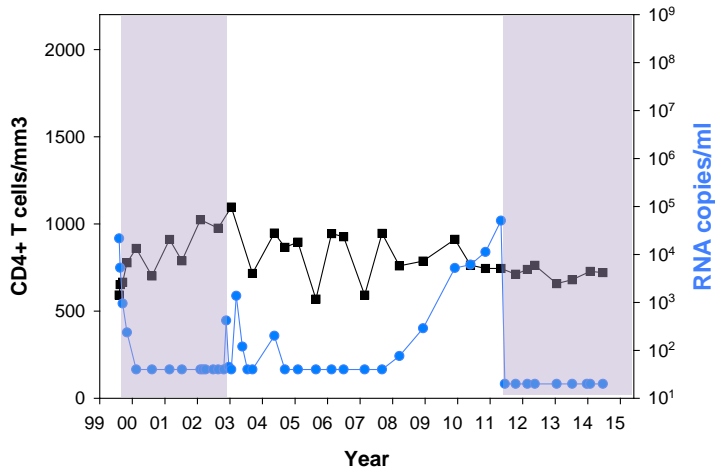
**ANRS CO6
"PRIMO"**

Weak HIV-specific T cell responses during period of control

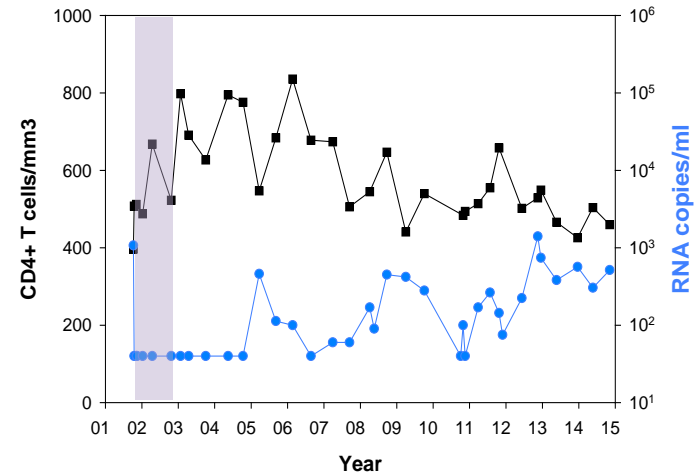


An update on the status of the original VISCONTI PTC

CXK: loss of viral control after ~6 years



KPV: multi year low level replication



Control maintained in all other PTCs at last visit

| | | |
|------|--------|--|
| OR1 | 10 y | <40 HIV RNA copies/ml |
| OR2 | 10.3 y | <20 HIV RNA copies/ml |
| OR3 | 10.9 y | 211 HIV RNA copies/ml |
| OR8 | 10.5 y | <20 HIV RNA copies/ml |
| LY1 | 8 y | <20 HIV RNA copies/ml TT resumption in the context of ORL cancer |
| LY2 | 8.6 y | <40 HIV RNA copies/ml |
| MO1 | 10 y | <20 HIV RNA copies/ml |
| SL2 | 10.3 y | <20 HIV RNA copies/ml |
| GXR | 7.2 y | <50 HIV RNA copies/ml loss for follow-up |
| MWP | 13.5 y | <40 HIV RNA copies/ml |
| JOGA | 8.3 y | <50 HIV RNA copies/ml |
| OCP | 9 y | <40 HIV RNA copies/ml |

New PTCs have been recruited in the VISCONTI study

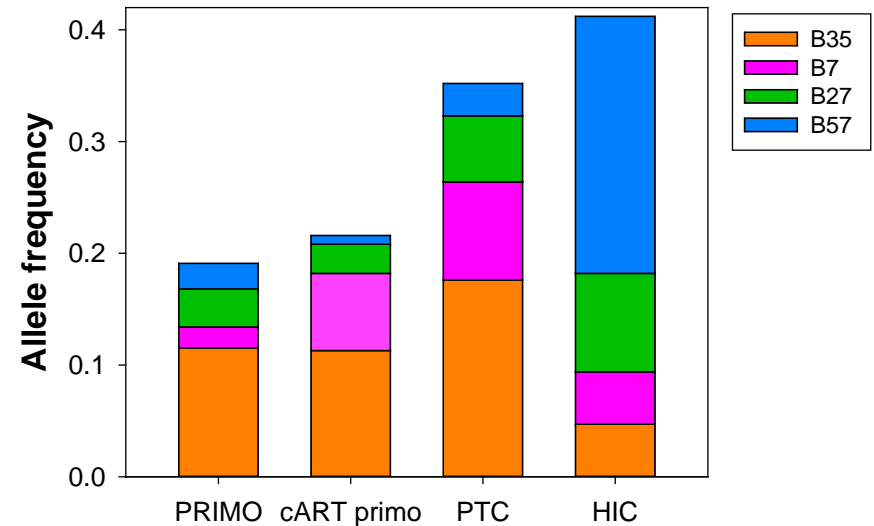
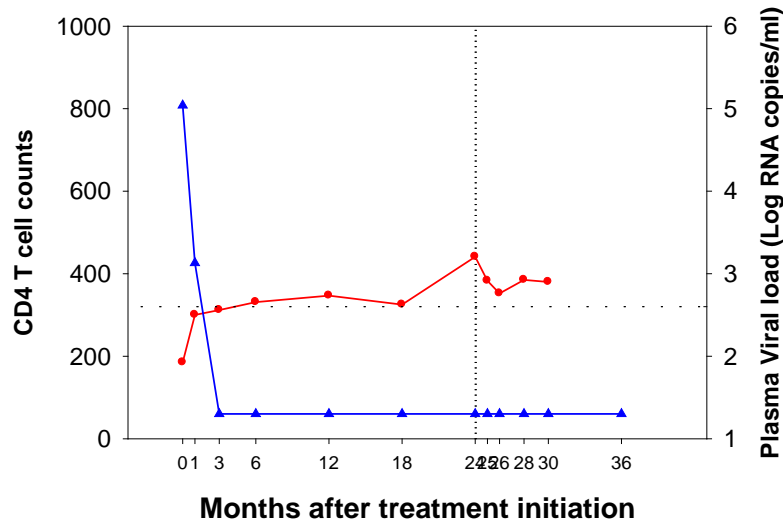
6 new PTC have been recruited recently. All treated early after infection.

Time off therapy: 6.5 years [2.8-14.0]

PTC-like patients identified in the ANRS OPTIPRIM trial: 2y cART initiated during primary infection (Cheret et al Lancet Inf Dis 2015)

63 patients interrupted treatment at M24: 4 kept VL<400 RNA copies/ml at M30

VQUR HLA-B35



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| 0101 | 0201 | 3501 | - | 0401 | - |
| 02 | - | 07 | 27 | 01 | 07 |