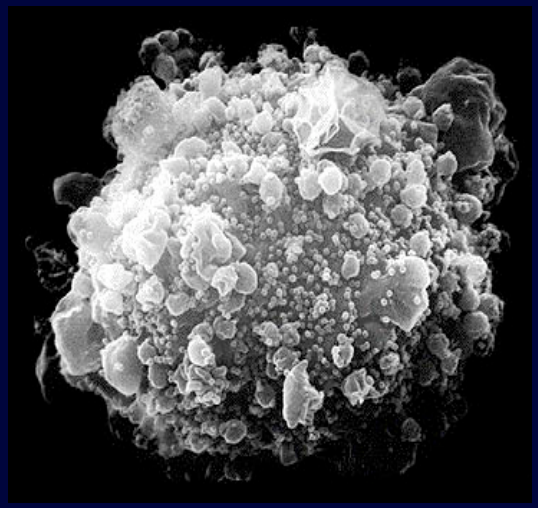
associazione NADIR onlus

fondazione NADIR onlus

L'ATTENZIONE "TERAPEUTICA" ALLA PENETRAZIONE NEI SANTUARI



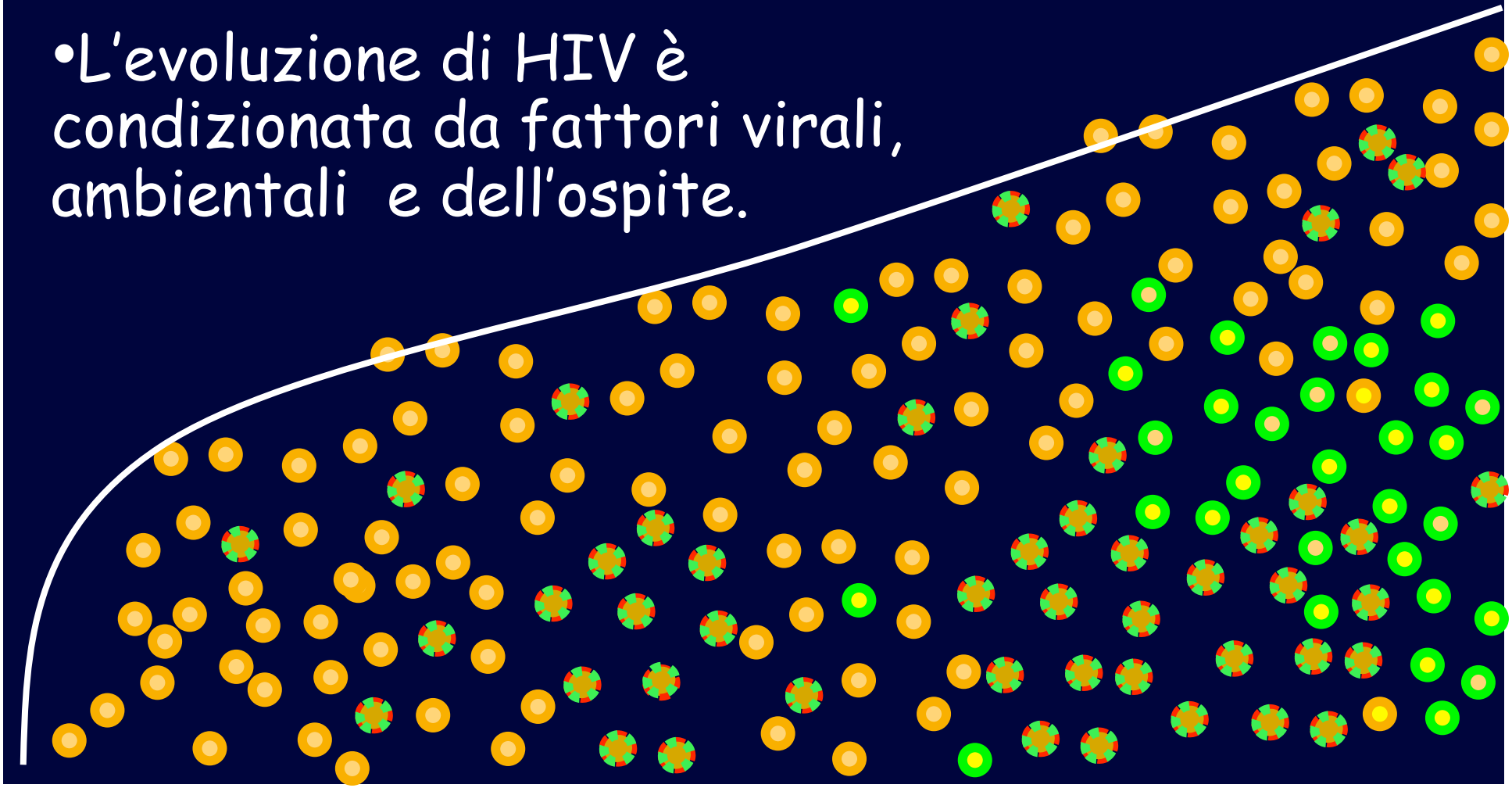
Massimo Andreoni

Malattie InfettiveUniversità Tor Vergata Roma

Roma, 18 Marzo 2011

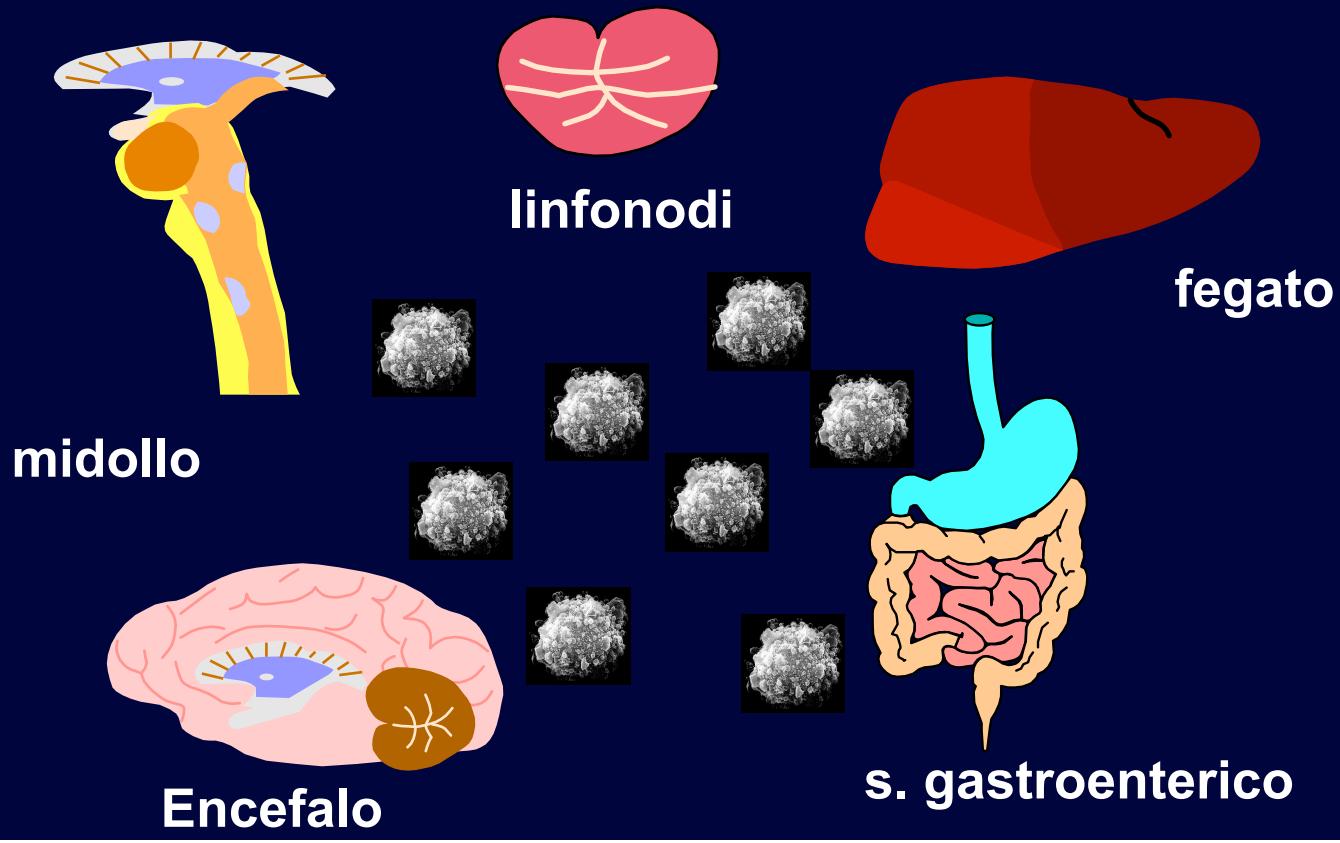
- La comprensione delle dinamiche e della evoluzione di sottopopolazioni di HIV nel paziente è cruciale per il disegno di strategie terapeutiche.

- L'evoluzione di HIV è condizionata da fattori virali, ambientali e dell'ospite.



Compartimentalizzazione di HIV-1

Nelle fasi precoci, HIV colonizza differenti organi e può costituire popolazioni alquanto separate, condizionate ad adattarsi a particolari ambienti e soggette a differenti pressioni selettive.

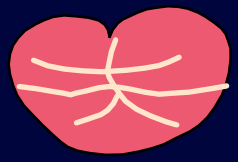


Meccanismi responsabili della Compartimentalizzazione

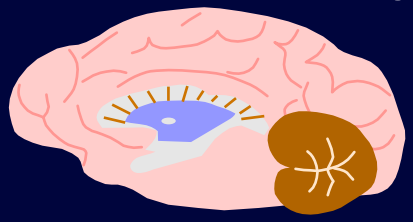
L'alto tasso di mutazioni in vivo può rapidamente accrescere la distanza molecolare tra sub-popolazioni.

1. Differenze di pressione selettiva imposta dal sistema immunitario.
2. Differenti cellule target per la replicazione.
3. Differenze nella concentrazione locale di farmaci.

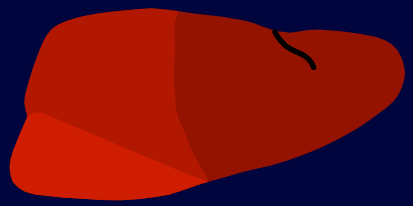
midollo



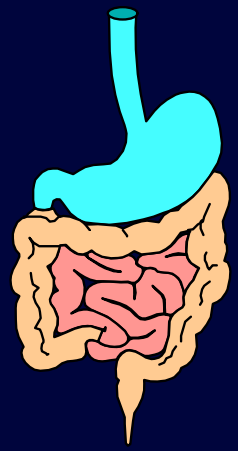
linfonodi



Encefalo



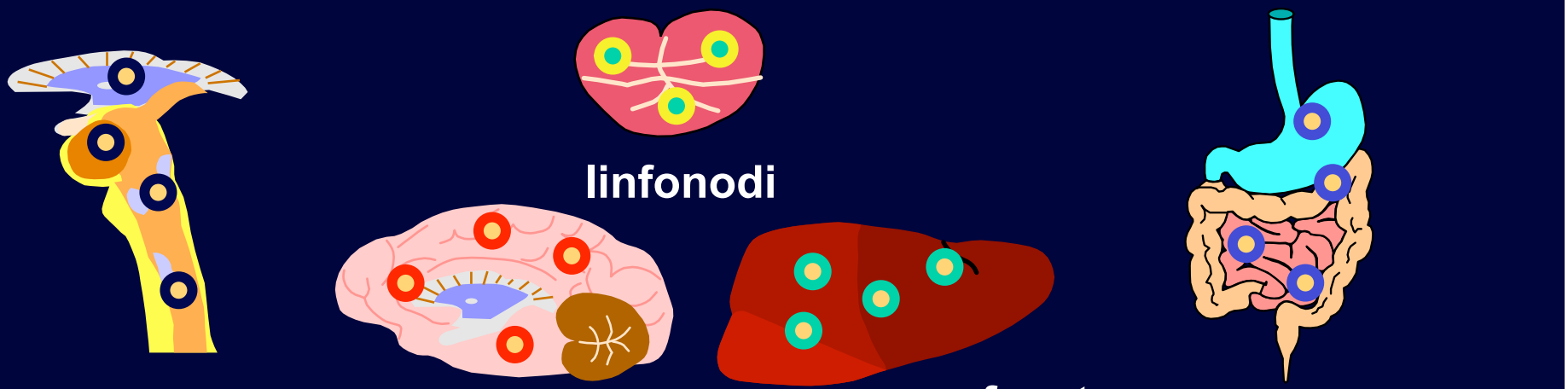
fegato



s. gastroenterico

Meccanismi responsabili della Compartimentalizzazione

- Se l'interscambio tra sub-popolazioni è ridotto, alcune possono divenire geneticamente distinte e compartimentalizzate.
- Popolazioni compartimentalizzate possono avere distinte caratteristiche fenotipiche, come tropismo, citopatogenicità, profilo di resistenza.



La compartimentalizzazione ed archiviazione di HIV avviene precocemente nei linfociti T di memoria del sangue circolante.

Drug-resistance mutations can be archived very early in HIV primary infection

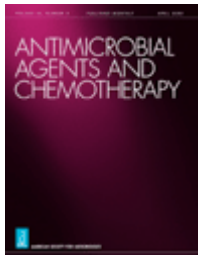
2006, 20:1337–1357

Parisi SG, Mazzi R, Boldrin C, Dal Bello F, Franchin E, Andreoni M, Palù G

The infection was sustained by at least two different strains, a resistant and a wild-type virus, suggesting that a compartmentalization may occur very early as a result of the different fitness

Table 1. Drug resistance mutations revealed in plasma and peripheral blood mononuclear cells.

Source	RT	PR	Source	RT	PR
Plasma, undiluted	**77FI**, 100FIL, 101K, 106IL, 108LV, **118DEV**, **215ST**	**30DEHQ**, 33V, 63S	**PBMC undiluted**	**41LM, 67DN, 118IV, 184MV, 210LV, 215NSTY**	10I, 33LV, 36IM, **46IM, 54IV**, 63FLPS, 77IV, **82CFGV**
Dilution 1 : 1000			**PBMC dilution 1 : 150**		
Regions amplified nos. 7, 18, 23, 25, 27, 29, 31, 32, 36b, 37, 40	None	33V 63S	Regions amplified nos. 45, 46, 49, 53, 58, 62, 68, 73, 74, 75, 77, 79	None	33V 63S
Region amplified no. 22	None	33V 36I 63S	Region amplified no. 14	**41LM, 67DN, 118IV 181HY, 184GMRV, 210LW, 215NSTY**	10IL, 20IKM, 33LV, 36IM, **46IM, 54IV**, 63FLPS, 77IV **82CFGV**
			PBMC dilution 1 : 450		
			Regions amplified nos. 19, 30, 40	None	33V 63S
			Region amplified no. 24	**67N, 184V, 210W, 215Y**	36I
			Region amplified no. 32	**M41L, D67N, V118I**	10I, 20I, 36I, **46I, 54V**, 77I, **82C**



Journal of Antimicrobial Chemotherapy (2009) **64**, 135–141
doi:10.1093/jac/dkp151
Advance Access publication 2 May 2009

High frequency of X4/DM-tropic viruses in PBMC samples from patients with primary HIV-1 subtype-B infection in 1996–2007: the French ANRS CO06 PRIMO Cohort Study

Pierre Frange[1,2]†, Julie Galimand[1]†, Cécile Goujard[3], Christiane Deveau[4], Jade Ghosn[1,3], Christine Rouzioux[1], Laurence Meyer[4] and Marie-Laure Chaix[1]*

[1]*Université Paris Descartes, EA 3620, AP-HP, Laboratoire de Virologie, Hôpital Necker—Enfants Malades, Paris, France;* [2]*Unité d'Immunologie, Hématologie et Rhumatologie pédiatriques, Hôpital Necker—Enfants Malades, AP-HP, Paris, France;* [3]*Service de Médecine Interne et Maladies Infectieuses, Hôpital Bicêtre, AP-HP, Le Kremlin-Bicêtre, France;* [4]*Inserm, U822, Université Paris-Sud, Faculté de Médecine Paris-Sud, AP-HP, Hopital Bicêtre, Service d'épidémiologie et de santé publique, 94276 Le Kremlin-Bicêtre, France*

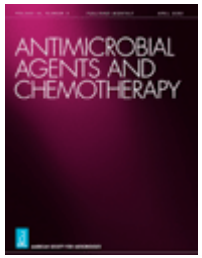
Received 4 February 2009; returned 1 March 2009; revised 30 March 2009; accepted 2 April 2009

***Objectives*: To estimate the frequency of viruses with X4 or dual-X4/DM tropism from peripheral blood mononuclear cells (PBMCs) of 390 human immunodeficiency virus type 1 (HIV-1) subtype-B patients diagnosed at the time of primary HIV-1 infection (PHI) between 1996 and 2007 and enrolled in the PRIMO Cohort.**

***Methods*: V3 loop sequences were amplified from HIV-1-DNA and analysed with a combination of five genotypic rules to predict tropism: (i) the '11/25 rule'; (ii) the net charge rule; (iii) the $PSSM_{X4/DM}$ algorithm; (iv) the $PSSM_{SI/NSI}$ algorithm; and (v) the $SVM_{Geno2pheno}$ algorithm.**

***Results*: A high proportion (62/390, 15.9%) of patients harboured X4/DM-tropic viruses. This prevalence was stable over time: 18.1% before 2003 versus 14.8% since 2003. No difference according to HIV tropism was noted in HIV-RNA levels, CD4 cell count, time between infection and enrolment, and HIV infection risk factor. The frequency of X4/DM-tropic virus was similar among patients infected with a resistant virus (12/62, 19.4%) compared with patients harbouring wild-type strains (50/328, 15.2%).**

***Conclusions*: This large French epidemiological study evidenced a high proportion of patients (15.9%) harbouring X4/DM-tropic viruses in PBMCs at the time of PHI, suggesting the existence of a cellular X4/DM viral reservoir that could persist for lengthy period of time. Several reports identified that HIV-1 CXCR4 usage was more frequent among patients who developed AIDS and was a powerful predictor of the response to antiretrovirals. Further studies are needed to evaluate the impact of such strains on the outcome of HIV disease, when they are detected at the time of primary infection.**



Frange P 2009

Journal of Antimicrobial Chemotherapy (2009) **64**, 135–141
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High frequency of X4/DM-tropic viruses in PBMC samples from patients with primary HIV-1 subtype-B infection in 1996–2007: the French ANRS CO06 PRIMO Cohort Study

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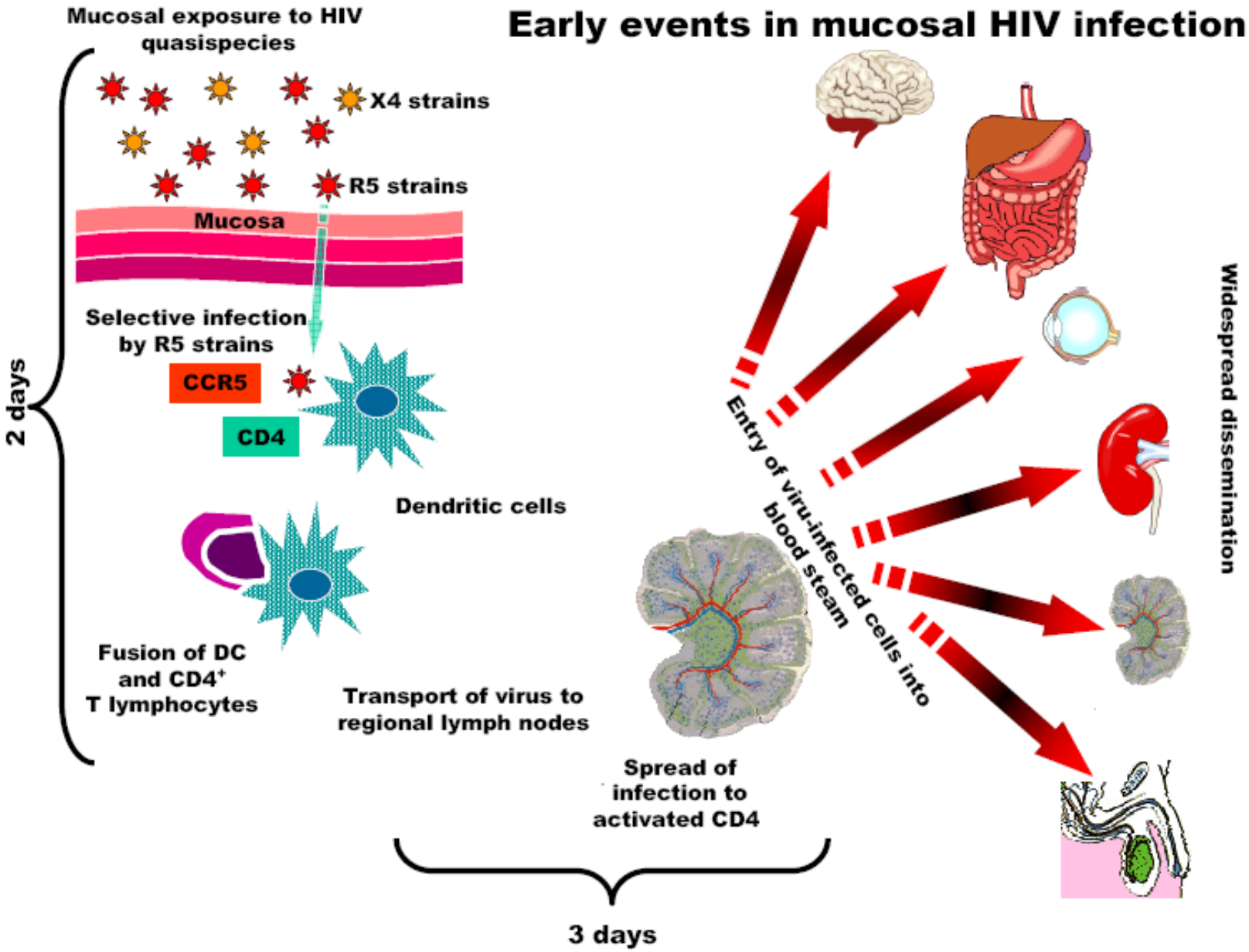
- The existence of a cellular X4/DM viral reservoir could persist for lengthy period of time.
- Further study are needed to evaluate the impact of such strains in PBMCs on the outcome of HIV disease

Significato della compartimentalizzazione di HIV nei PBMCs (*) nelle strategie terapeutiche:

- Selezione di ceppi virali resistenti durante HAART.
- Fallimento in regimi di semplificazione.

(*) = Periferical Blood Mononuclear Cells


Early events in mucosal HIV infection
Mucosal exposure to HIV quasispecies
X4 strains
R5 strains
Mucosa
Selective infection by R5 strains
CCR5
CD4
Dendritic cells
Fusion of DC and CD4+ T lymphocytes
2 days
Transport of virus to regional lymph nodes
Spread of infection to activated CD4
3 days
Entry of viru-infected cells into blood steam
Widespread dissemination

La compartimentalizzazione di HIV nell'apparato gastroenterico

Primary HIV Infection of Gut-Associated Lymphoid Tissue (GALT) is the First Pathogenic Event Leading to Substantial $CD4^+$ T cell Destruction and the main source of persistant activation

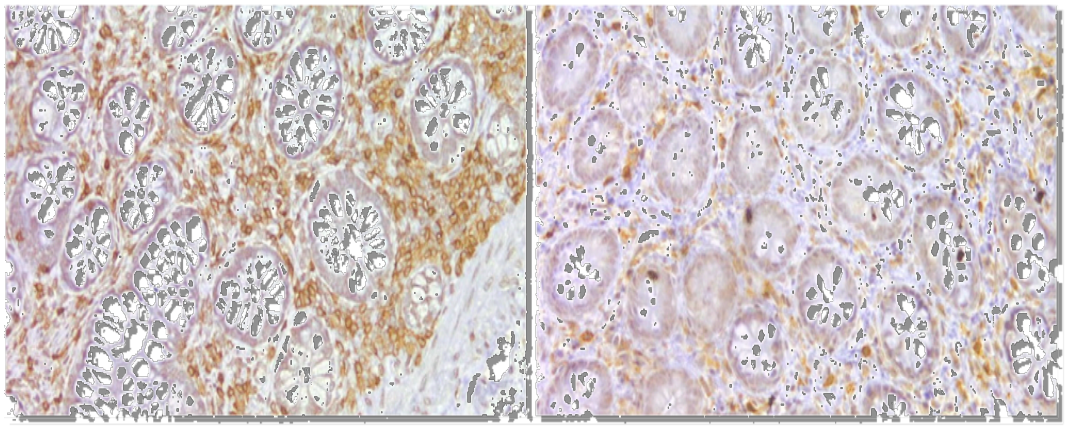
Lymph Nodes

G. Pantaleo et al., Nature 1994

GALT

HIV-

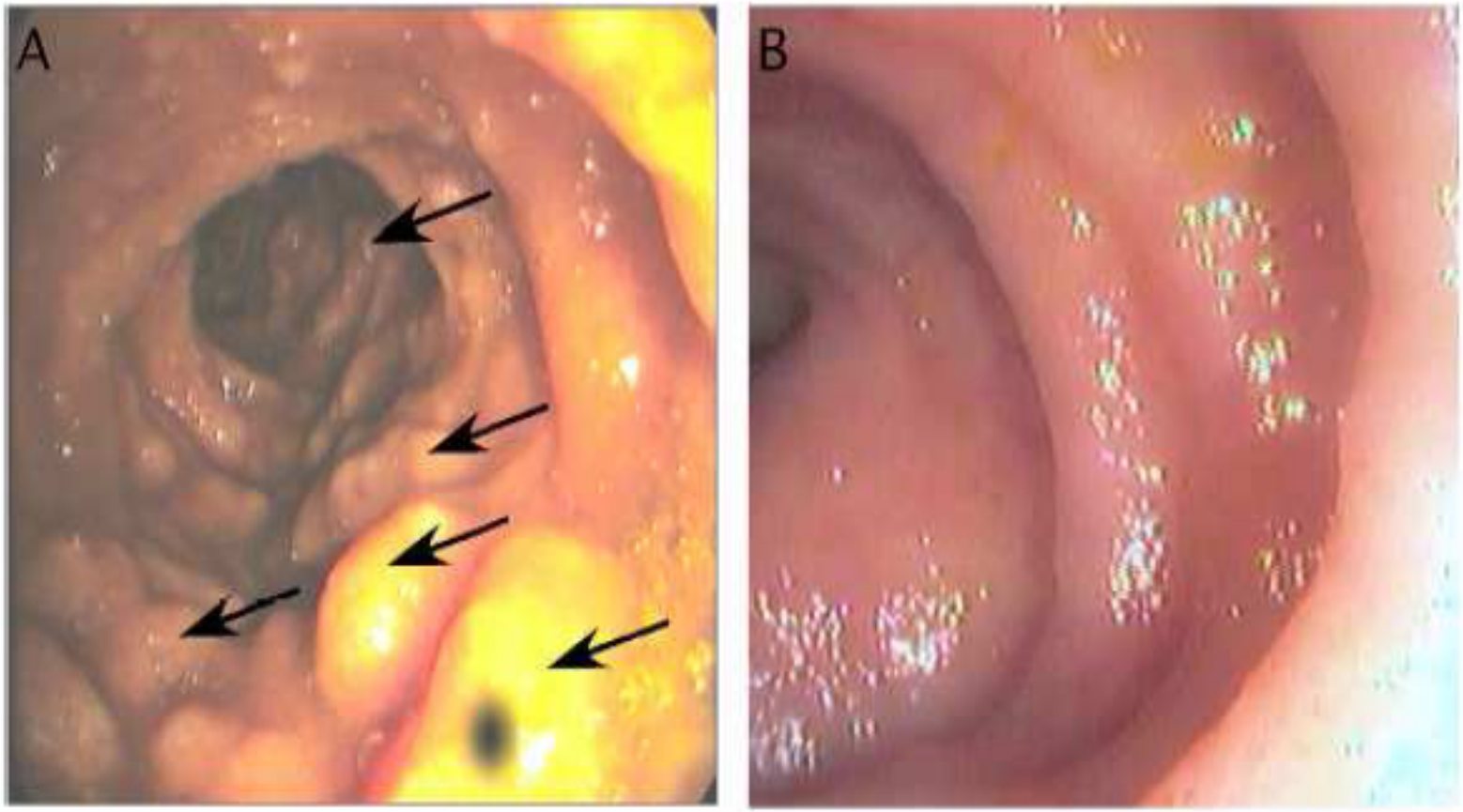
HIV+



Brenchley JM, et al
J Exp Med. 2004 Sep 20;200(6):749-59.

Terminal ileum, HIV uninfected

Terminal ileum, Week 3 HIV Infection



HIV infection results in a rapid and dramatic depletion of CCR5+ CD4+ memory T cells in gut (without evidence of increase activation/turnover)

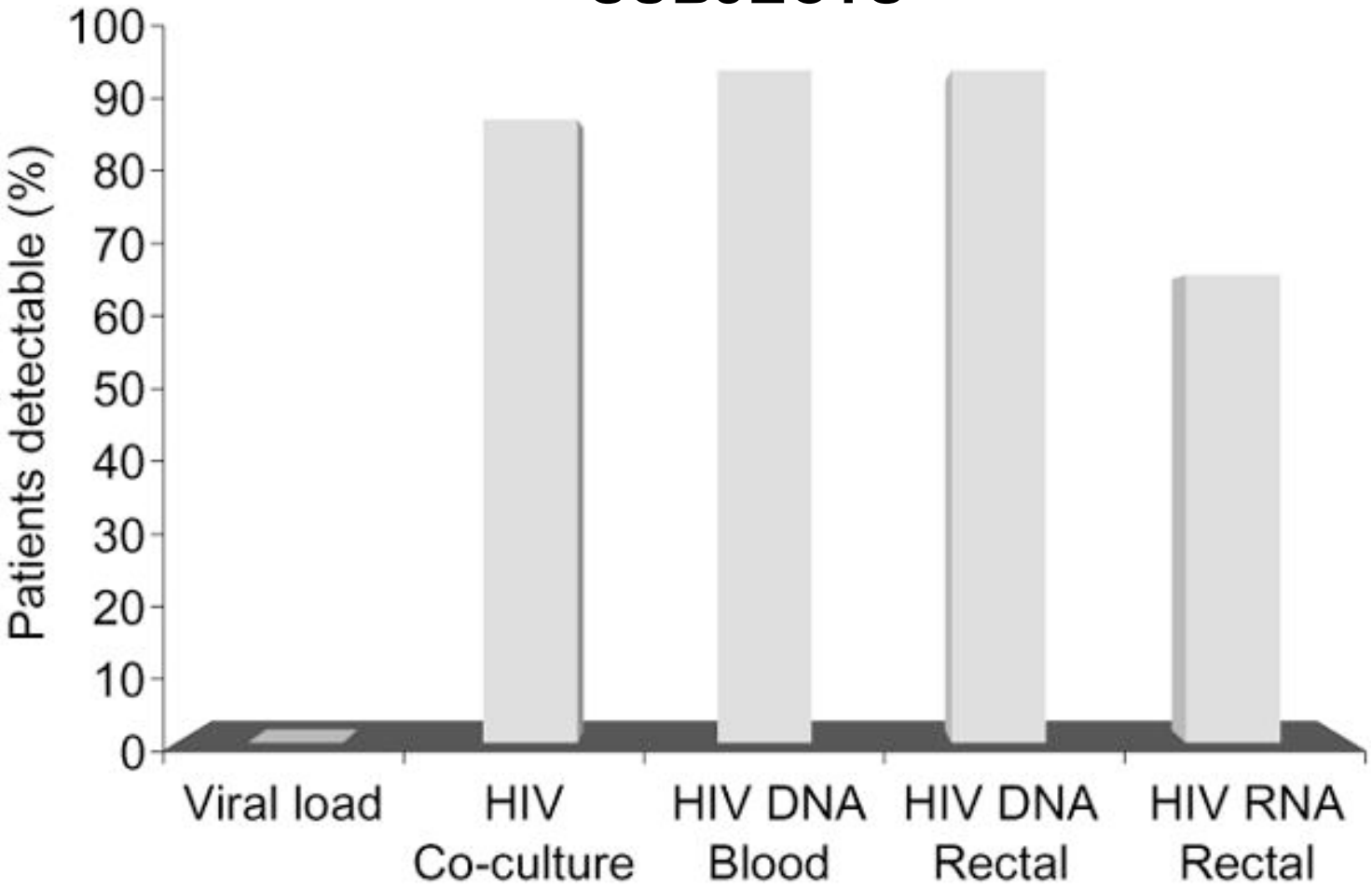
Brenchley et al; J. Exp. Med 2004

Multiple measures of HIV burden in blood and tissue are correlated with each other but not with clinical parameters in aviremic subjects

Peter A. Anton[a], Ronald T. Mitsuyasu[a], Steven G. Deeks[b], David T. Scadden[c], Bridget Wagner[d], Christine Huang[e], Catherine Macken[f], Douglas D. Richman[g], Cindy Christopherson[h], Flavia Borellini[j], Richard Lazar[j] and Kristen M. Hege[j]

AIDS 2003, **17**:53–63

HIV-1 LOAD IN BLOOD AND TISSUES OF AVIREMIC SUBJECTS



All reservoir assays demonstrated detectable HIV in the majority of subjects despite persistently undetectable levels in plasma (< 40 copies/ml).

Differences in HIV Burden and Immune Activation within the Gut of HIV-Positive Patients Receiving Suppressive Antiretroviral Therapy

Steven A. Yukl,[1,2] Sara Gianella,[6,a] Elizabeth Sinclair,[3,2] Lorrie Epling,[3,2] Qingsheng Li,[5,a] Lijie Duan,[5] Alex L. M. Choi,[1,2] Valerie Girling,[3,2] Terence Ho,[3,2] Peilin Li,[1,2] Katsuya Fujimoto,[1,2] Harry Lampiris,[1,2] C. Bradley Hare,[3,2] Mark Pandori,[4] Ashley T. Haase,[5] Huldrych F. Günthard,[6] Marek Fischer,[6] Amandeep K. Shergill,[1,2] Kenneth McQuaid,[1,2] Diane V. Havlir,[3,2] and Joseph K. Wong[1,2]

[1]San Francisco Veterans Affairs Medical Center, [2]University of California, San Francisco, [3]San Francisco General Hospital, and [4]Department of Public Health, San Francisco, California; [5]University of Minnesota, Minneapolis; [6]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Background. The gut is a major reservoir for human immunodeficiency virus (HIV) in patients receiving antiretroviral therapy (ART). We hypothesized that distinct immune environments within the gut may support varying levels of HIV.

Methods. In 8 HIV-1-positive adults who were receiving ART and had $CD4^+$ T cell counts of >200 cells/μL and plasma viral loads of <40 copies/mL, levels of HIV and T cell activation were measured in blood samples and endoscopic biopsy specimens from the duodenum, ileum, ascending colon, and rectum.

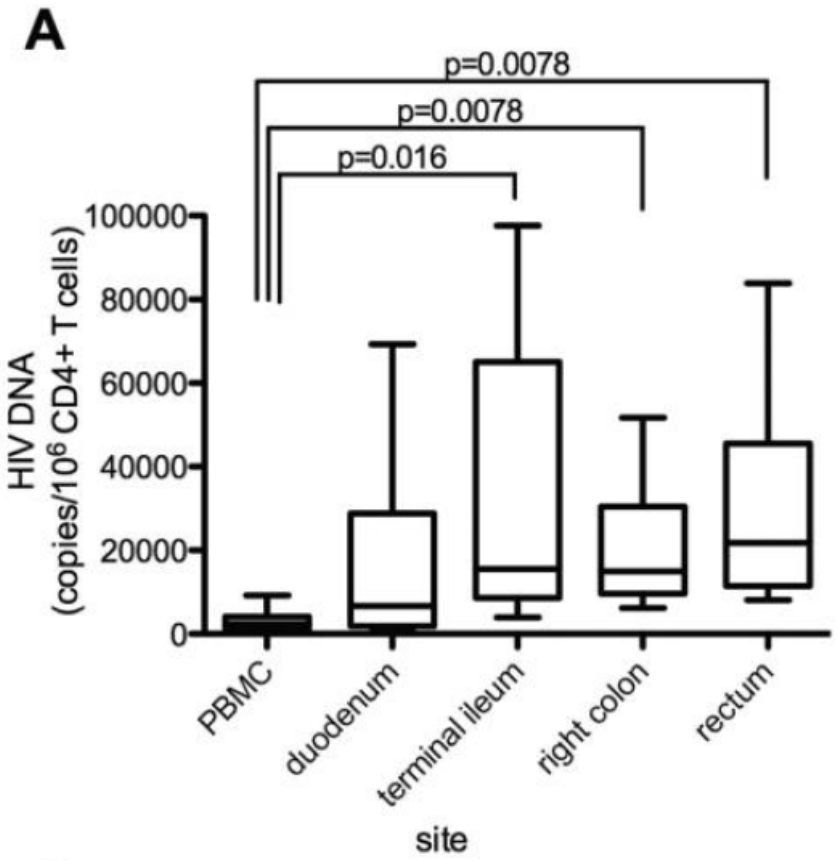
Results. HIV DNA and RNA levels per $CD4^+$ T cell were higher in all 4 gut sites compared with those in the blood. HIV DNA levels increased from the duodenum to the rectum, whereas the median HIV RNA level peaked in the ileum. HIV DNA levels correlated positively with T cell activation markers in peripheral blood mononuclear cells (PBMCs) but negatively with T cell activation markers in the gut. Multiply spliced RNA was infrequently detected in gut, and ratios of unspliced RNA to DNA were lower in the colon and rectum than in PBMCs, which reflects paradoxically low HIV transcription, given the higher level of T cell activation in the gut.

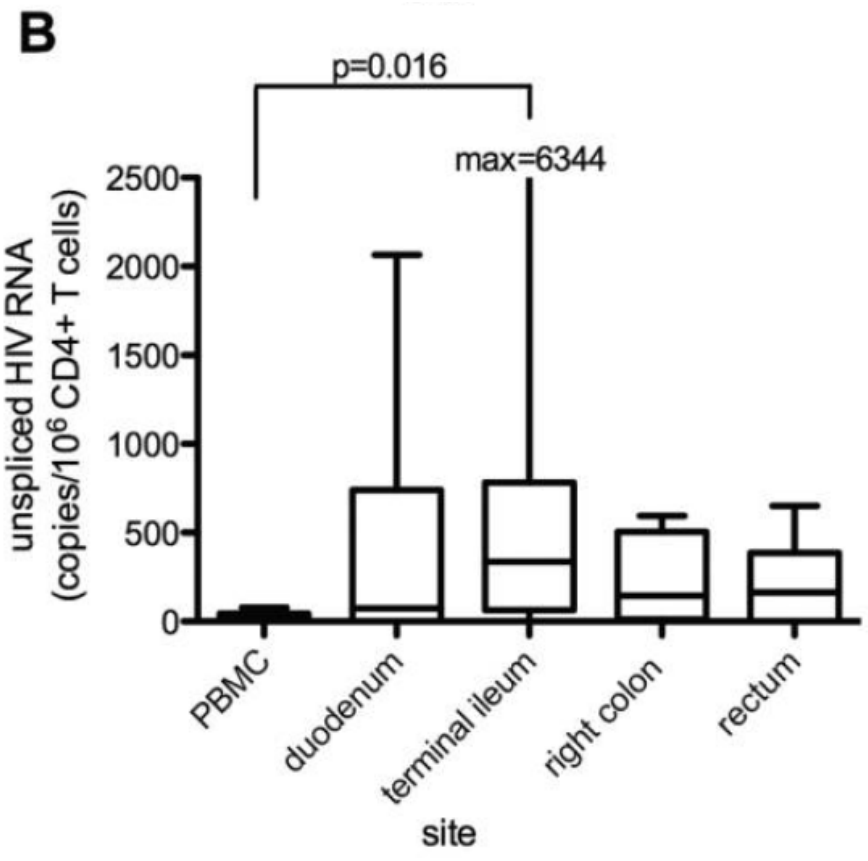
Conclusions. HIV DNA and RNA are both concentrated in the gut, but the inverse relationship between HIV DNA levels and T cell activation in the gut and the paradoxically low levels of HIV expression in the large bowel suggest that different processes drive HIV persistence in the blood and gut.

Trial registration. ClinicalTrials.gov identifier: NCT00884793 (PLUS1).

The Journal of Infectious Diseases 2010; 202(10):1553–1561

HIV DNA and RNA levels per CD4+ T cell were higher in all 4 gut sites compared with those in the blood.





The Journal of Infectious Diseases 2010; 202(10):1553–1561

HIV-DNA in rectal cells is well correlated with HIV-DNA in blood in different groups of patients, including long-term non-progressors

Véronique Avettand-Fenoel[a,b], Thierry Prazuck[c], Laurent Hocqueloux[c], Adeline Melard[a,b], Christophe Michau[d], Rémy Kerdraon[c], Eric Agoute[c] and Christine Rouzioux[a,b]

Most of the body's lymphoid tissue is in gut and constitutes an immense HIV reservoir. We quantified HIV-DNA in rectum and compared it with blood levels for 27 HIV-infected adults from different groups. We observed a large range of rectal and blood HIV-DNA levels. They were positively correlated ($r = 0.841$, $P < 0.0001$). Long-term non-progressors and patients in 'remission' after antiretroviral treatment interruption had the lowest blood and mucosal HIV-DNA levels.

AIDS 2008, 22:1875–1884

Long-term nonprogressors and patients in 'remission' after antiretroviral treatment interruption had the lowest blood and mucosal HIV-DNA levels

Table 1. Patient characteristics and total HIV-DNA in rectal cells and peripheral blood mononuclear cells.

						At inclusion					
Patient	Sex	Age	HIV infection duration (months)	Zenith HIV-RNA $\log_{10}$ copies/ml	CD4 T-cell nadir cells/μl	Plasma HIV-RNA $\log_{10}$ copies/ml	CD4 T-cell count in blood cells/μl	HIV-DNA $\log_{10}$ copies/10^6 PBMC	HIV-DNA $\log_{10}$ copies/10^6 rectal cells	Total aviremia duration (months)	Aviremia duration after treatment interruption (months)
Untreated patients at primary stage of infection (group 1)											
1	Male	40	1.0	5.2	729	5.1	726	3.6	4.0	0.0	
2	Female	30	1.0	5.8	483	4.9	526	3.6	3.9	0.0	
3	Male	50	3.0	5.8	267	5.8	322	3.3	3.3	0.0	
Patients initiating treatment for primary infection (group 2)											
4	Male	40	4.0	5.3	720	<1.7	850	3.2	3.9	0.5	
5	Male	43	0.5	6.2	815	4.9	1129	3.3	3.5	0.0	
Chronically infected patients, untreated (group 3)											
6	Male	59	117.0	4.9	377	4.3	425	3.7	4.0		
7	Male	51	12.0	5.5	267	5.0	267	3.7	3.8		
8	Male	49	38.0	5.8	252	5.7	251	3.6	3.5		
9	Female	28	120.0	6.0	15	6.0	15	3.8	3.3		
10	Male	47	22.0	5.7	261	4.6	469	3.3	3.0		
Chronically infected patients, on effective HAART initiated at the chronic phase of infection (group 4)											
11	Male	53	135.0	4.5	99	<1.7	473	3.2	2.9	66.0	
12	Male	43	96.0	4.7	45	<1.7	107	3.1	2.8	8.0	
13	Male	51	122.0	4.4	105	<1.7	270	3.5	2.8	49.0	
14	Female	24	64.0	5.3	222	<1.7	426	3.5	2.8	27.0	
15	Male	56	122.0	5.8	17	<1.7	503	3.5	2.5	41.0	
16	Female	33	125.0	5.0	12	<1.7	177	2.7	2.5	6.0	
17	Male	60	130.0	4.9	377	<1.7	808	3.4	2.5	58.0	
18	Male	42	132.0	5.1	225	<1.7	525	2.9	2.4	75.0	
Chronically infected patient, on effective HAART initiated for primary infection (group 5)											
19	Male	36	57.0	4.9	587	<1.7	648	1.5	2.1	53.0	
Patients in 'remission' after treatment interruption (group 6)											
20	Female	41	119.0	3.4	468	<1.7	565	2.0	2.2	111.0	29.0
21	Male	40	121.0	4.3	388	<1.7	1050	2.2	2.1	112.0	38.0
22	Female	35	54.0	4.5	490	<1.7	671	2.0	1.8	37.0	28.0
23	Female	37	70.0	4.6	502	<1.7	765	1.5	1.8	53.0	45.0
24	Female	39	99.0	5.0	640	<1.7	1000	1.9	1.8	90.0	9.0
Long-term non-progressors (group 7)											
27	Male	31	90.0	3.1	609	3.1	601	2.1	2.1		
26	Male	30	76.0	3.2	601	2.3	783	2.3	2.0		
25	Male	45	99.0	2.7	682	2.0	840	2.2	1.9		

AIDS 2008, 22:1875–1884

La compartimentalizzazione di HIV nel Sistema Nervoso Centrale

Early antiretroviral treatment prevents the development of central nervous system abnormalities in simian immunodeficiency virus-infected rhesus monkeys

Maria Cecilia G. Marcondes[a], Claudia Flynn[a], Salvador Huitron-Rezendiz[a], Debbie D. Watry[a], Michelle Zandonatti[a] and Howard S. Fox[a,b]

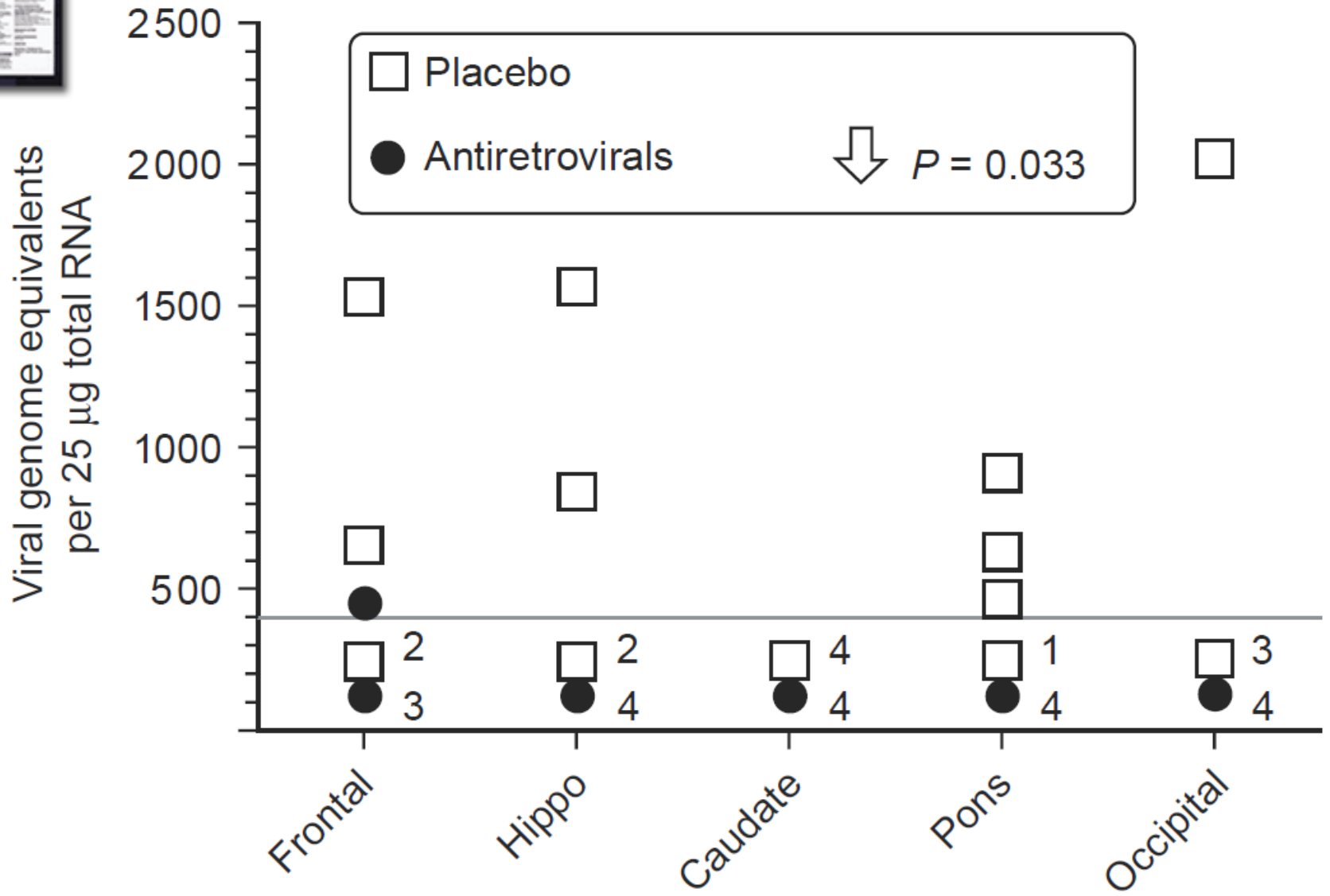
Objective: Neurocognitive disorders are devastating consequences of HIV infection. Although antiretroviral regimens have been efficacious in both improving life expectancy and decreasing dementia, there has not been an effect on the overall prevalence of HIV-associated neurocognitive disorders. Whether early institution of treatment, or treatment with drugs that effectively penetrate the blood–brain barrier, would help protect from such conditions is not known. Using the simian immunodeficiency virus/macaque model, we investigated the hypothesis that early introduction of antiretroviral treatment can protect the brain.

Design and methods: Animals were inoculated with simian immunodeficiency virus, and upon resolution of the acute infection period divided into two groups and treated, or not, with combination antiretroviral therapy. Viral, immune, and physiological parameters were measured during the course of infection, followed by assessment of viral, immune, and molecular parameters in the brain.

Results: We observed that even with agents that show poor penetration into the central nervous system, early antiretroviral treatment prevented characteristic neurophysiological and locomotor alterations arising after infection and resulted in a significant decrease in brain viral load. Although the number of infiltrating immune cells in the brain did not change with treatment, their phenotype did, favoring an enrichment of effector T cells. Early treatment also significantly lowered brain levels of interferon-α, a cytokine that can lead to neurocognitive and behavioral alterations.

Conclusion: Early antiretroviral treatment prevents central nervous system dysfunction by decreasing brain viral load and interferon-α levels, which can have a profound impact over the course of infection.

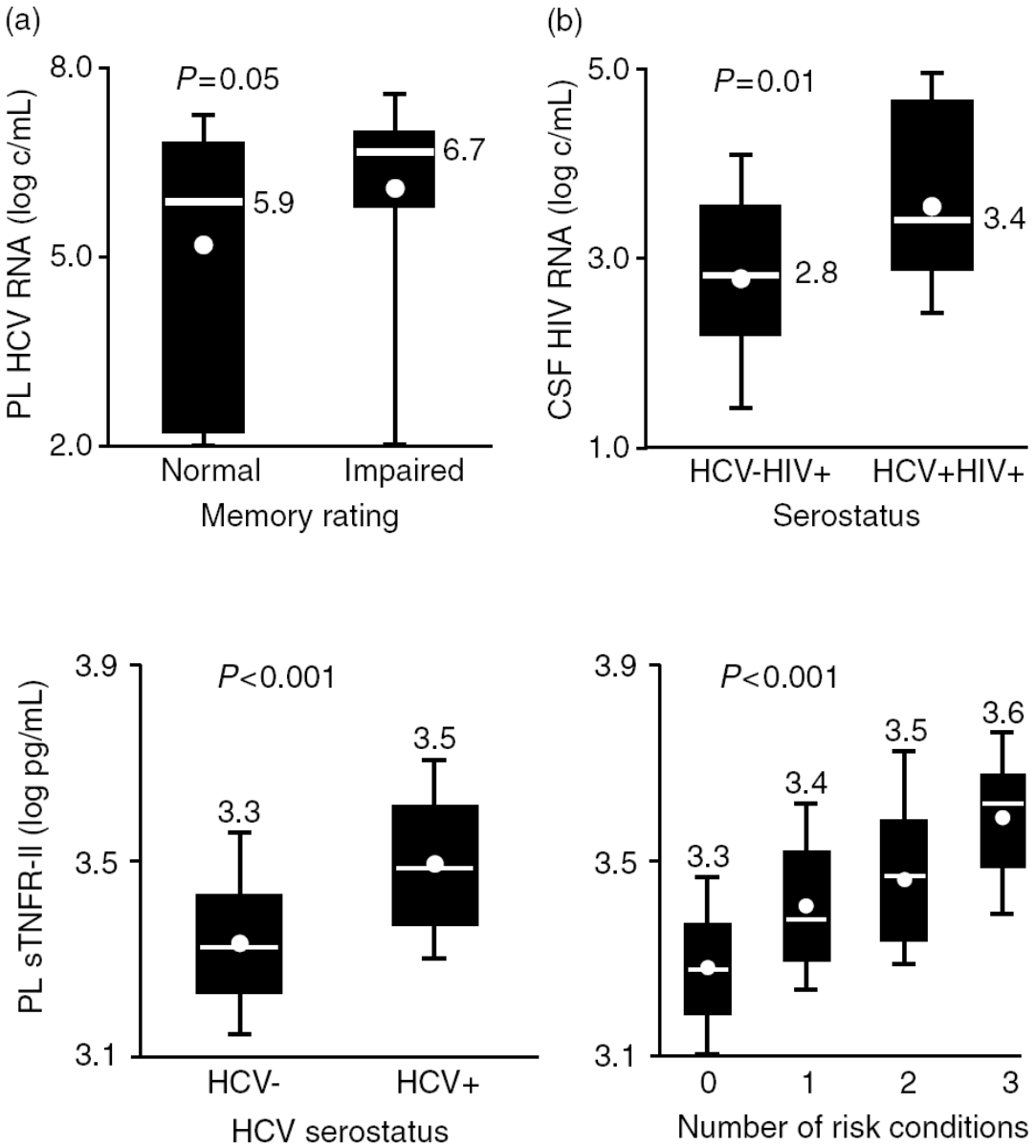
AIDS 2009, **23**:1187–1195



Marcondes AIDS 2009

Suscettibilità delle cellule del sistema nervoso centrale all'infezione da HIV

Cell Type	Chemokine receptor	CD4 antigen	HIV susceptibility	Productive infection
Perivascular macrophages	Yes	Yes	Yes	Yes
Microglia	Yes	Yes	Yes	Yes
Astrocytes	Yes	No	Yes	No
Oligodendrocytes	Yes	No	*In vitro*	No
Neurons	Yes	No	No	No
Brain microvascular endotelial cells	Yes	No	*In vitro*	No



Coinfezione HIV+/HCV+: effetto sull'RNA di HIV-1 nel CSF e markers di attivazione

CSF = Fluido cerebrospinale

Letendre, AIDS, 2005

Poster 381

Single Agent Therapy with Lopinavir/ritonavir Controls HIV-1 Replication in the Central Nervous System

Corresponding Author:
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Therapeutic Concepts
Houston, TX 77004

RF Yeh[1,2], S Letendre[3], IS Novak[4], BA Lipman[5], A Hermes[5], C Mayberry[1], B Miguel[1], J Nemecek[6], M Norton[5], JC Gathe Jr.[1]
[1]Therapeutic Concepts, Houston, TX; [2]University of Houston, Houston, TX; [3]University of California, San Diego, CA; [4]Park Plaza Hospital, Houston, TX; [5]Abbott Laboratories, Abbott Park, IL; [6]Donald R. Watkins Foundation, Houston, TX

Background

- Lopinavir/ritonavir (LPV/r) as single-agent therapy has exhibited virologic suppression comparable to combination HAART when utilized in a variety of treatment strategies.
- Inability to control HIV replication in sanctuary sites such as the central nervous system (CNS) may limit success of antiretroviral therapy.
- LPV/r has demonstrated control of HIV replication when used in combination with other antiretroviral therapy (ART). Although LPV concentrations in CSF are lower than plasma, studies have shown concentrations exceed levels that suppress wild-type HIV replication.
- Previous studies not detecting LPV in the cerebrospinal fluid (CSF) have been limited by insufficient assay sensitivity.
- Previous data describing CNS antiretroviral activity of LPV/r when used as a sole agent was limited by a short duration and was prior to full suppression.

Methods

IMANI-2 is an ongoing, prospective, open-label investigation of LPV/r in 40 antiretroviral naive HIV-1 infected subjects. LPV/r is administered as a single-agent, 400/100 mg twice daily.

Sub-study was approved by the Institutional Review Board and all participating subjects provided written, informed consent.

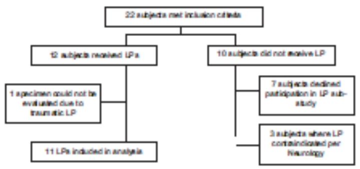
Inclusion criteria:

All subjects enrolled in IMANI-2 who had reached at least week 24 with 2 most recent plasma HIV-1 RNA < 75 copies (Bayer Versant™ HIV RNA 3.0, bDNA) by September 15, 2006, were approached for enrollment in this sub-study. Plasma HIV RNA were performed by LabCorp®.

Exclusion criteria:

Contraindication to lumbar puncture (LP) (e.g., coagulopathy).

IMANI-2 CSF Sub-study Subject Disposition



- LPs were performed by a board certified neurologist using standard technique.
- LPs were performed at median week 36 (range 24–48).
- CSF samples from 3 subjects for HIV RNA were obtained 0–6 hours after dosing and the remaining samples were obtained 6–12 hours after dosing. Plasma was also sampled at the time of LP. The median time between CSF and plasma sampling was 37 minutes (range -31–113).
- As there is no validated commercially available bDNA assay for CSF, HIV RNA in CSF was measured via RT-PCR (Roche Amplicor ultrasensitive version 1.5) with limits of detection at < 50 copies/mL.
- LPV was measured by liquid chromatography mass spectrometry (LC-MS) in CSF and high performance liquid chromatography (HPLC) in plasma lower limit of quantification (LLOQ) of 100 ng/mL and an inter-assay variability of <7.5%.
- LC-MS assay was modified from previously published version. LPV and internal standard (13C-amprenavir) were isolated from matrix by solvent extraction with methyl-tert-butyl ether (MTBE), resulting in a LLOQ of 0.5 ng/mL with variability <10%.
- LPV concentrations in CSF were compared to LPV's 50% inhibitory concentration (IC_{50}) derived from a panel of 2801 wild-type HIV-1 isolates by the Monogram Biosciences PhenoSense™ assay [median 3.8 nmol/L (1.6 ng/mL)].

Results

- Of the twelve CSF samples obtained, 11 were evaluable.
- One CSF sample was excluded because the LP was traumatic (RBC 125, WBC 3, 128 HIV RNA copies/mL).
- Included subjects represented diverse racial/ethnic background, age, and gender. (Table 1)

Table 1: Demographics

	n = 11	
Age (yrs) – median [range]	36	[25–60]
Gender male:female (n)		6:5
Ethnicity n (%)		
African American	5	(46)
Caucasian	3	(27)
Hispanic	2	(18)
Asian	1	(9)
Weight (lbs) – median [range]	165	[133–244]
BMI (kg/m2) – median [range]	25	[20.7–38.0]
Pretreatment CD4+ T cells (cells/mm³) – median [range]	264	[20.0–491]
Pretreatment HIV RNA (bDNA) (log10 copies/mL) – median [range]	4.26	[3.73–4.78]

With the exception of M41L in 1 subject, baseline genotypic resistance analyses showed only polymorphisms. (Table 2)

Table 2: Baseline mutations

Subject	Pre-drug plasma mutations in protease	Pre-drug mutations in reverse transcriptase
003	I13V, M36I, L63P, A71T, V77I, I93L	R211K
004	L63P, V77I, I93L	M41L, R211K, T215D, 335E, I135V, V179E
010	I13V, M36I, L63P, A71T, V77I, I93L	R211K
016	L63P, V77I, I93L	R211K
017	M36I, L63P, I93L	R211K
031	L63P	No mutations detected
032 (Sample 6/06)	M36I	No mutations detected
032 (Sample 1/07)	—	No mutations detected
036	L10I, L63P	No mutations detected
037	M36I	No mutations detected
041	No mutations detected	No mutations detected
044	No mutations detected	No mutations detected

- Median LPV/r exposure at the time of LP was 36 weeks (range 24–48)
- Median blood CD4+ cells at LP were 471 cells/mm³ (range 285–769)
- All subjects were asymptomatic at the time of LP (Table 3)

Table 3: Plasma viral load, CD4+ and week of LP

Subject	Week of LPV/r	Pre-treatment plasma CD4+ cells/mm³	Plasma CD4+ cells/mm³ at LP	Plasma copies/mL (bDNA)	CSF HIV RNA copies/mL
003	48	238	449	< 75	< 50
004	48	482	546	< 75	< 50
010	48	264	646	< 75	< 50
016	48	308	471	< 75	< 50
017	48	257	515	< 75	< 50
031	32	530	596	< 75	< 50
032 (Sample 6/06)	36	171	348	< 75	201
032 (Sample 1/07)	48	—	386	< 75	747
036	32	272	458	< 75	< 50
037	32	143	285	< 75	< 50
041	32	316	371	< 75	< 50
044	24	186	769	< 75	< 50

Results (continued)

- 11/11 subjects had quantifiable LPV plasma concentrations. (Table 4)
- Median plasma LPV concentration was 9,676 ng/mL (range 4887–17003).
- Median CSF LPV concentration was 24.3 ng/mL, mean 30.4 ng/mL (range 7.1–85.3).
- The median LPV/IC_{50} ratio was 12.8, mean 16.0 (range of 3.7–44.8).
- All subjects had LPV concentrations of at least 3-fold above the median IC_{50} for wild-type HIV-1.

Table 4: Drug concentrations and CSF viral load

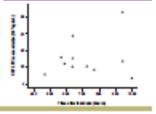
Subject	Plasma LPV ng/mL	Plasma RTV ng/mL	CSF LPV ng/mL	LPV/IC_{50} ng/mL	CSF:Plasma LPV ratio
003	10,984	918	24.3	12.8	0.22%
004	4,887	480	7.1	3.7	0.15%
010	17,003	871	27.1	14.3	0.16%
016	13,900	1,045	17.0	8.9	0.12%
017	7,702	410	11.8	6.2	0.15%
031	8,514	575	28.8	15.9	0.34%
032	11,666	616	85.3	44.9	0.73%
036	9,240	1,258	31.5	16.6	0.34%
037	13,753	838	57.3	30.2	0.42%
041	9,676	773	30.7	16.2	0.32%
044	6,888	486	21.3	11.2	0.31%

- LPV median post-dose CSF sampling interval was 6.38 hours (range 4.07–9.98).
- Post-dose plasma sampling interval was 6.0 hours (range 4.08–6.77).
- The median CSF-plasma ratio was 0.24% (range 0.12–0.73). (Table 5)
- The relationship between time after last dose and CSF concentration is displayed in Figure 1.

Table 5: LPV in CSF-plasma pairs

	< 6 h after dose n=3	≥6 h after dose n=8	Overall
CSF LPV (ng/mL) median (range)	24.3 (11.8–31.5)	24.2 (7.1–85.3)	24.3 (7.1–85.3)
Plasma LPV (ng/mL) median (range)	9,240 (7,702–10,984)	10,670 (4,887–17,003)	9,676 (4,887–17,003)
CSF-plasma ratio median (range)	0.22% (0.15–0.34)	0.28% (0.12–0.73)	0.24% (0.12–0.73)
Time after dose (h) median (range)	5.07 (4.07–5.87)	7.46 (6.35–9.98)	6.38 (4.07–9.98)

Figure 1: Lopinavir concentrations in CSF by post-dose time



Subject 032

The subject had quantifiable HIV RNA in 2 CSF specimens (201 and 747 copies/mL). On first LP, LPV CSF concentrations were not obtained. Second LP found a LPV CSF concentration of 85.3 ng/mL. This value exceeded 3 times the median LPV CSF concentration for the cohort. This value was the highest CSF LPV concentration found in our trial. Genotypic resistance testing was performed on HIV derived from CSF revealing no primary mutations in protease.

Detailed Clinical Summary of Subject 032

Subject 032 is a 36 year old Asian male born in Vietnam, residing in the U.S. since 1986, who was referred from a rheumatology clinic after evaluation in August 2005 for left-sided headache, decreased vision, pruritic maculopapular rash, joint pain, and right lower quadrant pain. He had unremarkable social history, no known HIV risk factors, was not receiving any medications and had no known allergies. Laboratory results were as follows:

Hemoglobin	10.8 gm/dL
Hematocrit	32.0%
Leukocytes	3.0 x 10³/µL
Erythrocyte sedimentation rate	125 mm/h (normal ≤15)
Antinuclear antibody screen	positive
Antinuclear antibody pattern	homogenous
Antinuclear antibodies	1:640 (> 1:80 elevated antibody level)

Results (continued)

He was diagnosed with optic neuritis and suspected systemic lupus erythematosus, treated with intravenous methylprednisolone and prednisone tapered over 3 weeks. When he did not respond, he was referred to our clinic where he was found to have:

Laboratory results		
	HIV-1 ELISA	positive
	Western blot	positive
	CMV PCR (retinitis primarily in left eye)	1700 copies/mL
	CD4 count	118 (9.1%)
	HIV RNA Roche Amplicor	577,000 copies/mL
	Hepatitis B surface antibody	> 200.0 mIU/mL
	Hepatitis B surface antigen	non-reactive
	Hepatitis B core antibody	non-reactive
	Hepatitis C antibody	non-reactive
	Hepatitis A antibodies	+ IgG

Other infectious disease work-up was negative. CMV retinitis was treated with intravenous ganciclovir for 4 weeks and maintenance therapy with oral valganciclovir prior to screening for IMANI-2.

Clinical course during IMANI-2 Trial

Week of Therapy	CD4 count (cells/mm³)	HIV viral load (copies/mL)*	Event
8/2005	118	577,000*	Genotype M36I, Phenotype to LPV 1.36 FC, RC=59.1%
11/2005	194	117,533	IMANI-2 screen
12/2005 (Week 0)	171	185,176	Start LPV/r
Week 4	218	783	
Week 6		94	Herpes zoster over left T-3 dermatome – resolved with oral famciclovir; hydrocodone/acetaminophen after 2 weeks
Week 8	338	142	RLQ pain, nausea, vomiting resolved with IV ketorolac, promethazine, and saline bolus
Week 12	382	< 75	
Week 24	386	< 75	
Week 32	384	170	
Week 36	348	< 75	1st lumbar puncture – CSF HIV RNA*- 201 copies/mL
Week 48	386	< 75	2nd lumbar puncture – CSF HIV RNA*- 747 copies/mL

* HIV RNA PCR (Roche Amplicor), other values obtained with Bayer Versant™ HIV-1 RNA 3.0, bDNA.

Discussion

This study demonstrated that single therapy with LPV/r suppressed CSF viral loads in all but one subject. Concentrations of LPV in the CSF while significantly lower compared to blood plasma, are likely adequate for suppression given the relatively protein free environment of CSF. In addition all CSF LPV concentrations did exceed the Monogram Biosciences median IC_{50} and 99th percentile IC_{50} [8.1 nmol/L (5.1 ng/mL)] for wild-type HIV-1.

1. Persistent HIV replication can occur in the plasma during treatment with boosted protease inhibitors in the absence of identifiable resistance. The reasons for this are not completely understood but this phenomenon might also occur in other compartments, such as the CNS. Detectable HIV RNA levels in CSF have been previously reported during otherwise successful therapy with triple agent HAART.
2. HIV replication in CSF could persist if LPV concentrations were sub-therapeutic. The LPV concentration in the CSF of this individual, however, was the highest in the group and exceeded the Monogram Biosciences median IC_{50} and 99th percentile IC_{50} by approximately 45- and 17-fold, respectively.
3. HIV with reduced susceptibility to LPV could continue to replicate in the presence of higher levels of LPV. However, genotype resistance testing of HIV derived from the CSF of this individual demonstrated the absence of primary protease resistance mutations.
4. Protease inhibitors inhibit production of infectious virions but not transcription of viral DNA or translation of viral polyproteins. In the absence of reverse transcriptase inhibition, viral RNA and polyproteins can accumulate in infected cells. This non-infectious viral RNA can be measured by RT-PCR assays, especially if the infected cells lyse during processing. Leukocytes were present in both CSF specimens from this individual and, according to the clinical lab, all leukocytes lysed in the second specimen before they could be counted. Since this subject had therapeutic levels of LPV in CSF and no evidence of reduced susceptibility, the production of intact virions is less likely. Instead, the measured RNA may have reflected release of intracellular HIV RNA from lysed lymphocytes.

Discussion (continued)

5. If the HIV RNA in this CSF specimen derived from lysis of trafficking replication competent lymphocytes, greater trafficking should lead to higher HIV RNA levels. We hypothesized that this individual might have high MCP-1/CCL2 levels in CSF because this potent chemokine induces trafficking of monocytes and lymphocytes into the CNS. The MCP-1/CCL2 concentration in this specimen was 824 pg/mL, a level that is at the ~90th percentile of an independent cohort of 119 HAART-treated individuals and is ~4 times more likely to come from an individual who has an A-to-G polymorphism in the promoter region of the gene encoding MCP-1/CCL2. Notably, MCP-1 has also been implicated in the neurologic complications of HIV and systemic lupus erythematosus.
6. Another possible explanation for the finding depends on the differences between CSF and brain tissue. Since CSF provides an imperfect window into brain events, HIV and LPV characteristics in CSF may not accurately reflect those in the brain. For example, the persistent HIV RNA in CSF could derive from compartmentalized replication in microglia or brain macrophages, which is more common in those with CD4 nadirs under 200/µL, and sub-therapeutic LPV concentrations in brain tissue despite having therapeutic concentrations in CSF. At present, this theory cannot be proven without obtaining brain tissue.

Conclusion

This study is the first to examine CSF viral load in a diverse cohort of naive subjects treated with LPV/r single-agent therapy for at least 24 weeks. Subjects were sampled throughout the dosing interval and 10 of 11 achieved suppression of CSF viral load < 50 copies/mL.

The LPV CSF median concentration of 24.3 ng/mL (range 7.1–85.3) in single agent therapy was above the previously reported median of 17.0. The median LPV/IC_{50} ratio in this study was 12.8 (mean 16.0) with a range of 3.7 to 44.8. All individual subject LPV concentrations exceeded the reference population median IC_{50} by at least 3-fold, and the mean CSF LPV concentration exceeded the reference population median IC_{50} by 16-fold. Therefore LPV/r delivers adequate LPV concentrations that reliably exceed the reference population median IC_{50} for wild-type virus.

In 10 of 11 subjects LPV/r given as single-agent therapy effectively controlled viral replication in the CSF compartment.

The implications of potential CNS viral replication during ARV in the absence of resistance, whether using single agent therapy or triple agent HAART, warrants further study.

Acknowledgements

- We are deeply indebted to our study subjects.
- Our thanks to Abbott for funding this as an investigator initiated study.
- Our thanks also goes to Freddie Reid, Jamie Durelle, Sarah Iglesias, Corey Smith, and Steve Kauzel (UCSD) for doing the biomarker, virology, and pharmacology assays that enabled us to make these conclusions.

References

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Table 3: Plasma viral load, CD4+ and week of LP

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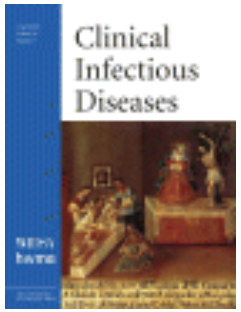


Discordance Between Cerebral Spinal Fluid and Plasma HIV Replication in Patients with Neurological Symptoms Who Are Receiving Suppressive Antiretroviral Therapy

Ana Canestri,[1,7] François-Xavier Lescure,[3] Stephane Jaureguiberry,[1] Antoine Moulignier,[3] Corinne Amiel,[4] Anne Geneviève Marcelin,[2,6,7] Gilles Peytavin,[5] Roland Tubiana,[1,7] Gilles Pialoux,[3,6] and Christine Katlama[1,6,7]

[1]Service de Maladies Infectieuses et Tropicales and [2]Laboratoire de Virologie, Hôpital Pitié-Salpêtrière, [3]Service de Maladies Infectieuses et Tropicales and [4]Laboratoire de Virologie, Hôpital Tenon, and [5]Service de Toxicologie, Hôpital Bichat-Claude Bernard, Assistance Publique–Hôpitaux de Paris, [6]Université Pierre et Marie Curie Paris, and [7]Institut National de la Santé et de la Recherche Médicale, U943, Paris, France

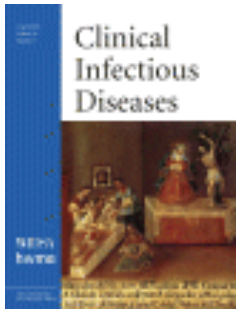
Objective. We report data on 11 patients with neurological symptoms and human immunodeficiency virus (HIV) cerebrospinal fluid (CSF) viremia contrasting with suppressed plasma HIV RNA during receipt of combined antiretroviral therapy.

Design. We retrospectively identified instances of central nervous system (CNS) symptoms in patients who had been receiving stable combination antiretroviral therapy. Discordance between plasma and CSF HIV RNA levels was defined by any detectable CSF HIV RNA level >200 copies/mL while plasma levels were <50 copies/mL or by a CSF HIV RNA level that was ⩾1 log greater than the plasma HIV RNA level.

Results. Eleven patients had experienced acute or subacute neurological symptoms. All but one patient had CSF pleocytosis and/or elevated protein levels. The median CSF HIV RNA level was 880 copies/mL (range, 558–12,885 copies/mL). Patients had been receiving stable combination antiretroviral therapy for a median of 13 months (range, 10–32 months). Eight of 11 patients had a plasma HIV RNA level <50 copies/mL, and 3 had plasma HIV RNA blips with their CSF HIV RNA level >1 log higher than their plasma HIV RNA level. Resistance-associated mutations were detected in 7 of 8 CSF HIV RNA genotypic strains. The median number of resistance-associated mutations was 6 (range, 2–8) to nucleoside reverse-transcriptase inhibitors and 3 (range, 1–9) to protease inhibitors. One patient had a virus harboring nonnucleoside reverse-transcriptase inhibitor mutations. The median central nervous system penetration-effectiveness (CPE) rank was 2 (range, 1–3), and 5 patients had a CPE ⩽1.5. After antiretroviral therapy optimization based on genotypes and CPE, all patients clinically improved, with normalization of CSF.

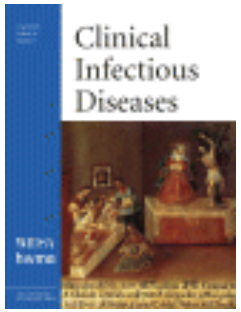
Conclusions. Despite successful suppression of plasma viremia with antiretroviral therapy, HIV may replicate in CSF, with development of CSF HIV resistance resulting in acute or subacute neurological manifestations.

Clinical Infectious Diseases 2010; 50:773–778



Canestri 2010

	CSF		Plasma			
Treatment	HIV RNA level, copies/mL	ART concentration trough, ng/mL	HIV RNA level, copies/mL	ART concentration trough, ng/mL	Neurological symptoms	Treatment
TDF FTC ATVr	12,885	12 NA <30	147	52 19 538	Persistent headache	TDF FTC ATVr
AZT 3TC IDVr T20	845	28 201 154 <50	<50	<10 244 565 1427	Memory disorders, cerebellar ataxia	AZT 3TC IDVr T20
3TC ABC ATV IDVr	1190	NA 75 <30 97	<50	597 86 980 893	Cerebellar dysarthria, cerebellar ataxia	3TC ABC ATV IDVr
TDF FTC fAPVr	870	NA NA 47	78	NA NA 1495	Tactile allodynia	TDF FTC fAPVr
3TC ABC TDF DRVr	5035	<10 332 191 207	<50	<10 270 878 8992	Glasgow Coma Score of 3	3TC ABC TDF DRVr
DRVr	580	<5	<50	3522	Persistent headache	DRVr
FTC ABC ATVr	558	NA NA 18	<50	NA NA 194	Memory disorders, cerebellar ataxia, pyramidal syndrome	FTC ABC ATVr
3TC AZT ABC EFV	1023	NA NA NA	<50	NA NA NA	Lower limb disesthesia and hypoesthesia	3TC AZT ABC EFV
3TC DdI TDF NVP	586	NA NA NA	<50	388 NA 28 4864	Memory disorders, left lower limb disesthesia	3TC DdI TDF NVP
3TC AZT ATV	880	NA NA NA	<50	NA NA NA	Temporospatial disorientation, cerebellar ataxia	3TC AZT ATV
LPVr	6999	NA	483	NA	Memory disorders, cerebellar dysarthria	LPVr



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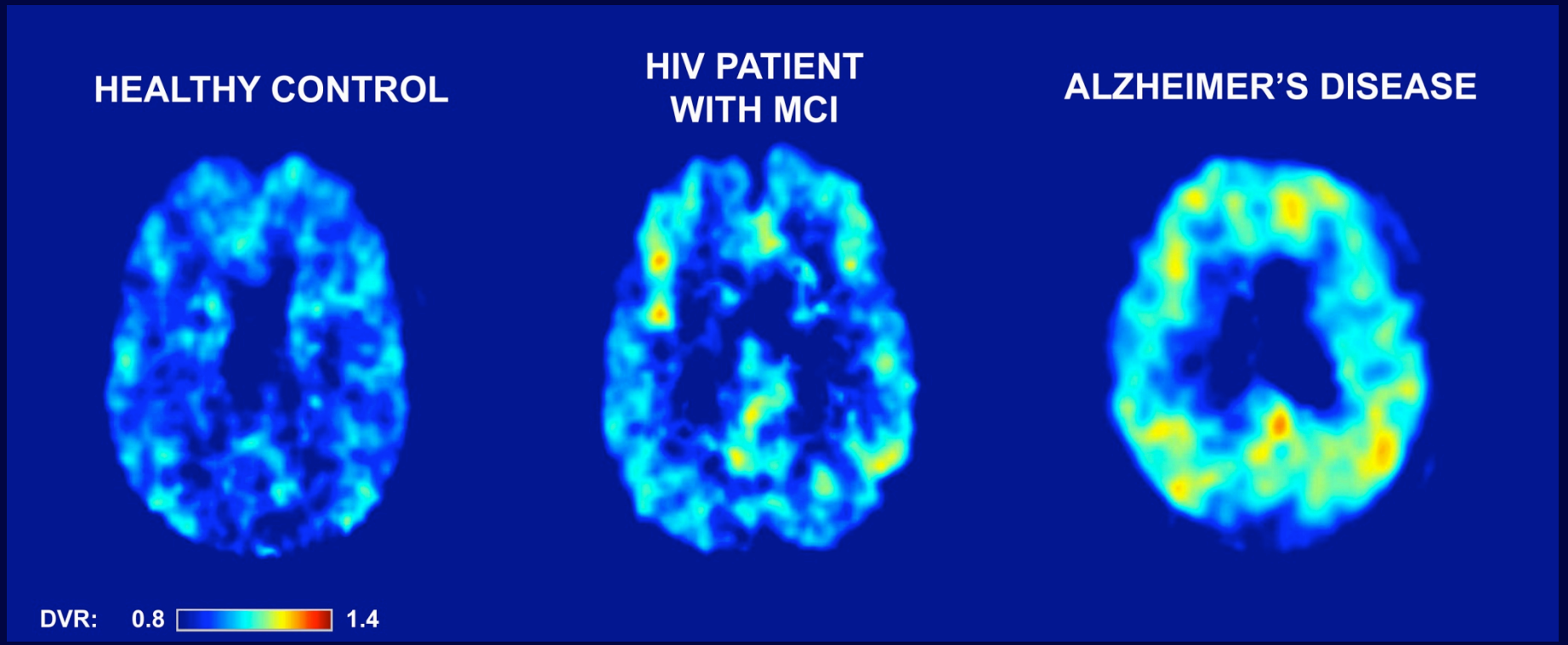
Despite successful suppression of plasma viremia with HAART, HIV may replicate in CSF, with development of CSF HIV resistance resulting in acute or subacute neurological manifestations.

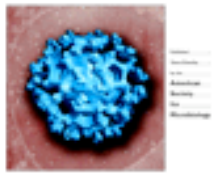
Nonstante la soppressione virologica plasmatica in corso di HAART, l'HIV può replicare nel CSF, con lo sviluppo di resistenze. Questa situazione può portare a manifestazioni neurologiche acute o subacute.

Clinical Infectious Diseases 2010; 50:773–778

FDDNP PET imaging of the HIV brain: the first in vivo evidence of amyloid



Achim CL, personal observation, 2007



Journal of Virology

JOURNAL OF VIROLOGY, Mar. 2010, p. 2395–2407 Vol. 84, No. 5
0022-538X/10/$12.00 doi:10.1128/JVI.01863-09

Compartmentalization and Clonal Amplification of HIV-1 Variants in the Cerebrospinal Fluid during Primary Infection[▽]

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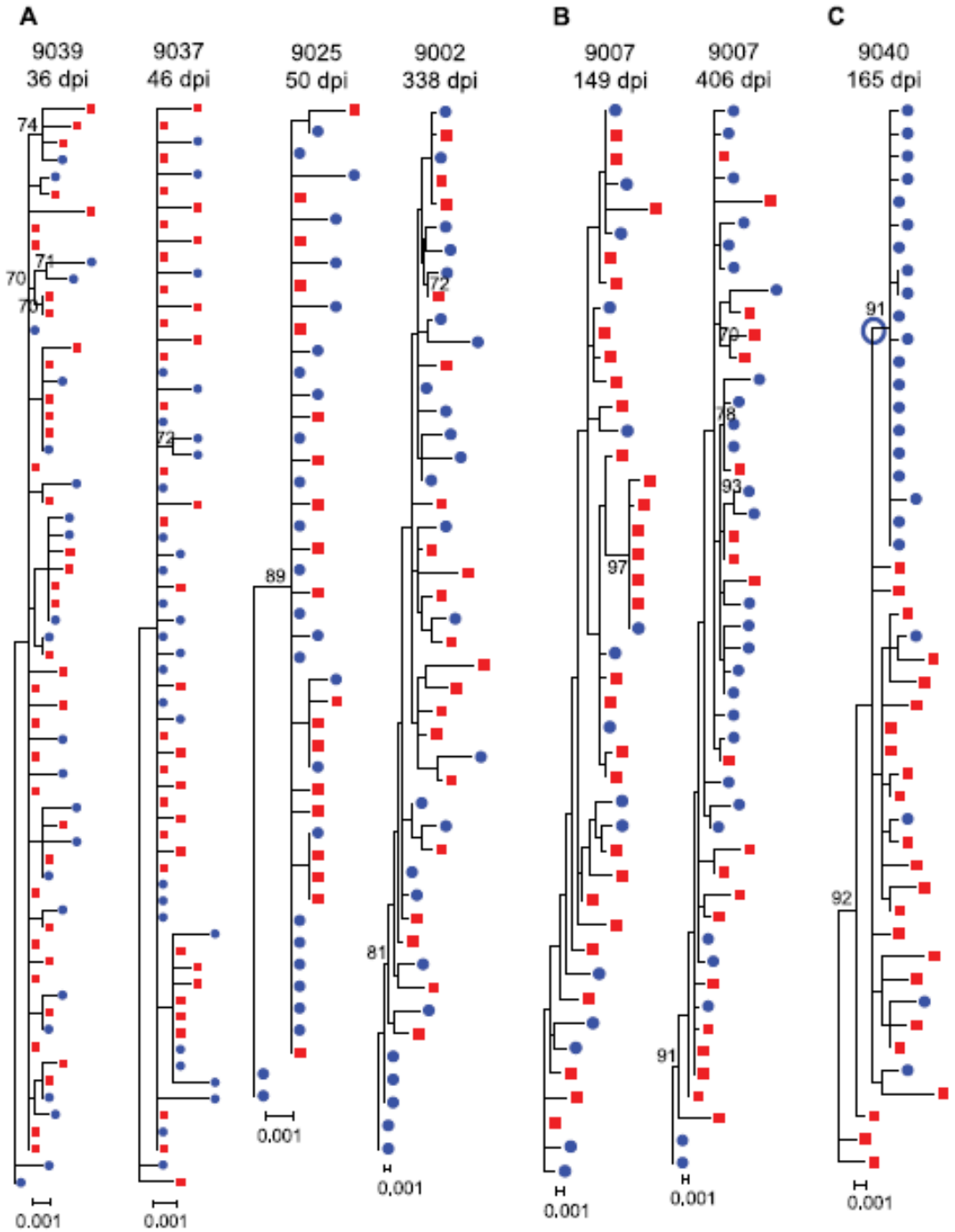
Received 2 September 2009/Accepted 8 December 2009

To assess HIV-1 genetic compartmentalization early during infection, we compared HIV-1 populations in the peripheral blood and CSF in 11 primary infection subjects, with analysis of longitudinal samples over the first 18 months for a subset of subjects.

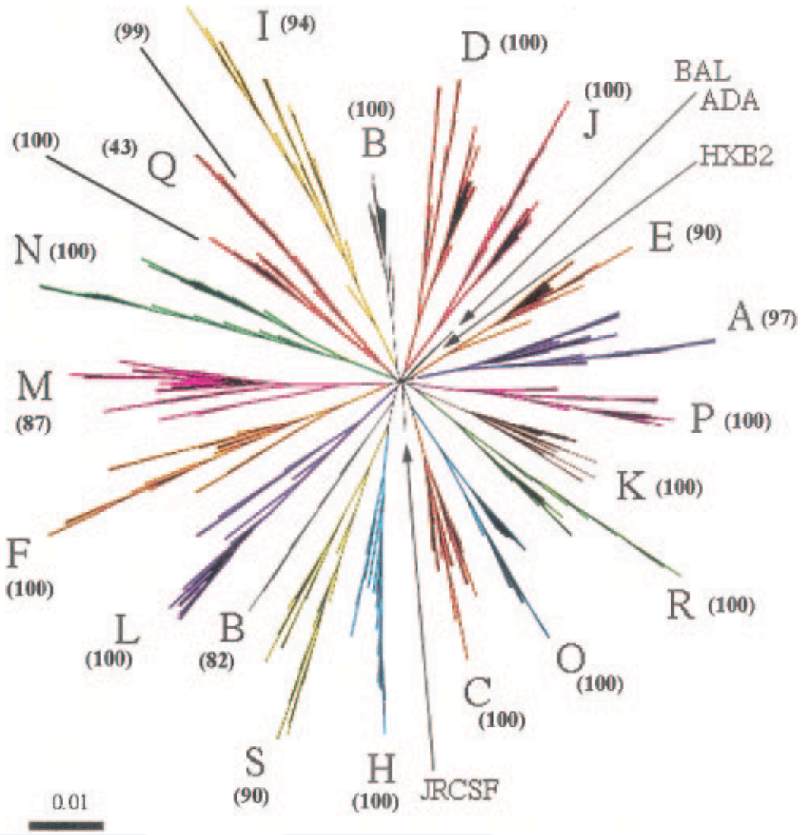


Phylogenetic analysis of plasma and CSF HIV-1 populations. (A) for 4 subjects with equilibration between blood plasma and CSF HIV-1 populations. (B) for subject 9007 at 149 days p.i. (dpi) and 406 days p.i. HIV-1 populations were equilibrated at 149 days p.i. but became slightly discordant at 406 days p.i. (C) for subject 9040, which displays significant compartmentalization in the CSF. Sequences obtained from the CSF are labeled with solid blue circles, and plasma sequences are labeled with solid red rectangles on the tree.

Schnell J Virol 2010

Journal of Virology

Compartimentalized CNS viral evolution and discordant resistance in HIV advanced patients



Elevated (50%) rate of discordant resistance between plasma and CSF

In 8 of 9 subjects with discordant resistance, mutations were noted in plasma but not in CSF (less selective drug pressure)

In 17 of 18 subjects, sequences from CSF and plasma from the same subject clustered more closely to one another than did either CSF-CSF or plasma-plasma sequences.

Strain, J Virol, 2005

HIV coreceptors and CNS

- Main cell target: microglia, infection via CD4/CCR5
- Subpopulations of neurons and glial cells may be infected via CXCR4 and undergo apoptosis
- Low levels of CXCR4 also expressed by astrocytes and endothelial cells (CD4-independent infection?)
- X4 and DM but not R5 virus induces neuronal and astrocyte apoptosis in primary human fetal brain cultures, however some R5 viruses (ADA) also induce neuronal apoptosis

HIV dementia occurs at late stages of disease, however individuals may progress to dementia with a pure R5 virus population

Gabuzda, JNV 2000

OPEN ACCESS Freely available online

PLoS PATHOGENS

Compartmentalized Human Immunodeficiency Virus Type 1 Originates from Long-Lived Cells in Some Subjects with HIV-1–Associated Dementia

Gretja Schnell[1], Serena Spudich[2], Patrick Harrington[3,4¤], Richard W. Price[2], Ronald Swanstrom[1,3,4*]

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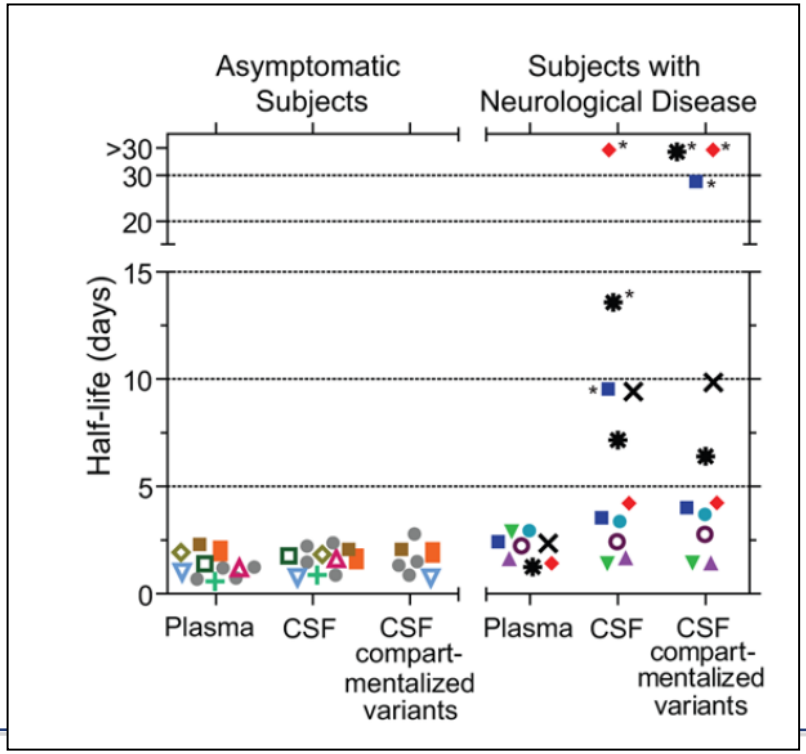
April 2009 | Volume 5 | Issue 4 |



BRIEF REPORT: CLINICAL SCIENCE

Presence of HIV-1 R5 Viruses in Cerebrospinal Fluid Even in Patients Harboring R5X4/X4 Viruses in Plasma

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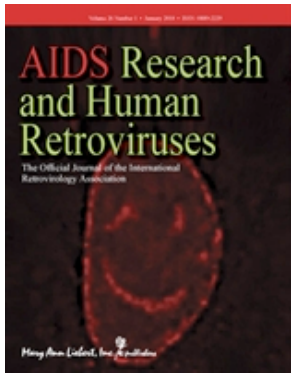
J Acquir Immune Defic Syndr. 2009 May 1;51(1):60-4.



AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 25, Number 12, 2009

DOI: 10.1089/aid.2009.0069

Mode of Coreceptor Use by R5 HIV Type 1 Correlates with Disease Stage: A Study of Paired Plasma and Cerebrospinal Fluid Isolates

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Our findings show that a discordance CSF and plasma virus coreceptor use is not uncommon. Furthermore, we provide support for an emerging paradigm, where the acquisition of a more flexible mode of CCR5 usage is a key event in R5 virus pathogenesis. This may, in turn, negatively impact the efficacy of CCR5 antagonist treatment in late stage HIV-1 disease.

TABLE 1. CHARACTERISTICS OF THE 28 SUBJECTS INCLUDED IN THE STUDY[a]

Patient	*CDC stage*	*$CD4^+$ T cell count ($\times 10^6$ cells/liter)*	*Plasma-RNA (copies/ml)*	*CSF-RNA (copies/ml)*	*CSF-neopterin (nmol/liter)*	*AIDS-related disease*[b]	*Coreceptor use in plasma*	*Coreceptor use in CSF*
1	A1	820	2,900	5,100	NA		R5	R5
2	A1	627	32,000	2,500	10		R5	R5
3	B1	532	23,000	75,000	17		R5	R5
4	A1	530	8,700	10,500	NA		R5	R5
5	A1	510	1,900	28,000	NA		R5	R5
6	**A1**	**510**	**70,000**	**1,450**	**NA**		**R5X4**	**R5**
7	A1	505	56,000	11,000	NA		R5	R5
8	A1	500	23,000	600	6		R5	R5
9	A2	490	52,000	119,000	31		R5	R5
10	**A2**	**490**	**17,000**	**49,000**	**28**		**R5**	**R5**
11	**A2**	**400**	**1,452**	**750,000**	**NA**		**R5**	**R5**
12	A2	330	67,000	29,000	NA		R5	R5
13	C2	230	257,000	254,000	74	ADC	R5	R5
14	C2	213	12,900	125,000	270	ADC	R5	R5
15	C3	168	58,000	114,000	31	KS	R5	R5
16	A3	150	77,000	118,000	33		R5	R5
17	**C3**	**138**	**89,000**	**21,000**	**121**	**ADC**	**R5X4**	**R5**
18	A3	134	165,000	225,000	39		R5X4	R5X4
19	**C3**	**87**	**36,000**	**64,000**	**102**	**ADC, MAC**	**R5**	**R5**
20	C3	60	682,000	750,000	46	ADC	R5X4	R5X4
21	**C3**	**49**	**534,000**	**88,000**	**50**	**ADC**	**R5**	**R5**
22	**C3**	**48**	**273,000**	**14,700**	**39**	**PCP**	**R5X4**	**R5**
23	**C3**	**42**	**53,000**	**70,000**	**34**	**C. esophagitis**	**R5**	**R5**
24	B3	40	15,000	139,000	21	*Cryptosporidium*	R5	R5
25	**A3**	**38**	**54,000**	**1,400**	**10**		**X4**	**R5X4**
26	C3	36	52,000	132,000	42	Lymphoma	R5	R5
27	C3	35	607,000	102,000	30	ADC, PCP	R5	R5
28	C3	27	41,000	7,900	52	PCP	R5X4	R5X4

JID 2005:191

HIV-1 Chemokine Coreceptor Utilization in Paired Cerebrospinal Fluid and Plasma Samples: A Survey of Subjects with Viremia

Group	Subjects, no.	Receiving ART, % of subjects	CD4 T cell count, cells/mm³	HIV RNA level, $\log_{10}$ copies/mL		CSF:plasma albumin ratio ($\times 10^{-3}$)	CSF WBC count, cells/mm³
				Plasma	CSF		
All subjects	46	19.5	244.5 (129.3–326.0)	4.77 (4.26–5.17)	3.84 (3.33–4.32)	5.8 (3.9–7.7)	5 (3–8)
R5 CSF							
R5 plasma, R5 CSF	36	16.7	267.0 (186.5–348.8)	4.71 (4.24–4.99)	3.90 (3.30–4.46)	5.6 (3.8–7.6)	6 (4–9)
R5+X4 plasma, R5 CSF	3	33.3	123.0 (85–228)	4.80 (3.46–4.80)	4.24 (3.66–4.29)	7.6 (4.2–7.9)	5 (0–73)
R5+X4 CSF							
R5 plasma, R5+X4 CSF	2	0.0	184.5 (102–267)	4.91 (4.01–5.81)	3.99 (3.84–4.15)	5.0 (4.5–5.5)	9 (6–12)
R5+X4 plasma, R5+X4 CSF	5	40.0	22.0 (5–142)	5.58 (5.37–5.64)	3.40 (3.17–3.70)	6.2 (3.8–8.6)	1 (0–3)

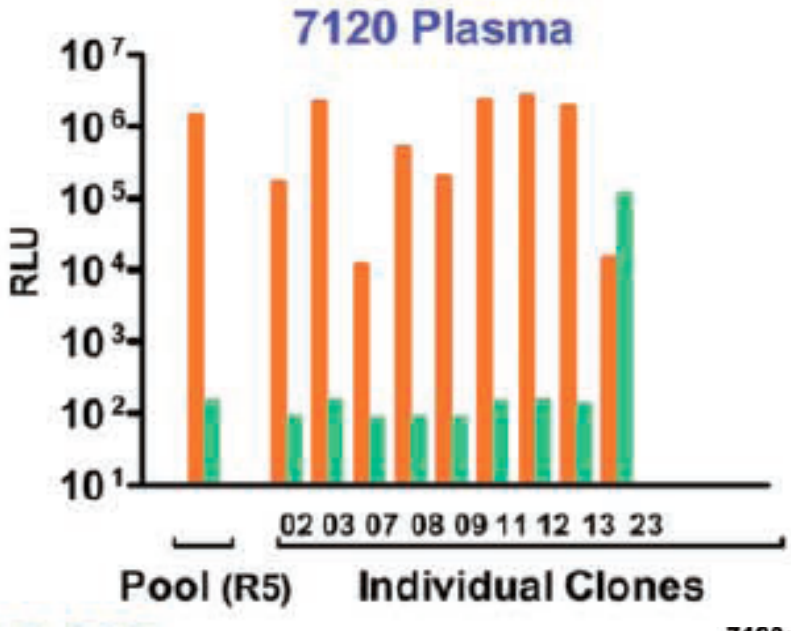
NOTE. ART, antiretroviral therapy; CSF, cerebrospinal fluid; WBC, white blood cell. Values for the "All subjects" group and for the "R5 plasma, R5 CSF" subgroup are medians (intraquartile ranges); values for the other 3 subgroups are medians (ranges). Normal values are as follows: CSF WBC count, <6 cells/mm³; CSF protein level, ≤51 ng/dL; mean ± SD CSF albumin ratio (albumin/serum or plasma albumin $\times 10^{-3}$), 4.6 ± 1.3 [38].

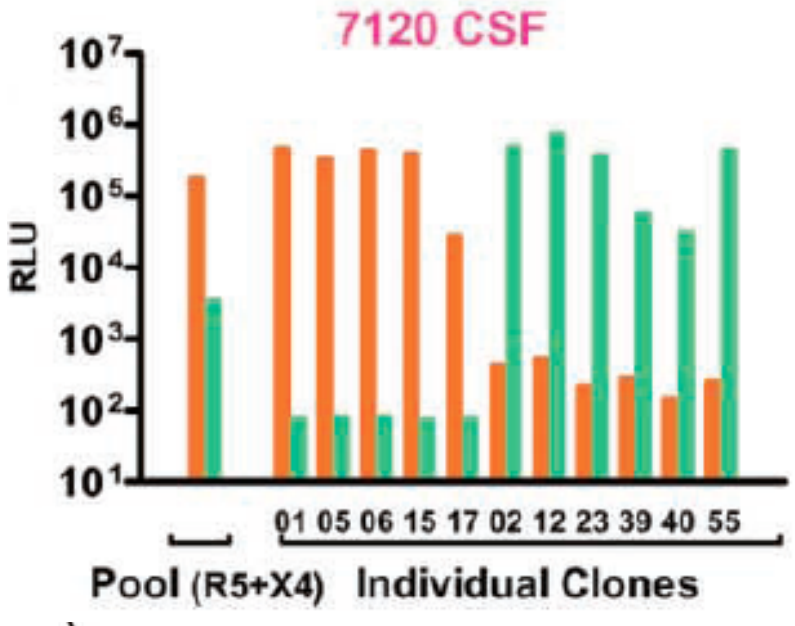
In the 2 compartiments discordance in both directions: in 2 subjects R5 strain in plasma and R5+X4 in CSF.

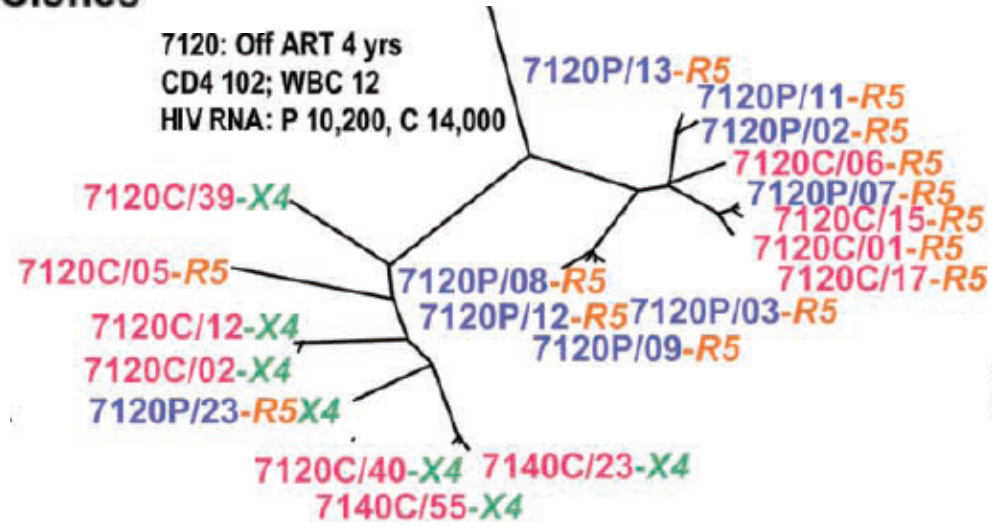
This latter finding is striking given the overall frequency of the R5 phenotype in CSF and the concept that "autonomous" infection in the CSF is more likely sustained in macrophages rather than lymphocytes.

JID 2005:191

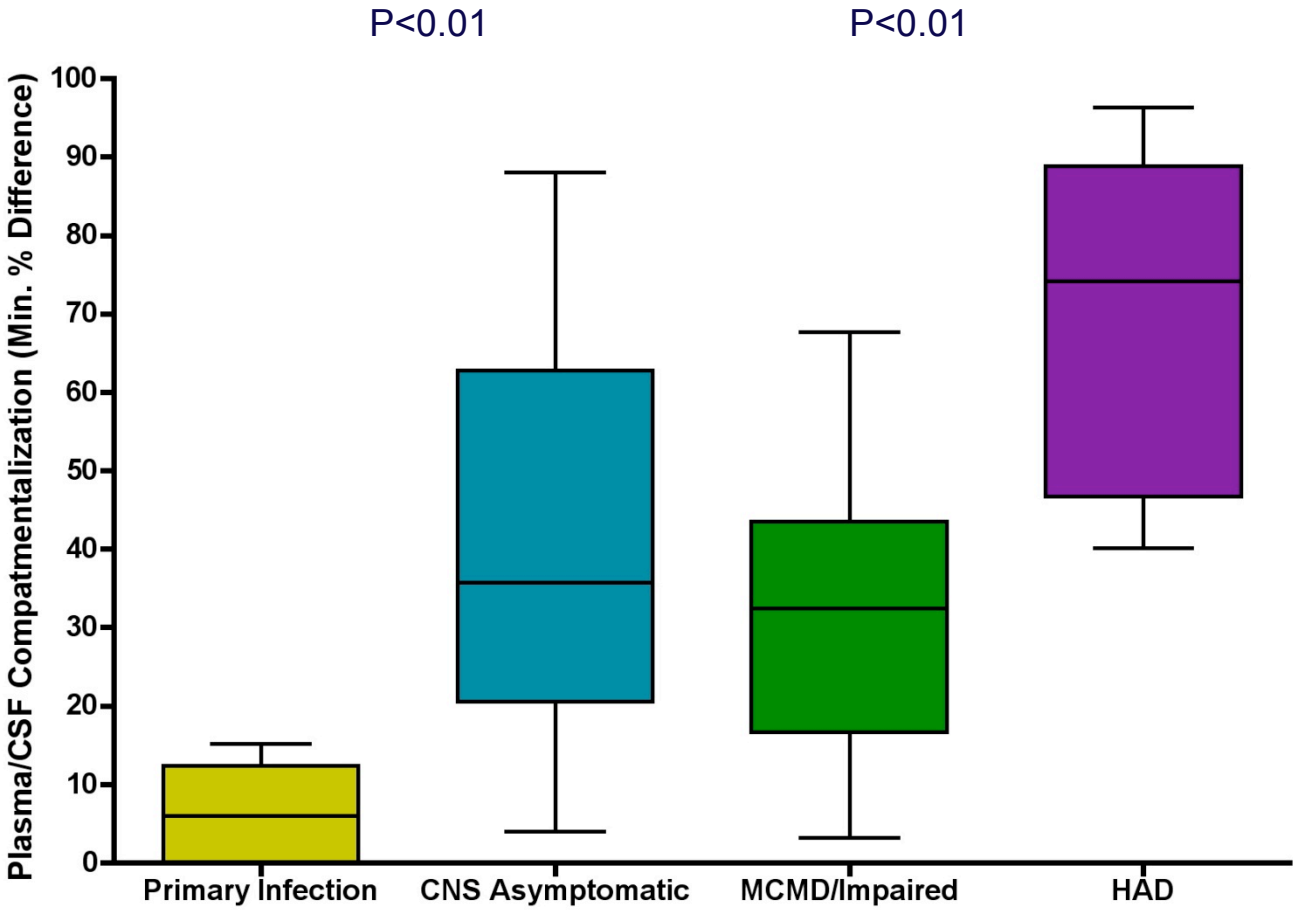
HIV-1 Chemokine Coreceptor Utilization in Paired Cerebrospinal Fluid and Plasma Samples: A Survey of Subjects with Viremia







Compartmentalization Between Plasma and CSF is Associated with Neurological Disease



***CSF viral population switch from a purely blood, or mixed blood and CNS source, to primarily a local CNS source in HAD subjects**

CPE score
(CNS penetration-effectiveness score)

- I farmaci antiretrovirali si differenziano in termini di penetrazione e di efficacia nel SNC, in base alle diverse caratteristiche chimico-fisiche e farmacocinetiche e alla loro capacità di interferire con la replicazione virale nei macrofagi.

- Lo score viene calcolato in base alla potenziale penetrazione-efficacia dei farmaci nel SNC.

- Il CPE score di un trattamento sarà ottenuto sommando i punteggi attribuiti ai singoli farmaci utilizzati.

CPE Score	NRTIs	NNRTIs	PIs	Fusion Inhibitors	CCR5 Antagonist	Integrase Inhibitor
4	Zidovudine	Nevirapine	Indinavir/ritonavir			
3	Abacavir Emtricitabine	Delavirdine Efavirenz	Darunavir/ritonavir Fosamprenavir/ritonavir Indinavir Lopinavir/ritonavir		Maraviroc	Raltegravir
2	Didanosine Lamivudine Stavudine	Etravirine	Atazanavir Atazanavir/ritonavir Fosamprenavir			
1	Tenofovir Zalcitabine		Nelfinavir Ritonavir Saquinavir Saquinavir/ritonavir Tipranavir/ritonavir	Enfuvirtide		

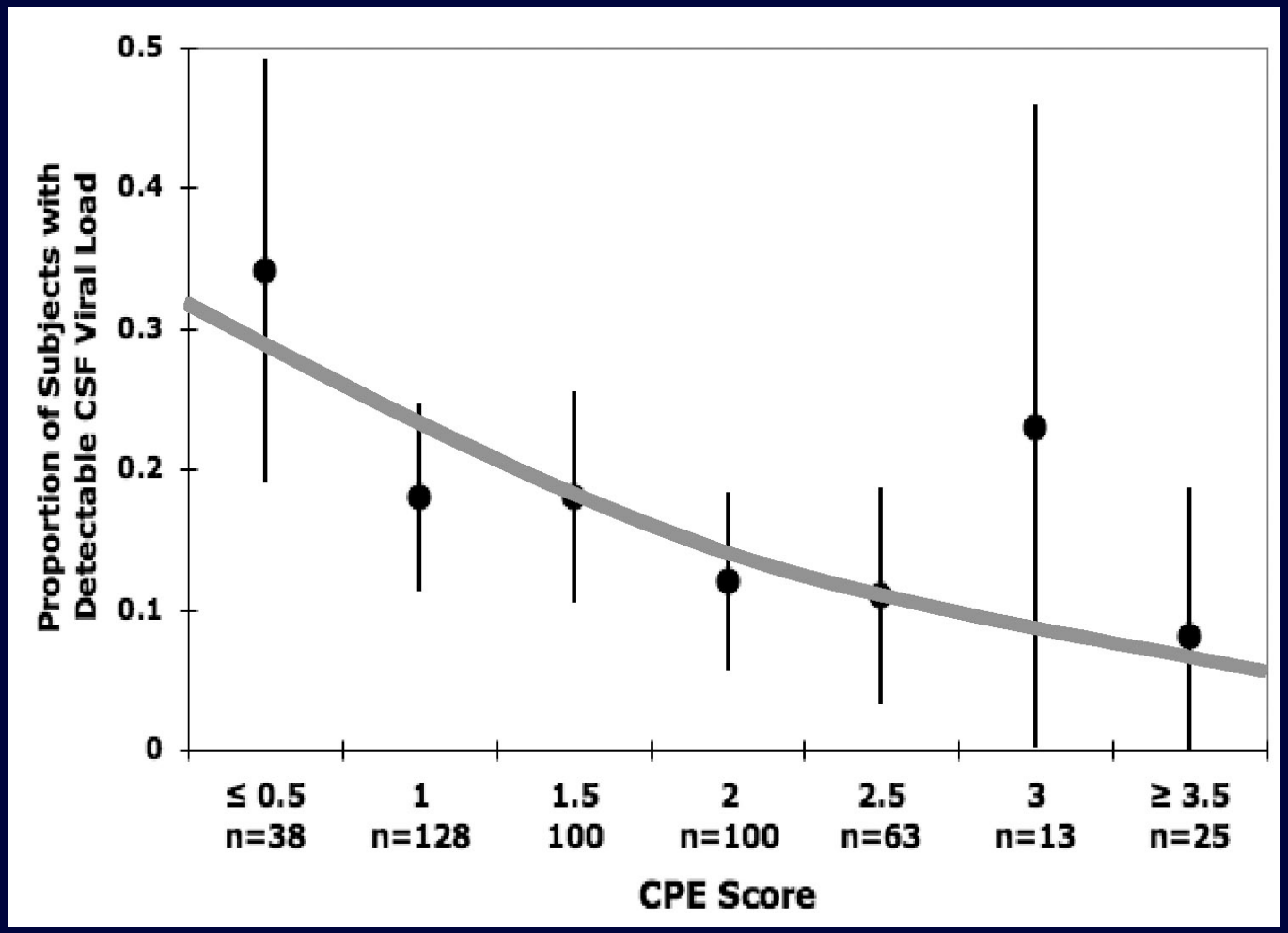
Letendre et al, 17°CROI 2010

CPE score
(CNS penetration-effectiveness score)

Alti livelli di *CPE score* sono risultati associati ad una minore rilevazione di HIV-RNA nel liquor e ad un più importante miglioramento neurocognitivo in corso di terapia.

Antiretroviral Effectiveness

Higher CPE Scores and Lower Viral Loads in CSF



Letendre et al, Arch Neurol 2008

CPE score
(CNS penetration-effectiveness score)

- I punteggi di penetrazione-efficacia sono stati attribuiti ai farmaci mediante analisi preliminari.

- Vi sono altri fattori che influenzano la risposta alla terapia nel SNC (l'entità dell'infezione produttiva nel SNC, la presenza di varianti virali resistenti).

- Questa classificazione rappresenta uno strumento dinamico, soggetto a variazioni continue per le nuove conoscenze e lo sviluppo di nuove molecole.

CPE score
(CNS penetration-effectiveness score)

Appare comunque ragionevole che una terapia che contenga farmaci ad elevata penetrazione ed efficacia nel SNC sia indicata per il trattamento di pazienti con alterazioni neurocognitive HIV-mediate.

Interpretazione HIV RNA nel liquor

- Although CSF is an integral component of the CNS, in the context of HIV-1 infection it more accurately serves as an intermediate compartment between the brain and the periphery.
- CSF viral loads often predict the neurological outcome of HIV-1 infection.

Harrington PR et al. J of Virology, 2005

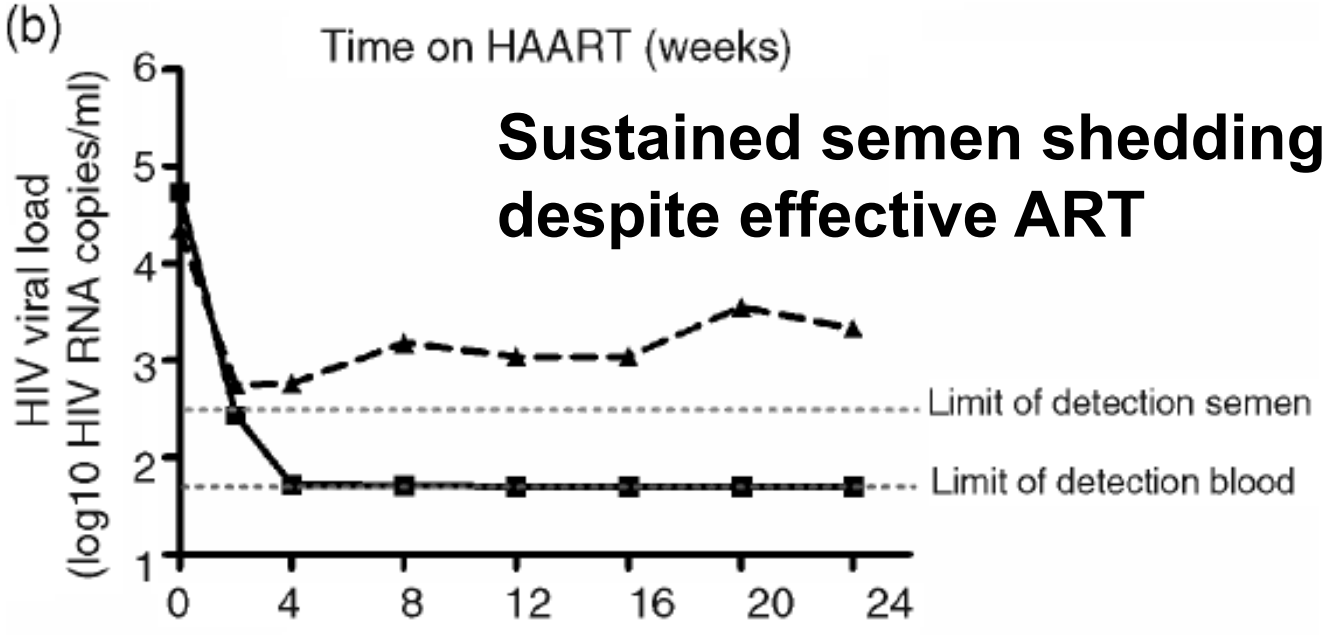
La compartimentalizzazione di HIV nell'Apparato Genitale

Persistent HIV RNA shedding in semen despite effective antiretroviral therapy

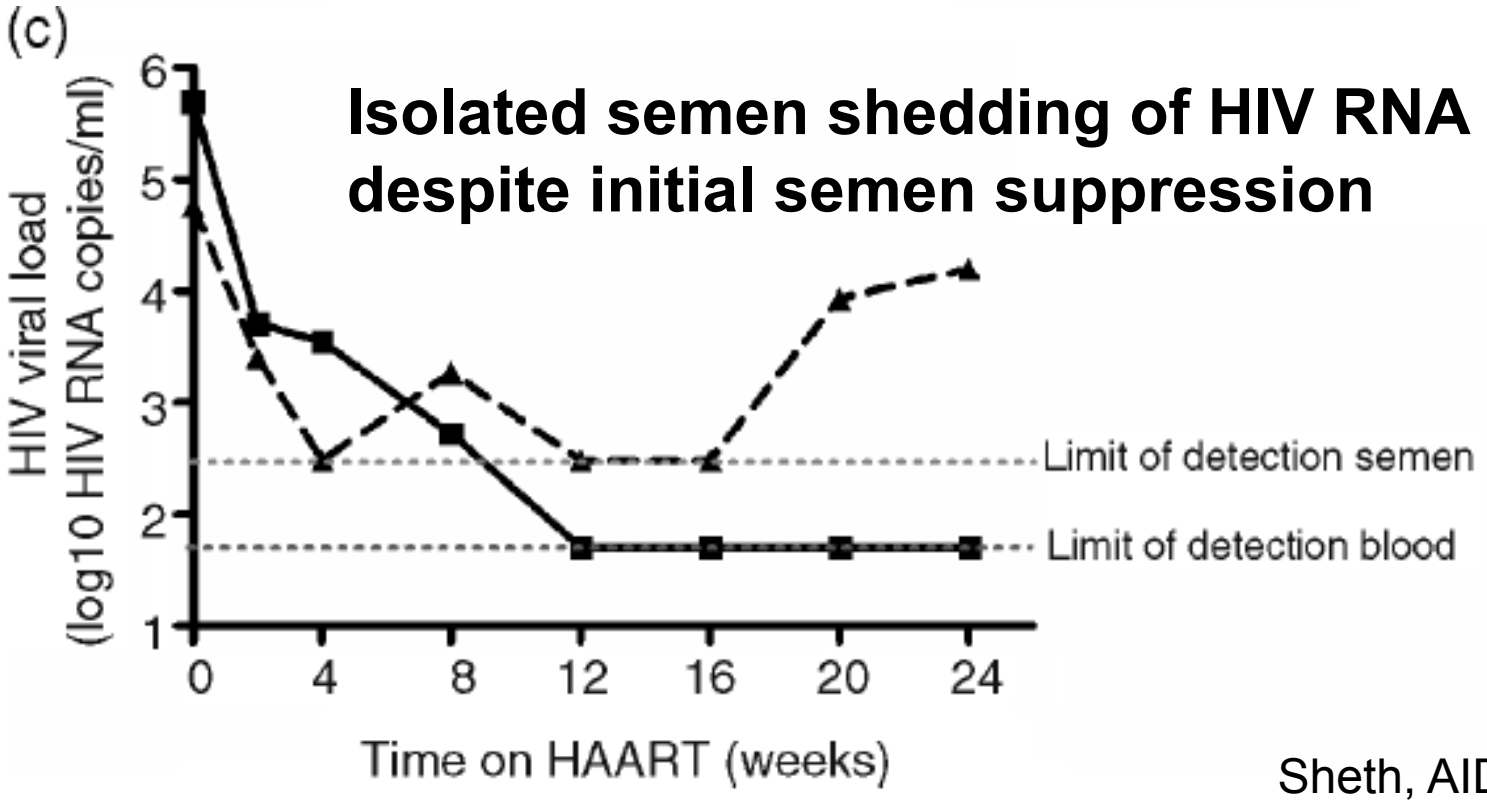
Prameet M. Sheth[a], Colin Kovacs[a,d], Kimdar S. Kemal[e], R. Brad Jones[c], Janet M. Raboud[b,j], Richard Pilon[f], Charles la Porte[g], Mario Ostrowski[c], Mona Loutfy[a,h,i], Harold Burger[e], Barbara Weiser[e], Rupert Kaul[a,c,j], the Toronto Mucosal Immunology Group

Effective antiretroviral therapy (ART) may reduce HIV sexual transmission by lowering genital HIV levels. A prospective study of men starting ART ($n = 25$) demonstrated rapid, substantial reductions in semen HIV RNA. However, despite an undetectable blood viral load, isolated semen HIV shedding was detected at more than one visit in 12 of 25 (48%) participants, with semen HIV RNA levels exceeding 5000 copies/ml in four of 25 (16%). Isolates were drug-sensitive, and this phenomenon was not associated with semen drug levels or regimen.

AIDS 2009, 23:2047–2059

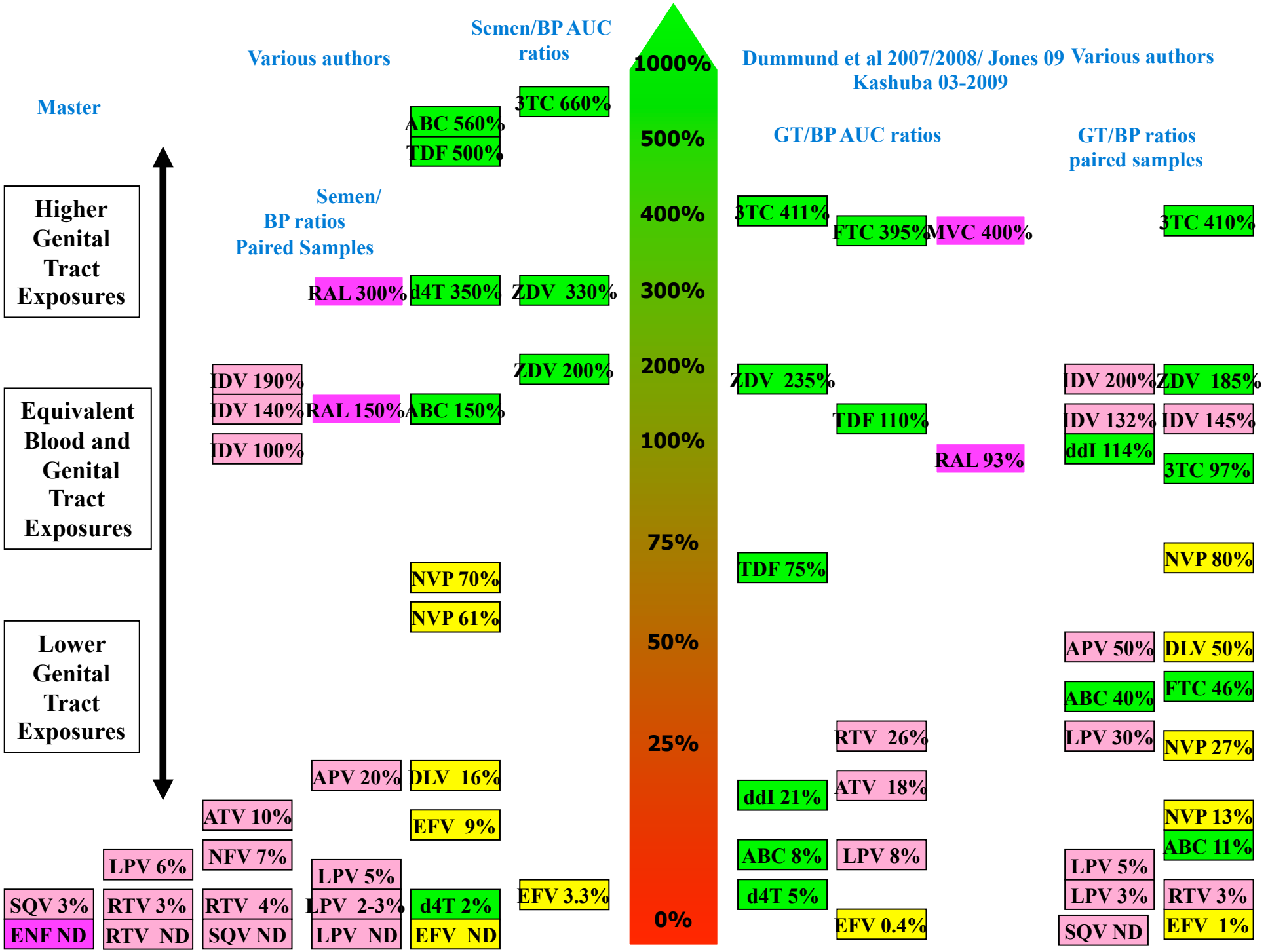


Sustained semen shedding despite effective ART



Isolated semen shedding of HIV RNA despite initial semen suppression

Sheth, AIDS 2009


Master
Various authors
Semen/BP AUC ratios
Dummund et al 2007/2008/ Jones 09
Various authors
Kashuba 03-2009
GT/BP AUC ratios
GT/BP ratios paired samples
Semen/ BP ratios Paired Samples
Higher Genital Tract Exposures
Equivalent Blood and Genital Tract Exposures
Lower Genital Tract Exposures
1000%
500%
400%
300%
200%
100%
75%
50%
25%
0%
3TC 660%
ABC 560%
TDF 500%
3TC 411%
FTC 395%
MVC 400%
3TC 410%
RAL 300%
d4T 350%
ZDV 330%
ZDV 200%
IDV 190%
IDV 140%
RAL 150%
ABC 150%
IDV 100%
ZDV 235%
TDF 110%
RAL 93%
IDV 200%
ZDV 185%
IDV 132%
IDV 145%
ddI 114%
3TC 97%
NVP 70%
NVP 61%
TDF 75%
NVP 80%
APV 50%
DLV 50%
FTC 46%
ABC 40%
LPV 30%
NVP 27%
APV 20%
DLV 16%
EFV 9%
ATV 10%
NFV 7%
RTV 26%
ATV 18%
ddI 21%
NVP 13%
ABC 11%
LPV 6%
LPV 5%
ABC 8%
LPV 8%
LPV 5%
LPV 3%
RTV 3%
EFV 1%
SQV 3%
ENF ND
RTV 3%
RTV ND
RTV 4%
SQV ND
LPV 5%
LPV 2-3%
LPV ND
d4T 2%
EFV ND
EFV 3.3%
d4T 5%
EFV 0.4%
SQV ND

Poster number
T-120/ # 608
17th CROI
February 16-19, 2010
San Francisco, USA

Raltegravir Concentrations in the Cervico-Vaginal Compartment in HIV-1 infected Women treated with Raltegravir: DIVA 01 study

Clavel C[1,2], Mandelbrot L[3], Marcelin AG[1,2], Crenn-Hebert C[3], Heard I[1,2], Bissuel F[4], Ichou H[3], Ferreira C[3], Tubiana R[1,2], Peytavin G[5].

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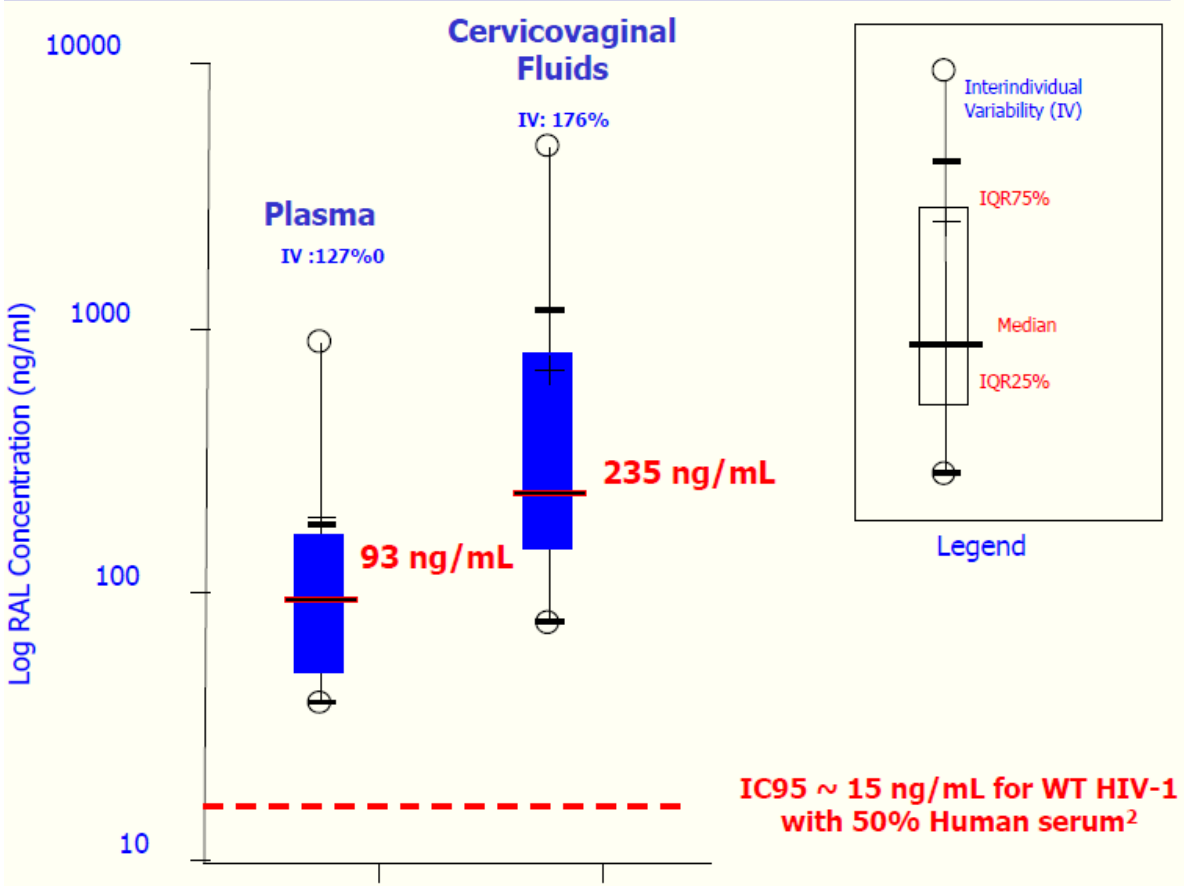
C.Clavel (drcyrilclavel@yahoo.fr)

Distribution of RAL concentrations in Blood Plasma and Cervicovaginal fluids (n=14)



- Accumulation of RAL in CVF with Concentration RAL CVF/BP=2.3
- Concentrations of RAL in CVF and Blood plasma > IC95
- Interindividual variability of RAL concentration is confirmed

La compartimentalizzazione di HIV nell'Occhio

Intraocular and plasma HIV-1 RNA loads and HIV uveitis

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Objective: The objective of this study was to analyze human immunodeficiency virus (HIV) dynamics across the blood–retinal barrier and to determine whether the high levels of HIV in the eye are associated with any ocular disorders in HIV-infected patients.

Design: This study included a prospective case series of 40 HIV-positive patients with uveitis.

Intervention: Clinical and laboratory examinations included plasma and intraocular HIV-1 RNA loads as well as the clinical manifestations of uveitis.

Results: Intraocular HIV-1 RNA was detected in 32% (13/40) of HIV-positive patients with uveitis. Intraocular HIV-1 RNA loads were associated with high HIV-1 RNA plasma loads ($P < 0.001$) and not being on HAART therapy ($P = 0.005$). In addition, detectable intraocular HIV-1 RNA levels were higher in patients with the absence of retinal lesions ($P = 0.008$). In three patients, the HIV load in the eye largely exceeded that of plasma. These three patients had all bilateral anterior uveitis and/or vitritis without retinal lesions and exhibited no evidence of other intraocular infectious agents causing uveitis than HIV itself.

Conclusion: The eye can form a sanctuary where HIV might replicate and cause an inflammatory reaction.

AIDS 2011, **25**:81–86

Intraocular and plasma HIV-1 RNA loads and HIV uveitis

In three patients with uveitis, the HIV load in the eye largely exceeded that of plasma.
The eye can form a sanctuary where HIV might replicate and cause an inflammatory reaction.

Patient number	Age (years)	Sex	HAART >2 months	HIV-1 RNA plasma load (copies/ml)	HIV-1 RNA ocular load (copies/ml)	Location
1	40	Female	No	169 000	89 800 000	Anterior chamber
2	40	Male	No	92 400	9 370 000	Anterior chamber, vitreous
3	50	Male	Yes[b]	540 000	2 460 000	Anterior chamber, vitreous
4	35	Male	No	512	2200	Anterior chamber, vitreous, retina

Pathanapitoon AIDS 2011

Conclusione

Per una corretta impostazione ed un valido monitoraggio della terapia antiretrovirale diventa quindi sempre più frequente la necessità di valutare quantitativamente e qualitativamente il virus presente in diversi organi ed apparati.