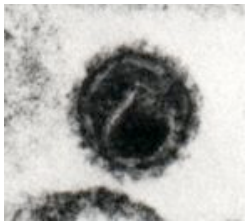
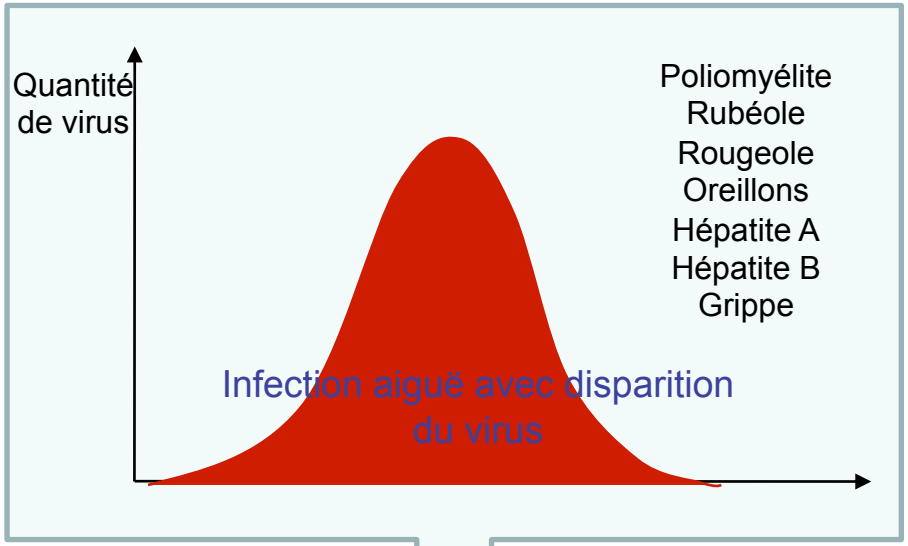
Anticorps neutralisants et VIH-1:
évolution, perspectives immunoprophylactiques et immunothérapeutiques



F Barin
Centre National de Référence du VIH, Inserm UMR966,
Université F Rabelais, CHU Bretonneau
Tours, France

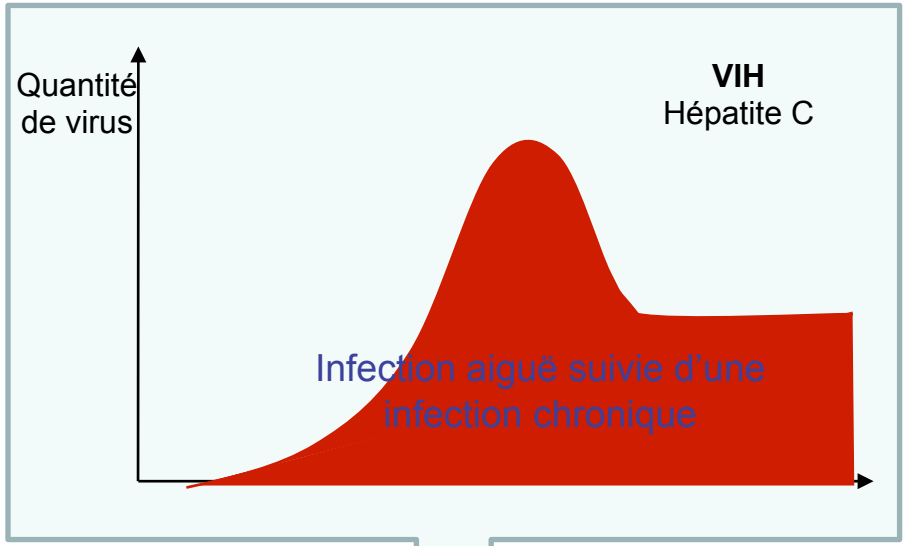
Infections virales et anticorps neutralisants

Anticorps neutralisants: inhibent l'infection cellulaire *in vitro*; inhibent des étapes précoces du cycle cellulaire viral (attachement, entrée, fusion, …).



Maladies immunisantes

- Anticorps neutralisants empêchant la réinfection
- Vaccins induisent le même type d 'immunité

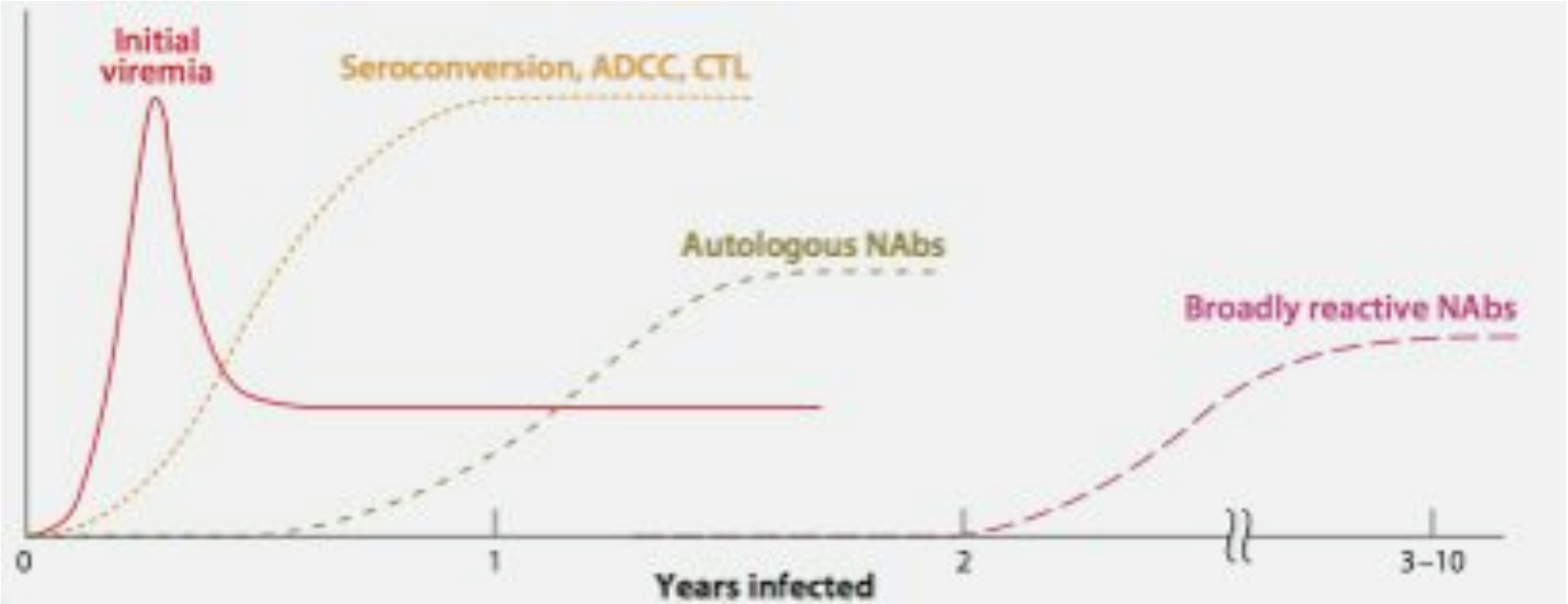


Maladies non-immunisantes

- Contrôle insuffisant de l'infection
- Réinfections possibles
- Rôle des anticorps neutralisants et comment obtenir un vaccin?

Anticorps neutralisants et VIH-1

Anticorps neutralisants: faire face à la diversité du VIH …



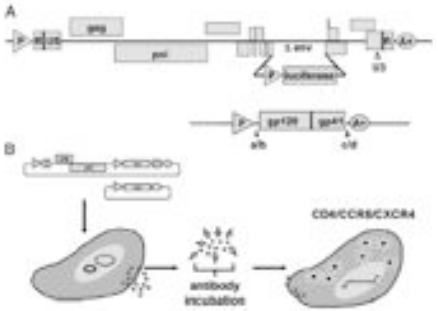
J Mascola & D Montefiori
Annu. Rev. Immunol. 2010

Rapid evolution of the neutralizing antibody response to HIV type 1 infection

Douglas D. Richman*†, Terri Wrin‡, Susan J. Little*, and Christos J. Petropoulos‡

*Departments of Pathology and Medicine, Veterans Affairs San Diego Healthcare System and the University of California at San Diego, La Jolla, CA 92093-0679; and ‡ViroLogic, Inc., 345 Oyster Point Boulevard, South San Francisco, CA 94080

Communicated by Robert M. Chanock, National Institutes of Health, Bethesda, MD, January 28, 2003 (received for review December 10, 2002)



D Richman et al., PNAS 2003

Rapid evolution of the neutralizing antibody response to HIV type 1 infection

D. Richman et al., PNAS 2003

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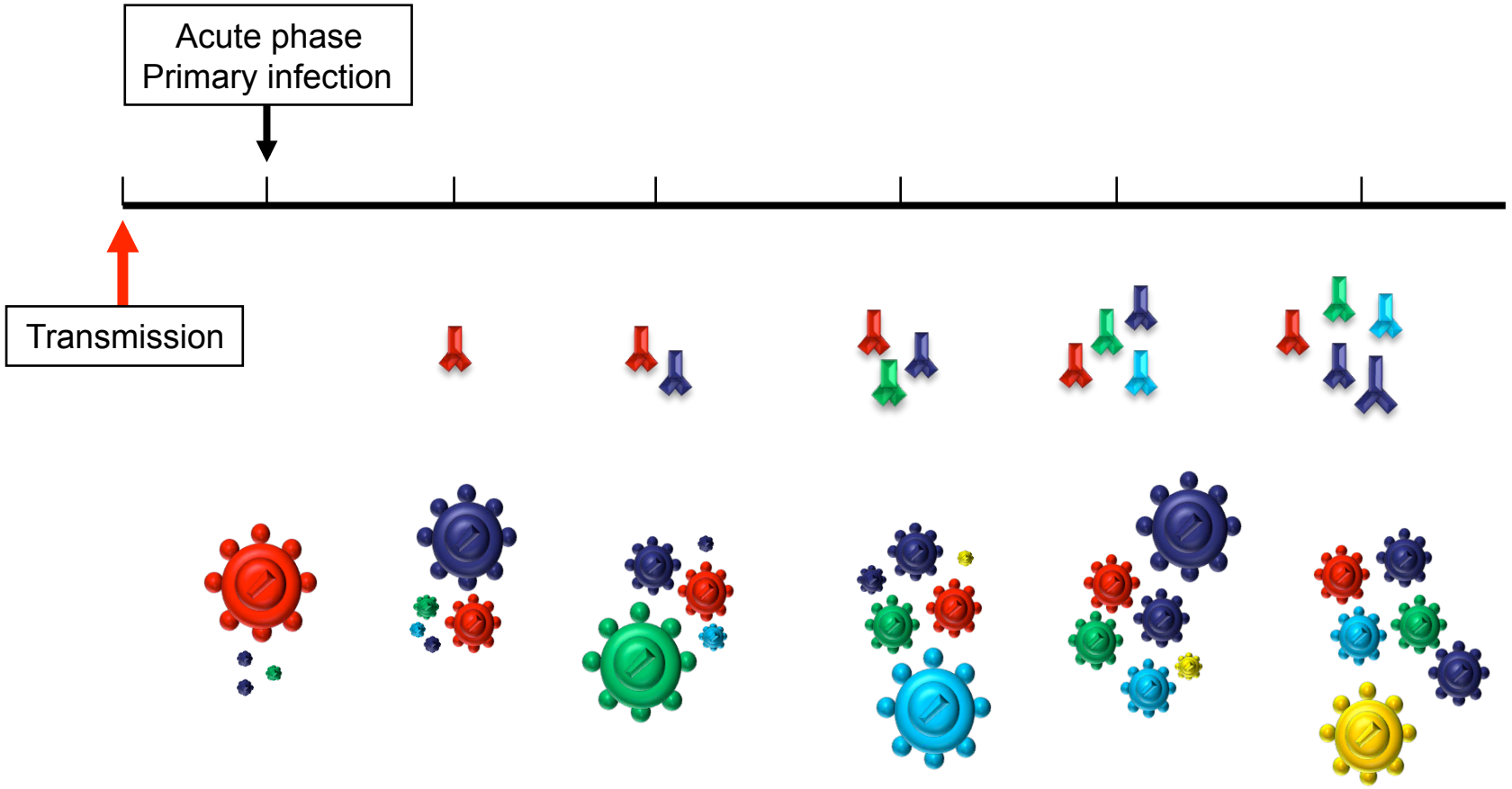
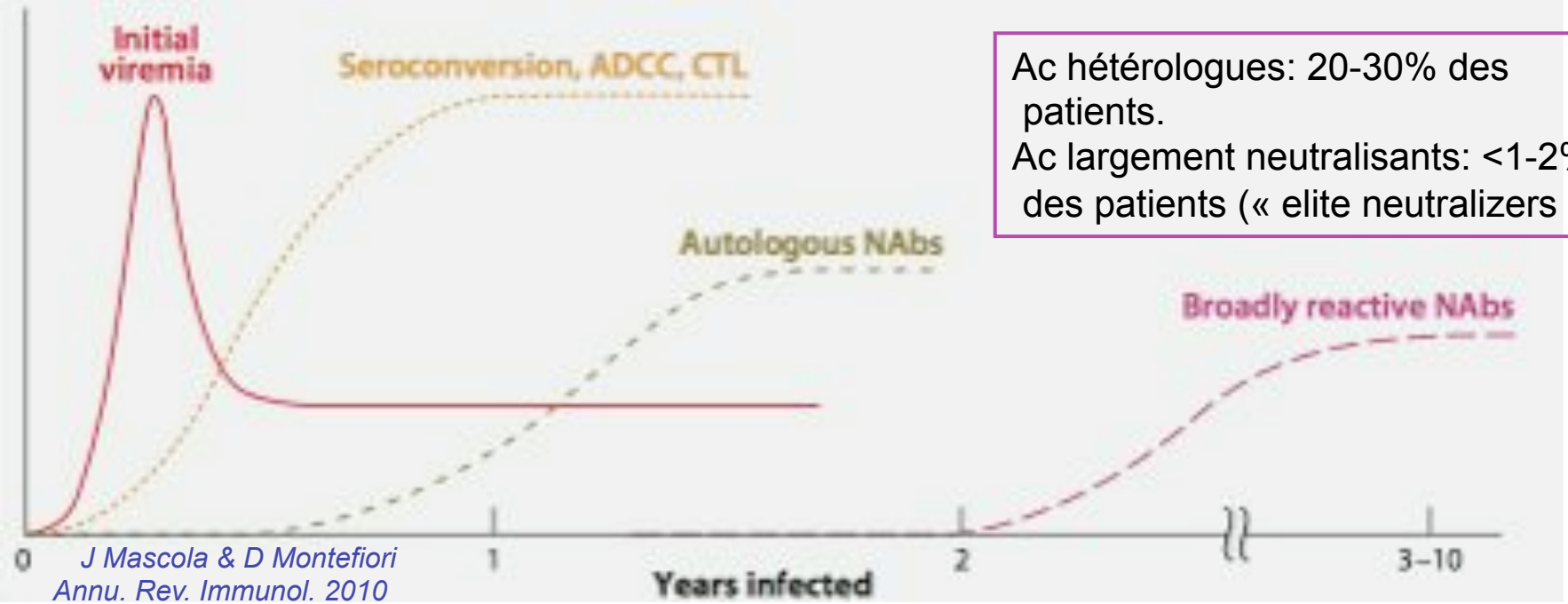


Les anticorps neutralisants exercent une pression de sélection en partie responsable de la diversification du virus.

Anticorps largement neutralisants et VIH-1



J Mascola & D Montefiori
Annu. Rev. Immunol. 2010

Ac hétérologues: 20-30% des patients.
Ac largement neutralisants: <1-2% des patients (« elite neutralizers »)

Les anticorps largement neutralisants ne semblent pas jouer un rôle majeur dans la non-progression, une fois l'infection établie.

- ✓ Apparaissent tardivement, plusieurs années après l'infection.
- ✓ Ne sont pas associés à l'évolution clinico-biologique.
- ✓ Sont présents chez des patients répliquant le virus (charge virale élevée).
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Antibodies to conserved epitopes of the HIV-1 envelope in sera from long-term non-progressors: prevalence and association with neutralizing activity

Martine Braibant[a], Sylvie Brunet[a], Dominique Costagliola[b], Christine Rouzioux[c], Henri Agut[d], Hermann Katinger[e], Brigitte Autran[f] and Francis Barin[a]

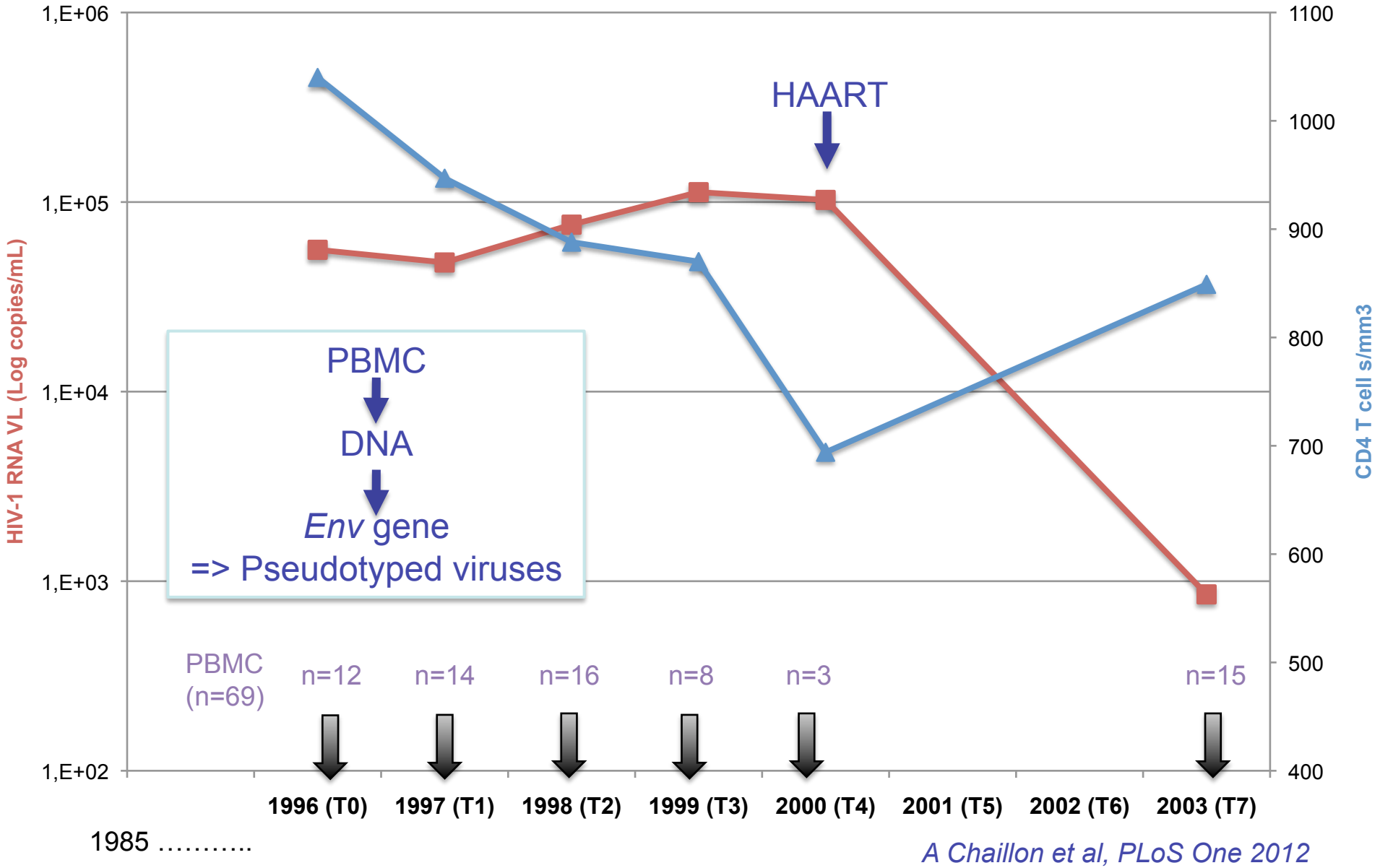
Primary isolate	Primary isolates (*n*)	Neutralizing sera [*n* (%)]
KON (CRF02_AG)	NA	24 (36)
FRO (B)	NA	33 (49)
GIL (F)	NA	29 (43)
MBA (CRF01_AE)	NA	13 (19)
NA	0	24 (36)
NA	1	17 (25)
NA	2	7 (10)
NA	3	8 (12)
NA	4	11 (16)

14/24 (56%) of Nab_{neg} LTNPs developed AIDS within 5 years post-entry in the cohort.

9/11 (82%) of Nab_{pos} LTNPs developed AIDS within 5 years post-entry in the cohort.

M Braibant et al., AIDS 2006

HIV-1 continues to evolve more than 10 years post-infection even in presence of increasing levels of autologous Nabs and broadly Nabs.



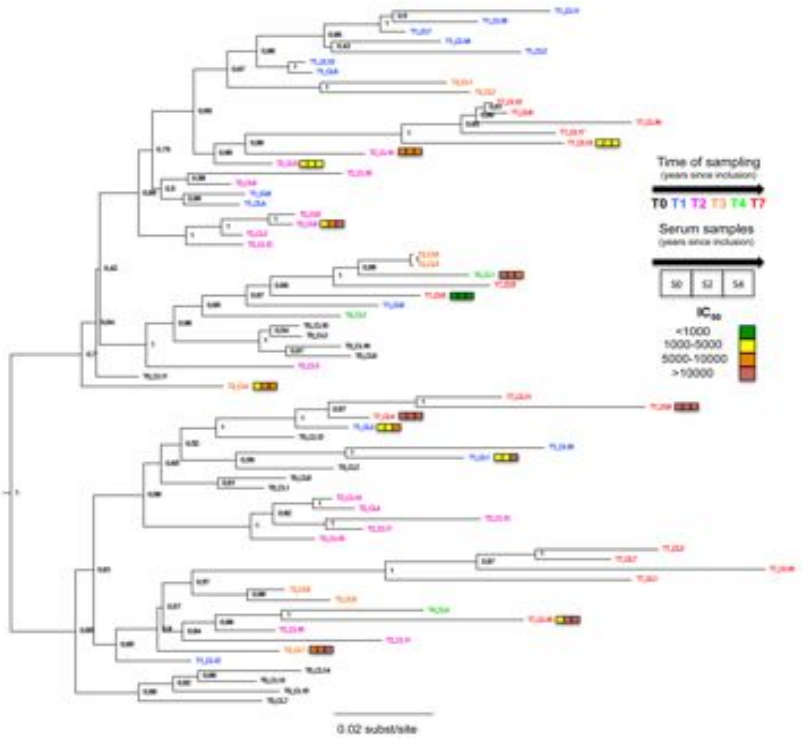
A Chaillon et al, PLoS One 2012

HIV-1 continues to evolve more than 10 years post-infection even in presence of increasing levels of autologous Nabs and broadly Nabs.

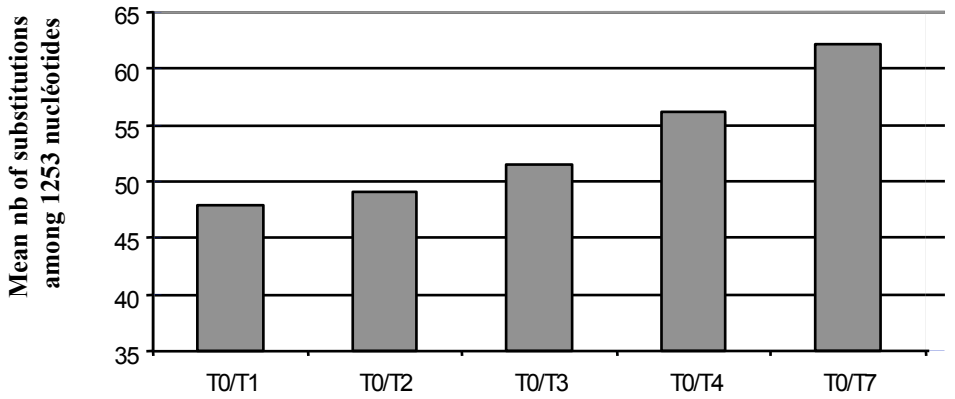
69 *env* clones issued from sequential samples collected over a 7 year-period after entry in the LTNP cohort (16 years of infection)

Elite neutralizer

		Clade B			Clade A		Clade C	Clade F	CRF 01AE		CRF02_AG
serum	Year	FRO	BIG	92BR020	94UG103	92RW020	93IN905	GIL	MBA	92TH021	KON
T0	1996	NA	NA	>540	207	285	>540	NA	NA	>540	NA
T2	1998	NA	NA	>540	349	357	>540	NA	NA	>540	NA
T4	2000	>540	>540	>540	153	315	>540	>540	206	>540	55



Evolutionary divergence



A Chaillon et al, PLoS One 2012

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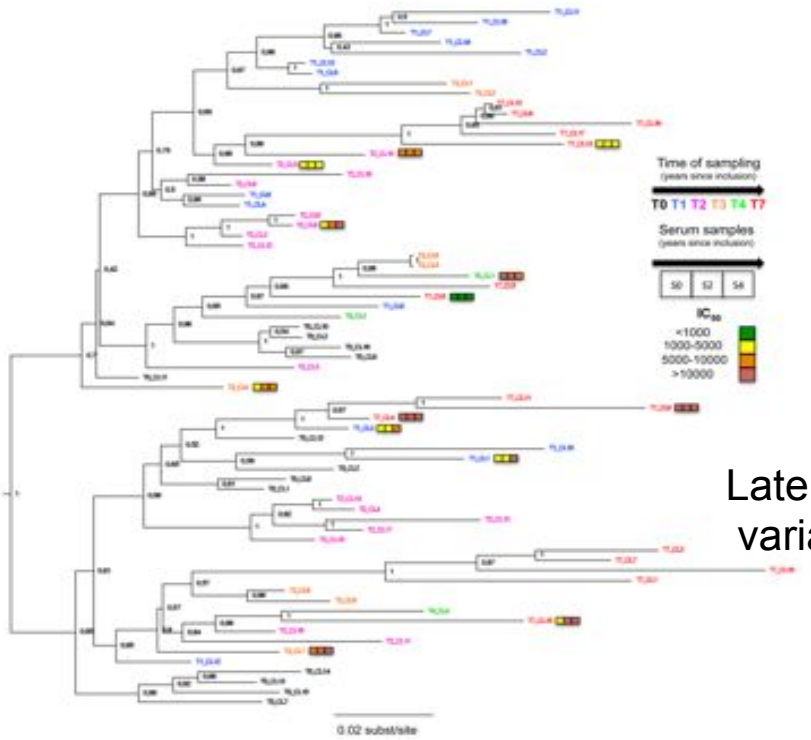

Late escape variant →

Autologous neutralization

	IC_{50} (dilution)		
	Plasma T0	**Plasma T2**	**Plasma T4**
CL1T1	3099	3040	17989
CL3T1	3142	2265	5229
CL5T2	1684	1598	1514
CL9T2	2748	6692	22217
CL10T2	7477	6490	7551
CL7T3	9000	43066	56216
CL1T4	14880	13222	7703
CL3T4	4073	5276	8927
CL4T7	22561	17704	21398
CL6T7	13382	16422	16025
CL8T7	430	869	643
CL13T7	1548	3440	2510
CL15T7	3357	12940	27924
Mean IC_{50}	**6491**	**12953**	**15065**

A Chaillon et al, PLoS One 2012

Antibodies to conserved epitopes of the HIV-1 envelope in sera from long-term non-progressors: prevalence and association with neutralizing activity

Martine Braibant[a], Sylvie Brunet[a], Dominique Costagliola[b], Christine Rouzioux[c], Henri Agut[d], Hermann Katinger[e], Brigitte Autran[f] and Francis Barin[a]

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Plasma RNA level and proviral DNA level are higher in $bNabs_{pos}$ LTNPs than in $bNabs_{neg}$ LTNPs

RNA: 34,000 *vs* 4,300 cps/mL (p=0.04)

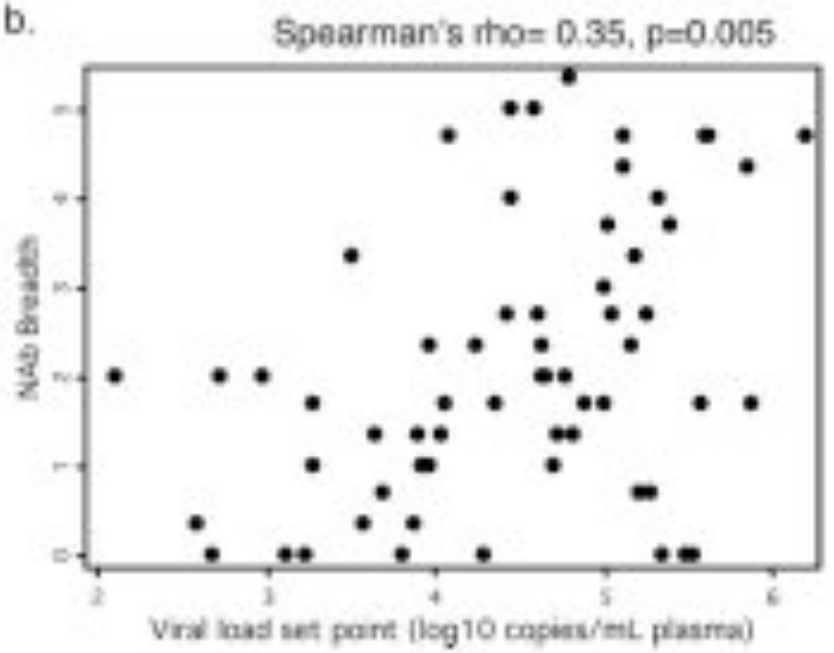
DNA: 685 *vs* 139 cps/106 cells (p=0.02)

M Braibant et al., AIDS 2006

Breadth of Neutralizing Antibody Response to Human Immunodeficiency Virus Type 1 Is Affected by Factors Early in Infection but Does Not Influence Disease Progression[▽]

Anne Piantadosi,[1] Dana Panteleeff,[1] Catherine A. Blish,[1,3] Jared M. Baeten,[2,3] Walter Jaoko,[5] R. Scott McClelland,[3,4,5] and Julie Overbaugh[1]*

- Nab response breadth was measured 5 years after infection.
- Greater Nab response breadth was associated with a higher VL set point and greater HIV-1 env diversity early in infection.

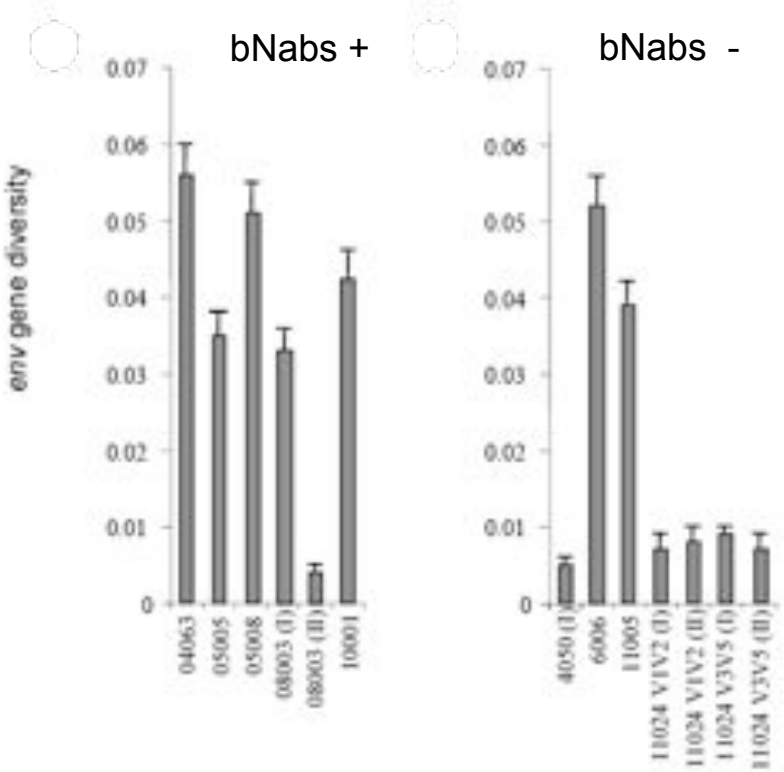


A Piantadosi et al, J Virol 2009

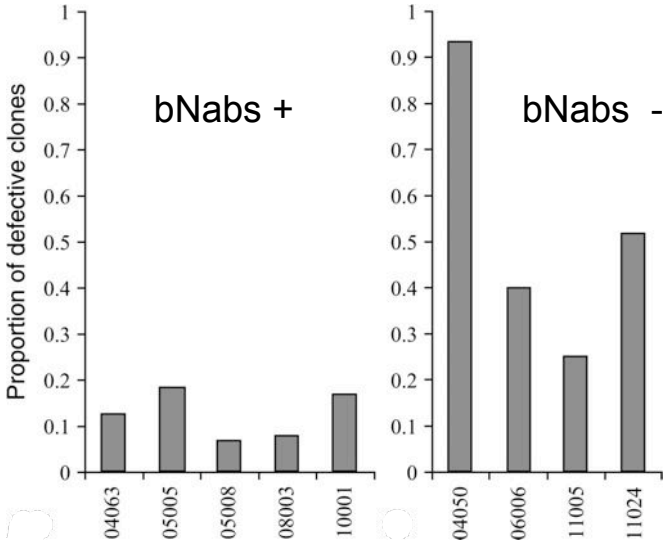
Characteristics of the *env* Genes of HIV Type 1 Quasispecies in Long-Term Nonprogressors With Broadly Neutralizing Antibodies

Martine Braibant, PhD, Henri Agut, MD, PhD,† Christine Rouzioux, PharmD, PhD,‡ Dominique Costagliola, PhD,§ Brigitte Autran, MD, PhD,‖ and Francis Barin, PharmD, PhD**

Higher diversity of the env gene in bNabs$_{pos}$ LTNPs

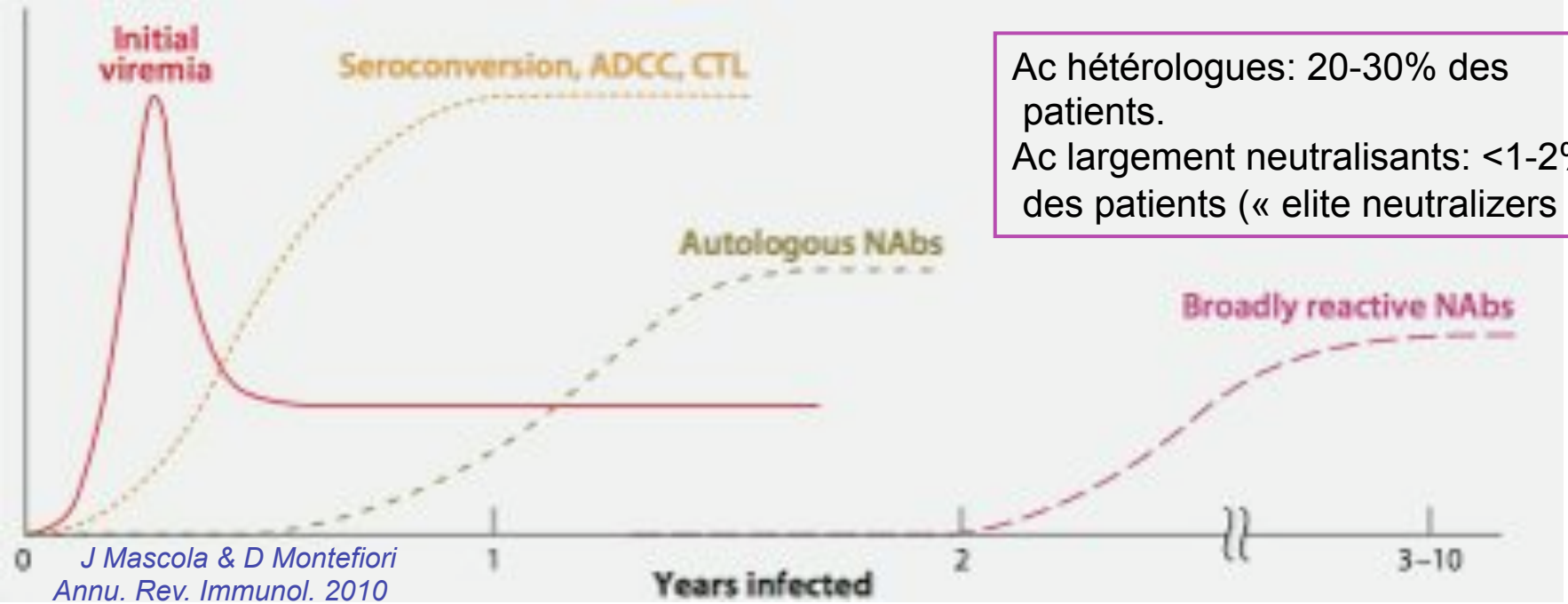


Higher frequency of defective env genes (25-93%) in bNabs$_{neg}$ LTNPs *vs* bNabs$_{pos}$ LTNPs (7-19%)



Braibant et al, J AIDS 2008

Anticorps largement neutralisants et VIH-1



J Mascola & D Montefiori
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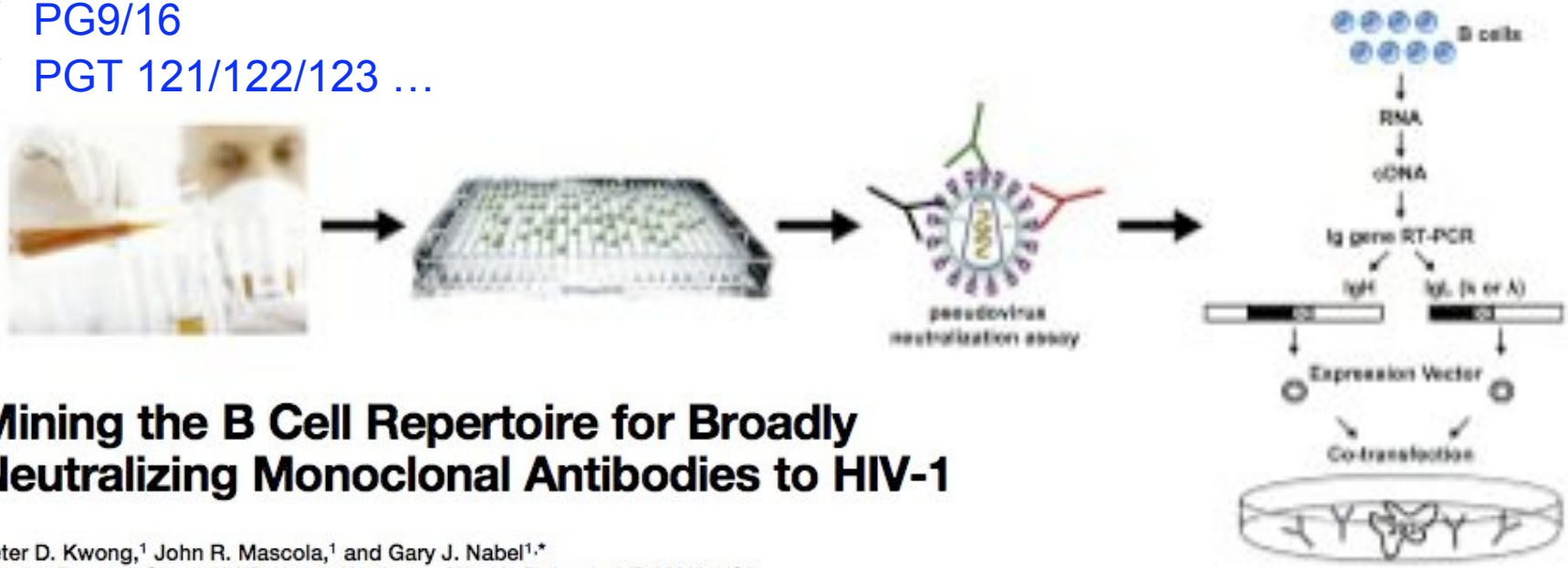
Anticorps monoclonaux humains largement neutralisants

- ✓ CD4BS: F105, IgG1b12, VRC01/03 …, HJ16
- ✓ CD4i: 17b, X5
- ✓ Glycan dependant: 2G12 — < 2009
- ✓ gp41: 2F5, 4E10, z13 — ≥ 2009
- ✓ PG9/16
- ✓ PGT 121/122/123 …



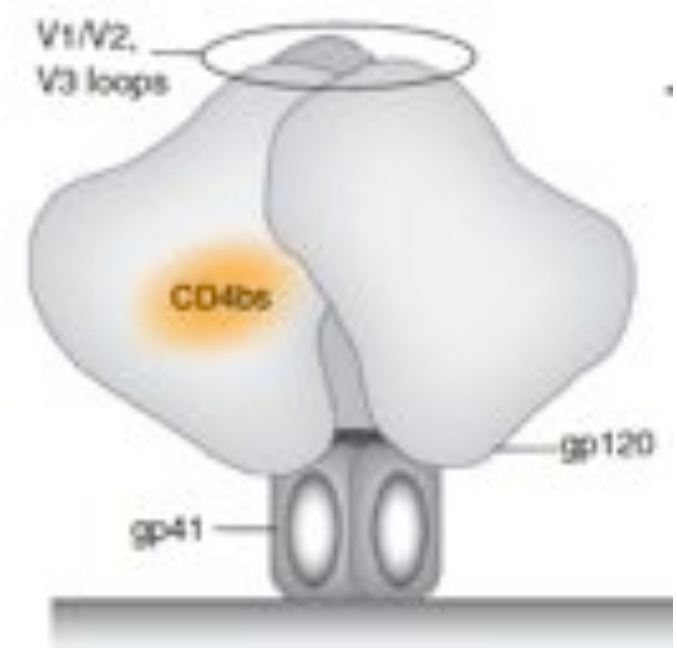
Mining the B Cell Repertoire for Broadly Neutralizing Monoclonal Antibodies to HIV-1

Peter D. Kwong,[1] John R. Mascola,[1] and Gary J. Nabel[1,*]
[1]Vaccine Research Center, NIAID, National Institutes of Health, Bethesda, MD 20892, USA

1. Select special subjects with broadly neutralizing, potent antisera
2. Isolate and stimulate individual B cells (10 ml of blood yield 30,000 activated B cells)
3. Assess neutralizing antibody levels in individual B cell wells (3 viral isolates screened with 15 ul of IgG supernatant collected at 1 week)
4. PCR amplify and express IgG of HIV-1 specific neutralizing antibodies

P Kwong et al, Cell Host Microbe 2009

Anticorps monoclonaux humains largement neutralisants



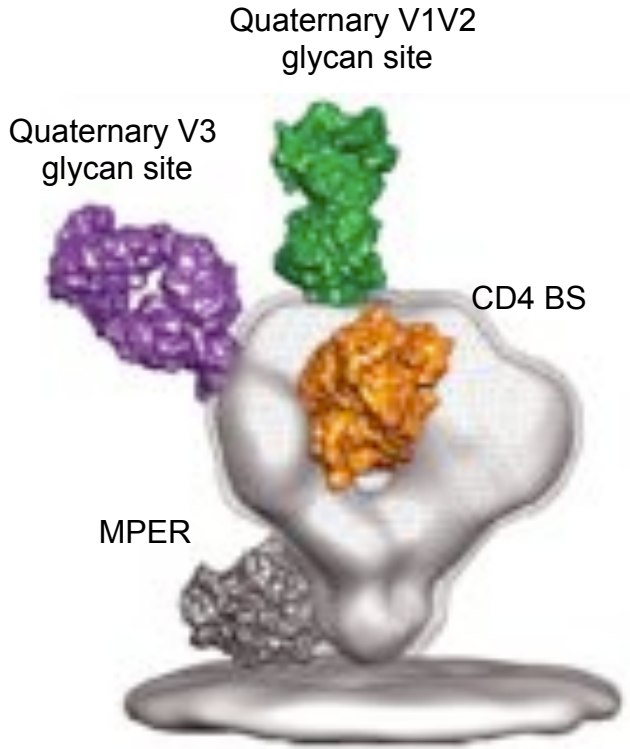
CD4 binding site		Glycan-V3	V1/V2 loop	gp41	Others
b12	1NC9	PGT121-PGT123	PG9/PG16	4E10	8ANC195
HJ16	12A12, 12A21	10-1074	PGT141–145	2F5	2G12
NIH45-46, 45-46^{G54W}	8ANC131, 8ANC134	PGT125-128,130,131	CH01-CH04	10E8	3BC176/ 3BC315
VRC01-03, VRC06	CH30-CH34	PGT135-137		HK20	
3BNC117, 3BNC60	VRC23	VRC24		Z13	
VRC-PG04	CH103				

F Klein et al, Science 2013

New highly potent neutralizing HuMabs

Broad neutralization coverage of HIV by multiple highly potent antibodies

Laura M. Walker[1]*, Michael Huber[1,2]*, Katie J. Doores[1,2]*, Emilia Falkowska[1,2], Robert Pejchal[3], Jean-Philippe Julien[3], Sheng-Kai Wang[4], Alejandra Ramos[1], Po-Ying Chan-Hui[5], Matthew Moyle[5], Jennifer L. Mitcham[5], Phillip W. Hammond[5], Ole A. Olsen[5], Pham Phung[6], Steven Fling[7], Chi-Huey Wong[4], Sanjay Phogat[7], Terri Wrin[6], Melissa D. Simek[7], Protocol G. Principal Investigators†, Wayne C. Koff[7], Ian A. Wilson[3], Dennis R. Burton[1,2] & Pascal Poignard[1,7]



F Klein et al, Science 2013

	Median IC_{50}
PGT121	0.03
PGT122	0.05
PGT123	0.03
PGT125	0.04
PGT126	0.04
PGT127	0.06
PGT128	0.02
PGT130	0.16
PGT131	0.52
PGT135	0.17
PGT136	7.81
PGT137	3.46
PGT141	0.35
PGT142	0.21
PGT143	0.31
PGT144	2.06
PGT145	0.29
PG9	0.23
VRC01	0.32
PGV04	0.20
b12	2.82
2G12	2.38
4E10	3.41

Key: < 0.2 (μg ml^{-1}), 0.2–2 (μg ml^{-1}), 2–20 (μg ml^{-1})

	Viruses neutralized		
	IC_{50} < 50 μg ml^{-1}	IC_{50} < 1 μg ml^{-1}	IC_{50} < 0.1 μg ml^{-1}
PGT121	70	57	44
PGT122	65	48	36
PGT123	67	54	40
PGT125	52	40	32
PGT126	60	50	40
PGT127	50	37	27
PGT128	72	60	50
PGT130	52	35	23
PGT131	40	23	13
PGT135	33	23	13
PGT136	16	6	3
PGT137	22	8	4
PGT141	56	36	15
PGT142	57	40	23
PGT143	56	37	17
PGT144	38	16	3
PGT145	78	52	27
PG9	77	54	29
VRC01	93	74	20
PGV04	88	65	25
b12	34	10	2
2G12	32	11	1
4E10	96	13	1

Key: > 90 %, 60 - 90 %, 30 - 60 %, 1 - 30 %

L Walker et al., Nature 2011

Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus

Hua-Xin Liao[1,2]*, Rebecca Lynch[3]*, Tongqing Zhou[3]*, Feng Gao[1,2]*, S. Munir Alam[1,2], Scott D. Boyd[4], Andrew Z. Fire[4], Krishna M. Roskin[4], Chaim A. Schramm[3], Zhenhai Zhang[3], Jiang Zhu[3], Lawrence Shapiro[3,5], NISC Comparative Sequencing Program†, James C. Mullikin[6,7], S. Gnanakaran[8], Peter Hraber[8], Kevin Wiehe[1,2], Garnett Kelsoe[1,2], Guang Yang[1,2], Shi-Mao Xia[1,2], David C. Montefiori[1,2], Robert Parks[1,2], Krissey E. Lloyd[1,2], Richard M. Scearce[1,2], Kelly A. Soderberg[1,2], Myron Cohen[9], Gift Kamanga[10], Mark K. Louder[3], Lillian M. Tran[3], Yue Chen[1,2], Fangping Cai[1,2], Sheri Chen[1,2], Stephanie Moquin[3], Xiulian Du[3], M. Gordon Joyce[3], Sanjay Srivatsan[3], Baoshan Zhang[3], Anqi Zheng[3], George M. Shaw[11], Beatrice H. Hahn[11], Thomas B. Kepler[12], Bette T. M. Korber[8], Peter D. Kwong[3], John R. Mascola[3] & Barton F. Haynes[1,2]

Liao et al, Nature 2013

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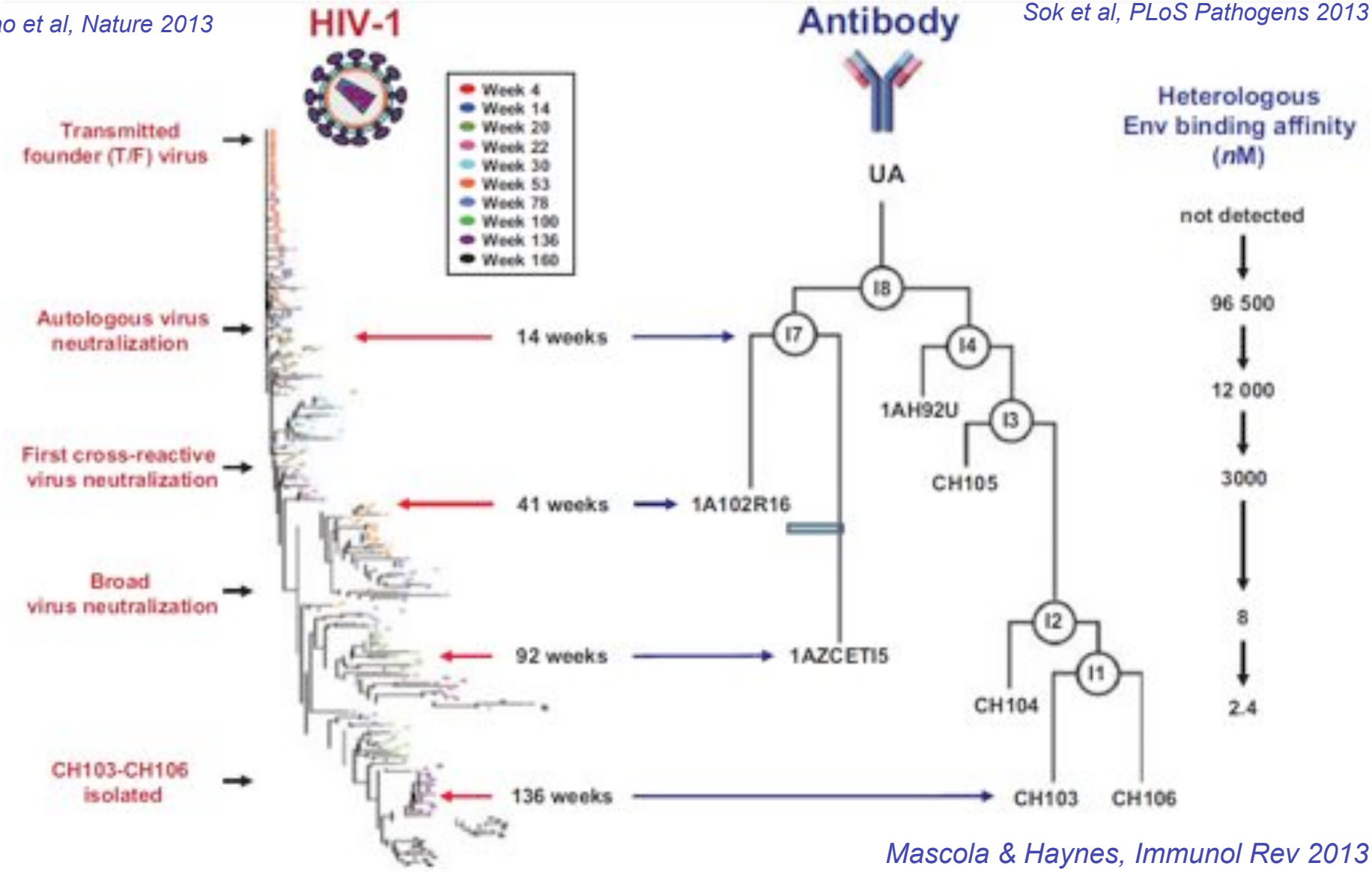
PLOS | PATHOGENS

The Effects of Somatic Hypermutation on Neutralization and Binding in the PGT121 Family of Broadly Neutralizing HIV Antibodies

Devin Sok[1,2,3¤], Uri Laserson[4,5,6¤], Jonathan Laserson[7¤], Yi Liu[7,8¤], Francois Vigneault[6,9], Jean-Philippe Julien[2,3,10], Bryan Briney[1,2,3], Alejandra Ramos[1,2,3,11], Karen F. Saye[1,2,3], Khoa Le[1,2,3], Alison Mahan[12], Shenshen Wang[13,14], Mehran Kardar[14], Gur Yaari[15], Laura M. Walker[1], Birgitte B. Simen[16], Elizabeth P. St. John[16], Po-Ying Chan-Hui[17], Kristine Swiderek[17], Stephen H. Kleinstein[15], Galit Alter[12], Michael S. Seaman[18], Arup K. Chakraborty[12,13,14,19], Daphne Koller[7], Ian A. Wilson[2,3,10], George M. Church[5,6], Dennis R. Burton[1,2,3,12]*, Pascal Poignard[1,2,11]

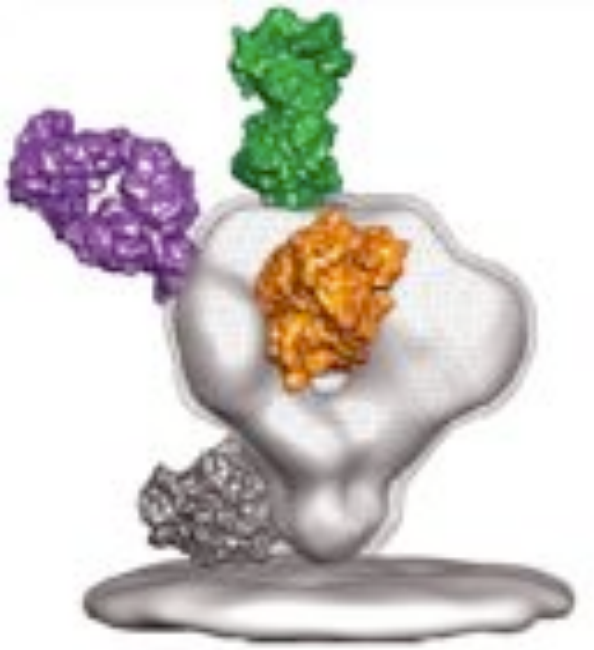
Sok et al, PLoS Pathogens 2013

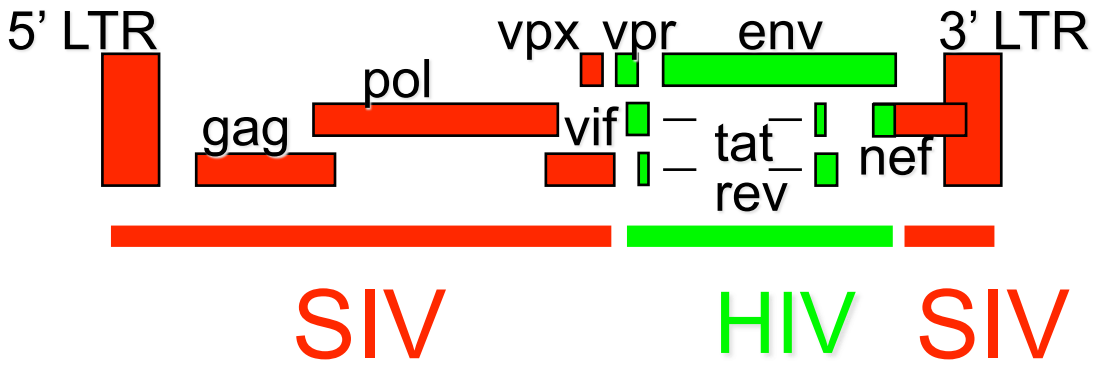


Mascola & Haynes, Immunol Rev 2013

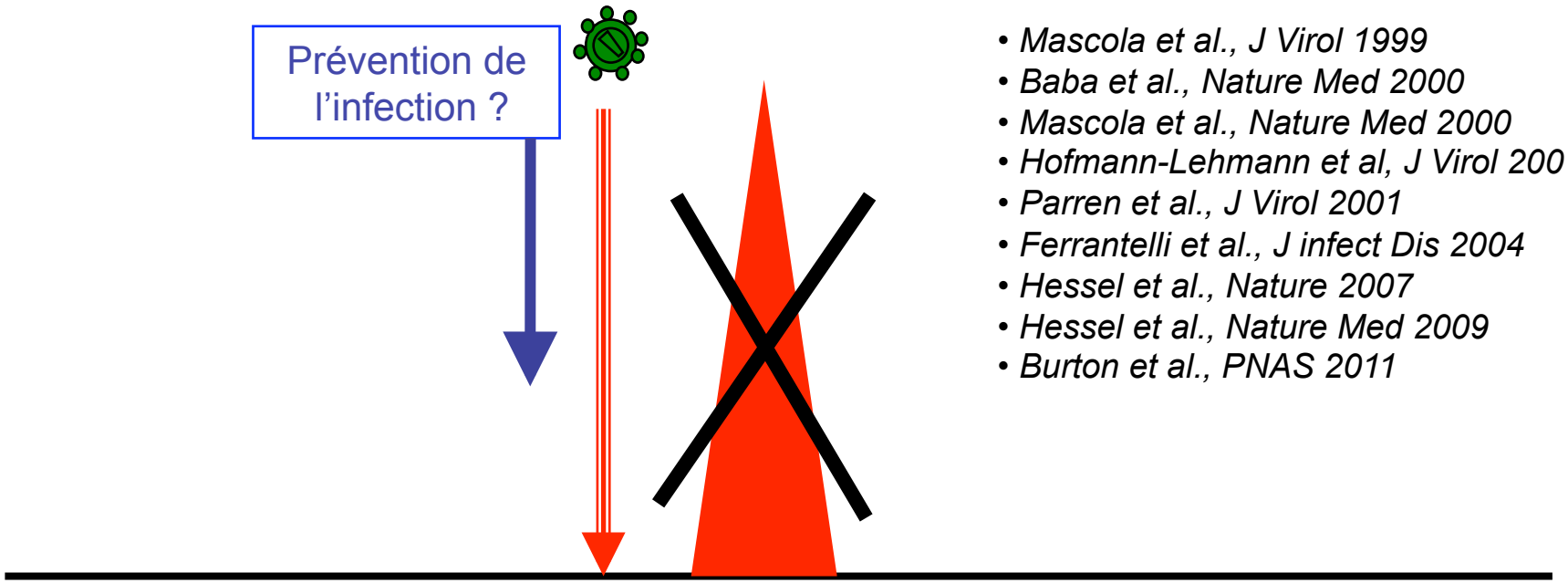
Understanding the role of broadly Nabs in prevention of transmission.

Human Mabs / SHIV model





Ac neutralisants: pré-exposition



- *Mascola et al., J Virol 1999*
- *Baba et al., Nature Med 2000*
- *Mascola et al., Nature Med 2000*
- *Hofmann-Lehmann et al, J Virol 2001*
- *Parren et al., J Virol 2001*
- *Ferrantelli et al., J infect Dis 2004*
- *Hessel et al., Nature 2007*
- *Hessel et al., Nature Med 2009*
- *Burton et al., PNAS 2011*

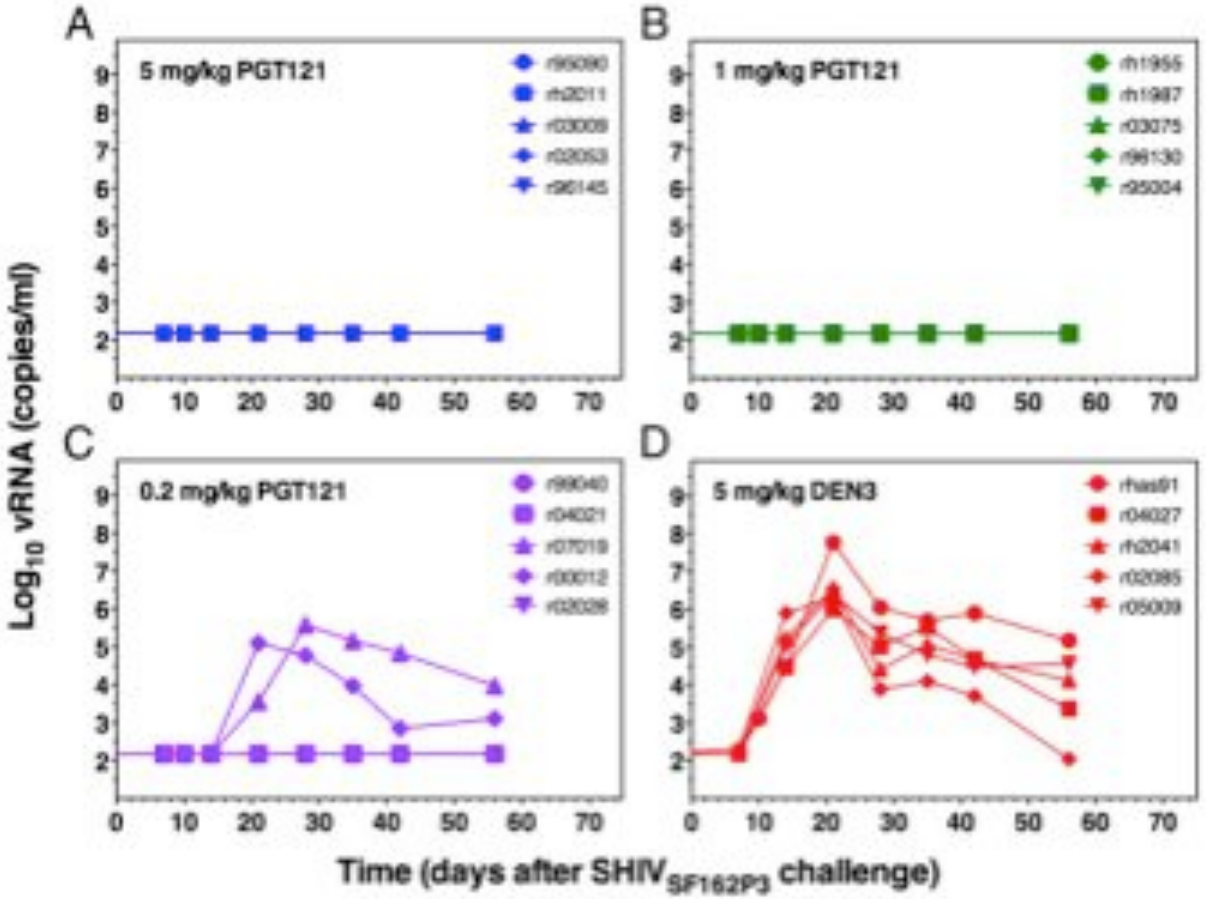
Des anticorps neutralisants monoclonaux de large spectre préviennent l'infection (voie IV, vaginale, rectale, et transmission mère-enfant) dans les modèles SHIV-macaque.

Les anticorps neutralisants sont protecteurs

Highly potent HIV-specific antibody neutralization in vitro translates into effective protection against mucosal SHIV challenge in vivo

Brian Moldt[a], Eva G. Rakasz[b], Niccole Schultz[a], Po-Ying Chan-Hui[c], Kristine Swiderek[c], Kimberly L. Weisgrau[b], Shari M. Piaskowski[b], Zachary Bergman[b], David I. Watkins[d], Pascal Poignard[a,e,1], and Dennis R. Burton[a,f,1]

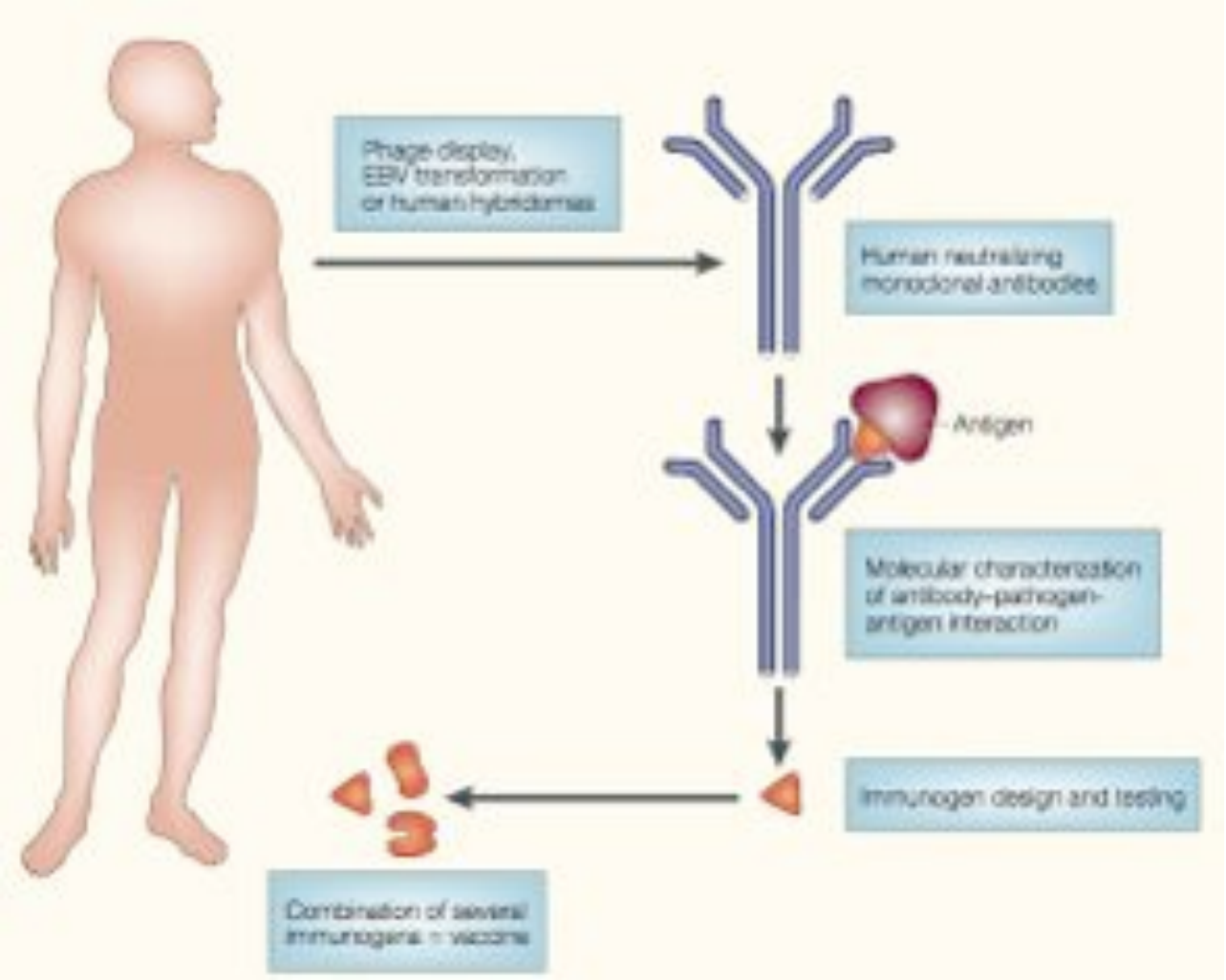
PGT121 *vs* SHIV



B Moldt et al., PNAS 2012

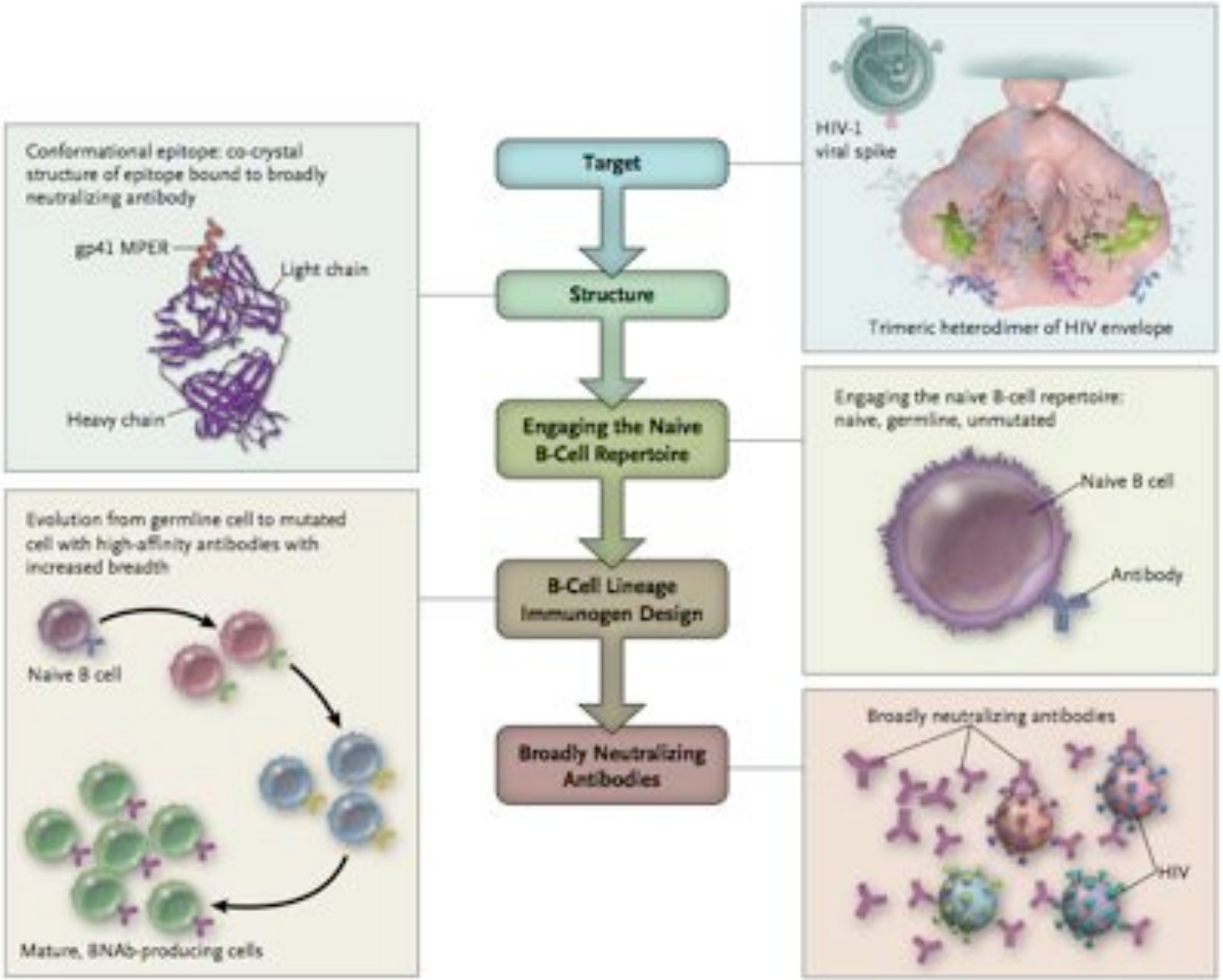
Connaissance de la (des) cible(s) de la réponse neutralisante et conception vaccinale

« Reverse vaccinology »



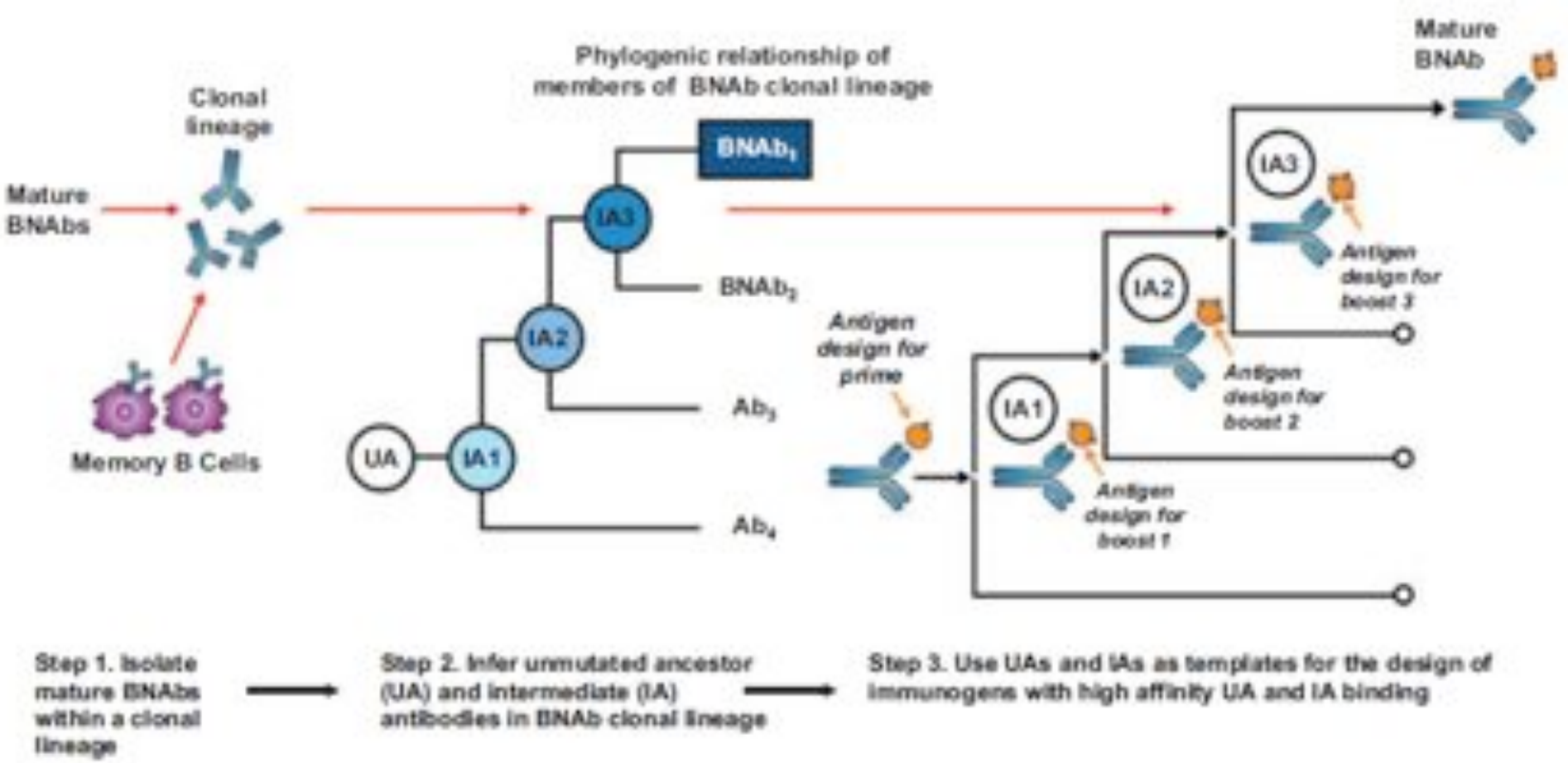
D Burton, Nature Rev Immunol 2002

Connaissance de l'évolution de la réponse neutralisante et conception vaccinale



Fauci, NEJM 2014

Connaissance de l'évolution de la réponse neutralisante et conception vaccinale



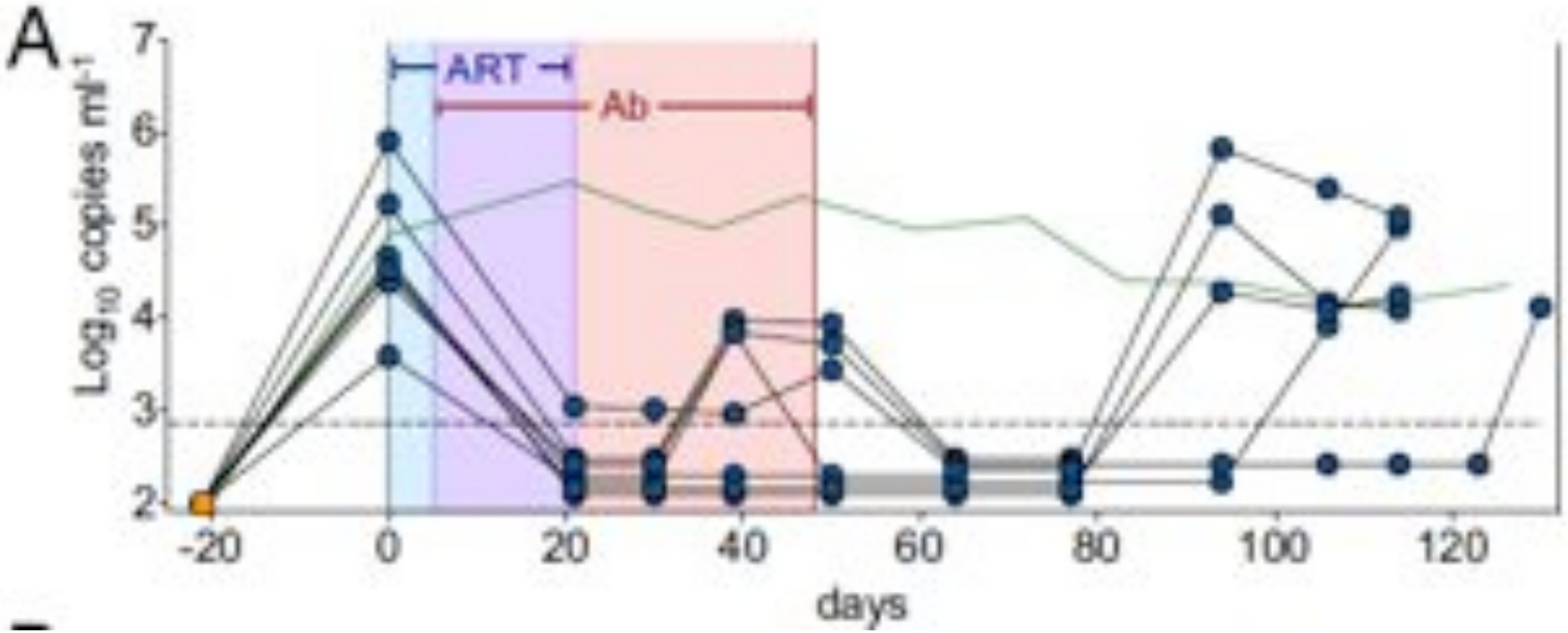
Mascola & Haynes, Immunol Rev 2013

Les anticorps neutralisants en thérapeutique

PNAS

HIV-1 suppression and durable control by combining single broadly neutralizing antibodies and antiretroviral drugs in humanized mice

Joshua A. Horwitz[a], Ariel Halper-Stromberg[a], Hugo Mouquet[a,b], Alexander D. Gitlin[a], Anna Tretiakova[c], Thomas R. Eisenreich[a], Marine Malbec[d], Sophia Gravemann[e], Eva Billerbeck[f], Marcus Dorner[f], Hildegard Büning[e], Olivier Schwartz[d], Elena Knops[e], Rolf Kaiser[e], Michael S. Seaman[g], James M. Wilson[c], Charles M. Rice[f], Alexander Ploss[f,h], Pamela J. Bjorkman[i,j], Florian Klein[a,1], and Michel C. Nussenzweig[a,k,1,2]



F Klein et al., Nature 2012, & JA Horwitz et al., PNAS 2013

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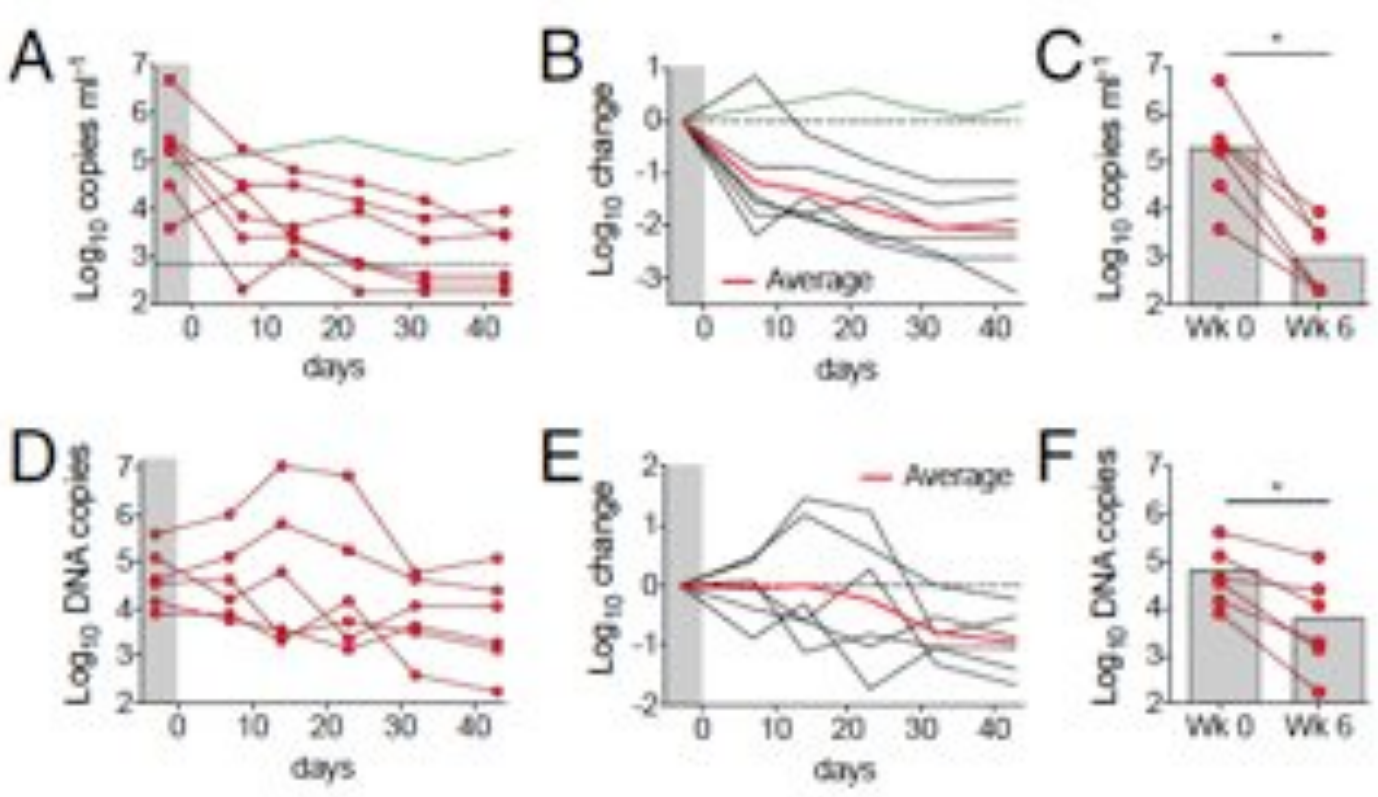


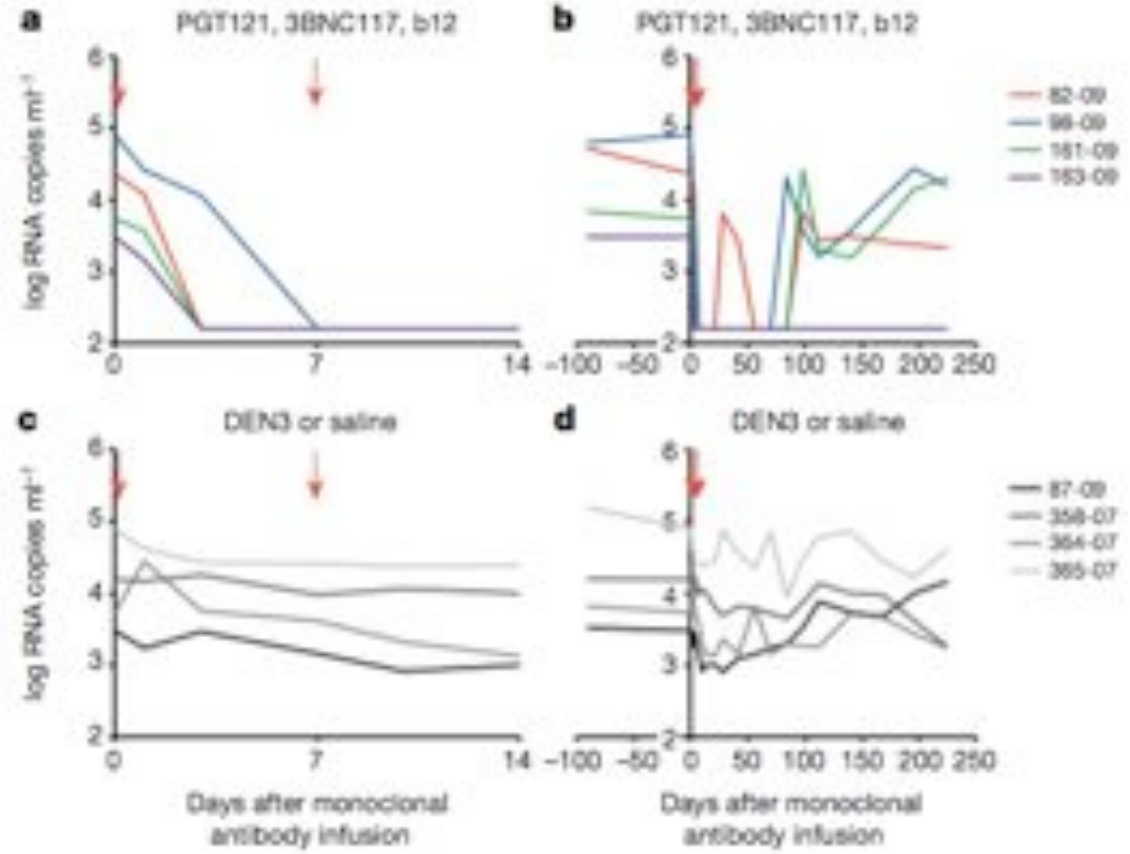
F Klein et al., Nature 2012, & JA Horwitz et al., PNAS 2013

Broadly Nabs as therapeutic agents

Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys

Dan H. Barouch[1,2], James B. Whitney[3], Brian Moldt[3], Florian Klein[4], Thiago Y. Oliveira[4], Jinyan Liu[1], Kathryn E. Stephenson[1], Hui-Wen Chang[1], Karthik Shekhar[3], Sanjana Gupta[3], Joseph P. Nkolola[1], Michael S. Seaman[3], Kaitlin M. Smith[1], Erica N. Borducchi[1], Crystal Cabral[1], Jeffrey Y. Smith[1], Stephen Blackmore[1], Srisowmya Sanisetty[1], James R. Perry[1], Matthew Beck[5], Mark G. Lewis[7], William Rinaldi[8], Arup K. Chakraborty[2,3], Pascal Poignard[3], Michel C. Nussenzweig[4,9]* & Dennis R. Burton[2,3]*

- 8 animaux infectés SHIV -SF162 P3, puis 9 mois post -infection:
  - ✓ 4 animaux: association 3 bnAbs, & 4 animaux: Ac anti -DEN3.
  - ✓ 2 perfusions à J0 et J7 (10 mg/kg de chaque bnAb)
- Chute rapide la charge virale (ARN plasmatique), et maintien pendant la durée de vie des bnAbs.



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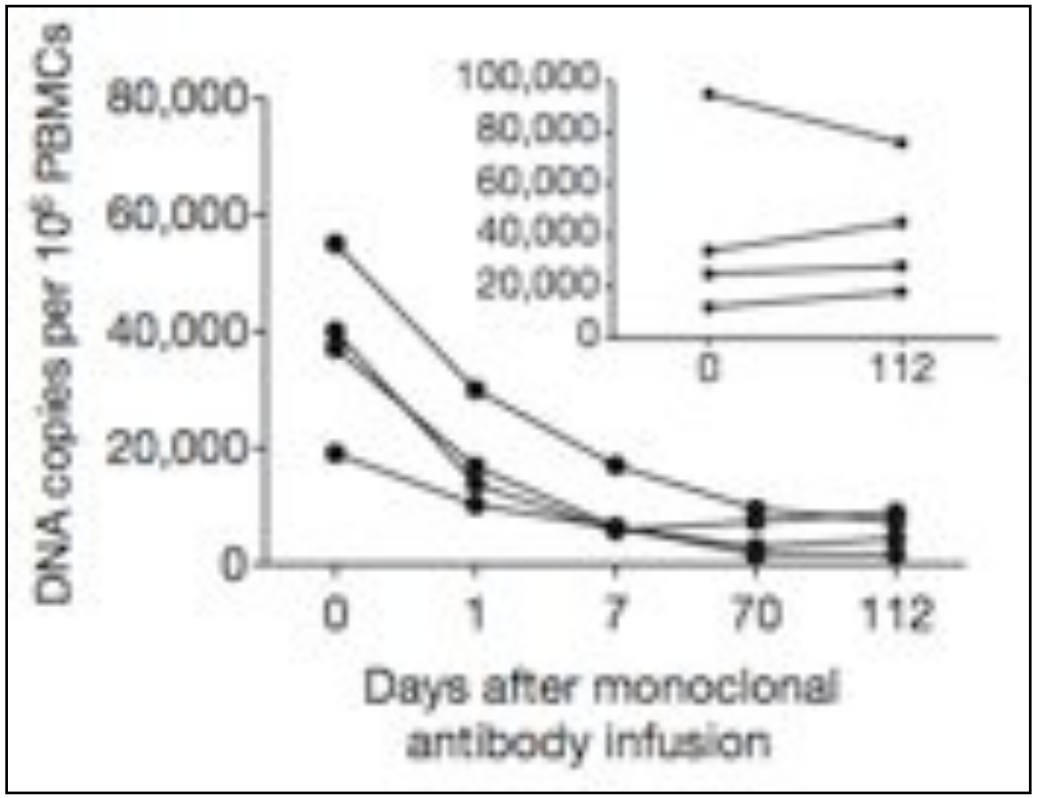
  - ✓ 4 animaux: association 3 bnAbs, & 4 animaux: Ac anti -DEN3.
  - ✓ 2 perfusions à J0 et J7 (10 mg/kg de chaque bnAb).
- Chute rapide de la charge virale ADN VIH dans les PBMCs.



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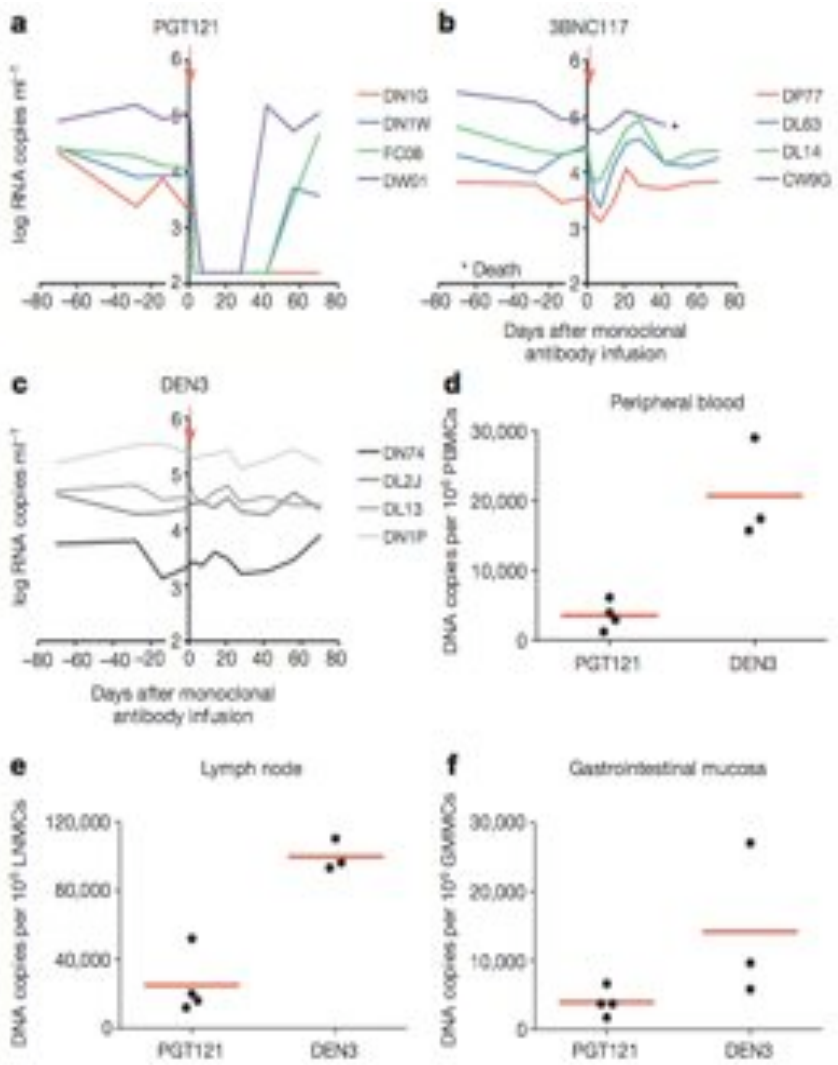


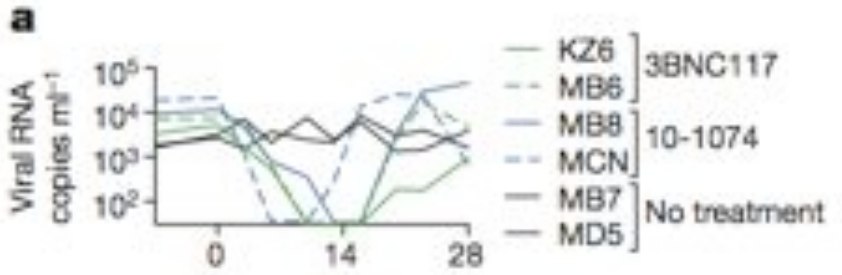
- Résultats confirmés dans la même étude:
  - ✓ Après administration de 2 bnAbs seulement: PGT121 + 3BNC117.
  - ✓ Après administration d'une monothérapie: PGT 121 (mais pas 3BNC117).

DH Barouch et al., Nature 2013.

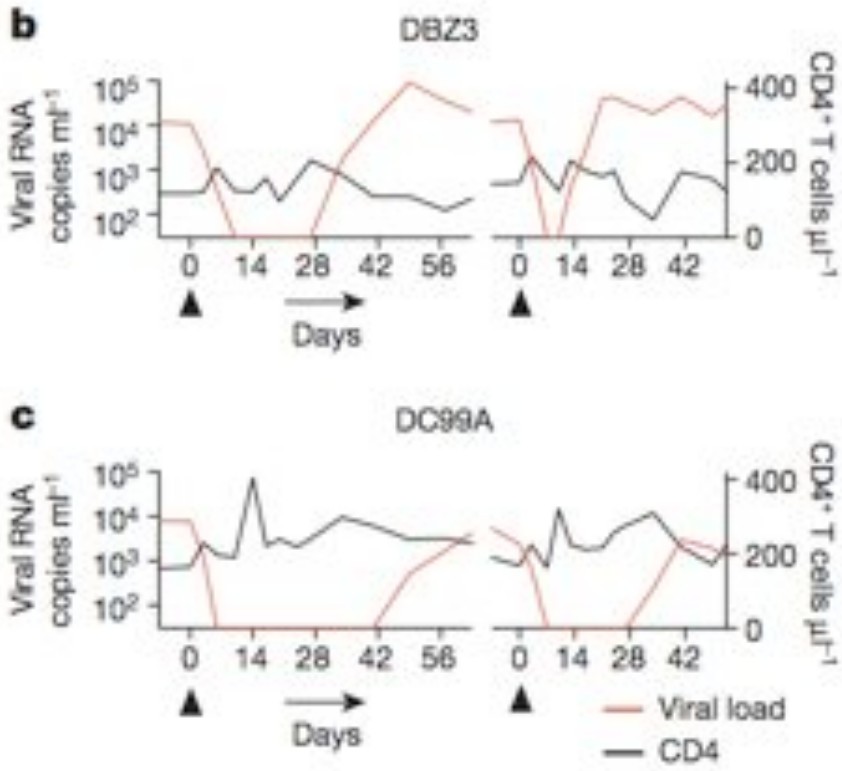
Broadly Nabs as therapeutic agents

Antibody-mediated immunotherapy of macaques chronically infected with SHIV suppresses viraemia

Masashi Shingai[1]*, Yoshiaki Nishimura[1]*, Florian Klein[2], Hugo Mouquet[3], Olivia K. Donau[1], Ronald Plishka[1], Alicia Buckler-White[1], Michael Seaman[4], Michael Piatak Jr[5], Jeffrey D. Lifson[5], Dimiter S. Dimitrov[6], Michel C. Nussenzweig[2] & Malcolm A. Martin[1]

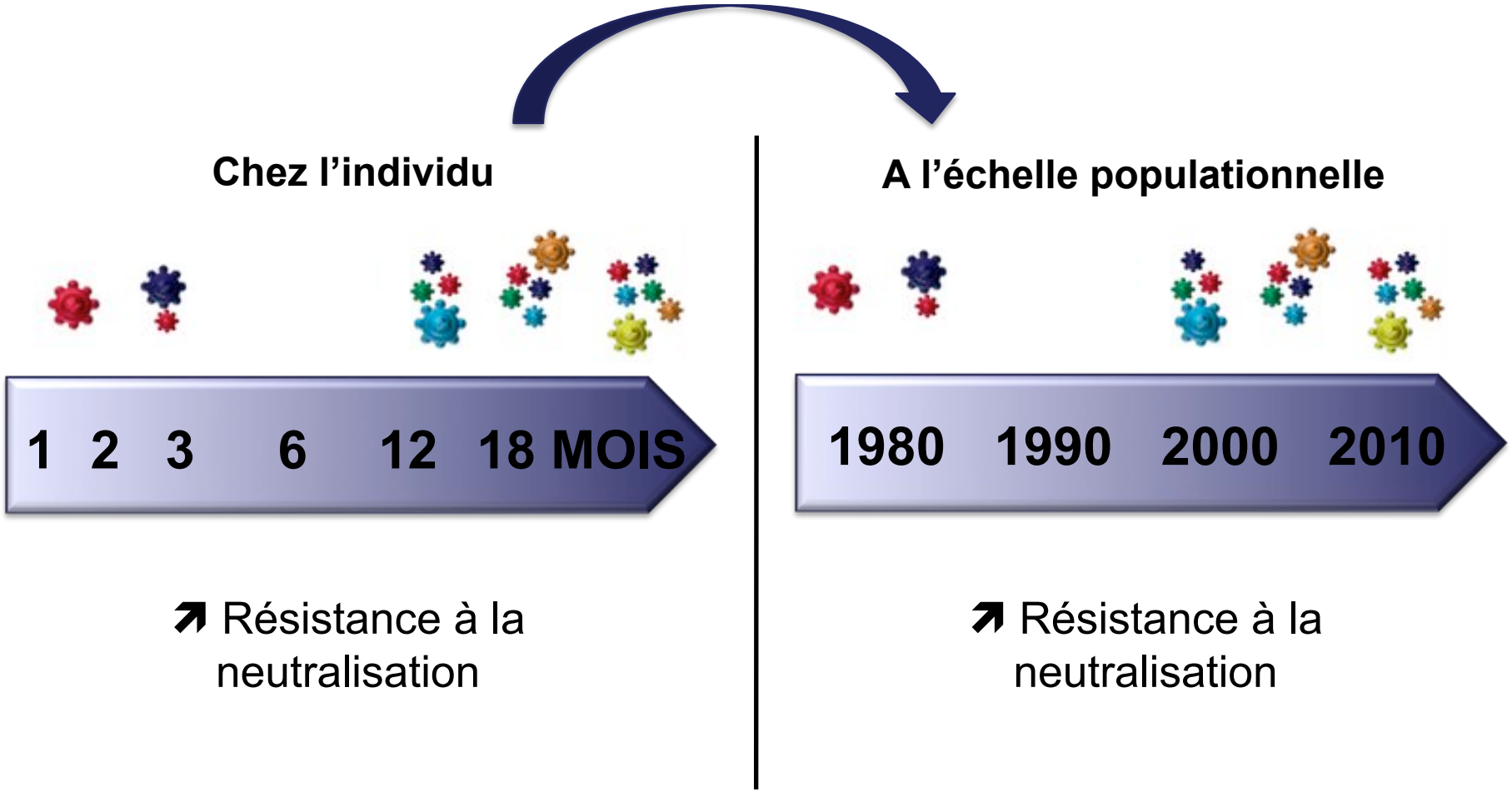


- Résultats confirmés dans une autre étude indépendante.
  - ✓ bnAbs: 3BNC117 [α CD4bs] et 10-1074 [α V3] (10 mg/kg).
  - ✓ Traitement des animaux 12 semaines post -infection (exp. 1), ou 159 semaines post -infection (exp. 2) : résultats similaires.
  - ✓ ARN VIH indétectable tant que la concentration de bnAb est ≥ 5 µg/mL.
  - ✓ Rebond rapide après seconde administration lié à la sélection d'un mutant d'échappement N332D.



M Shingai et al., Nature 2013

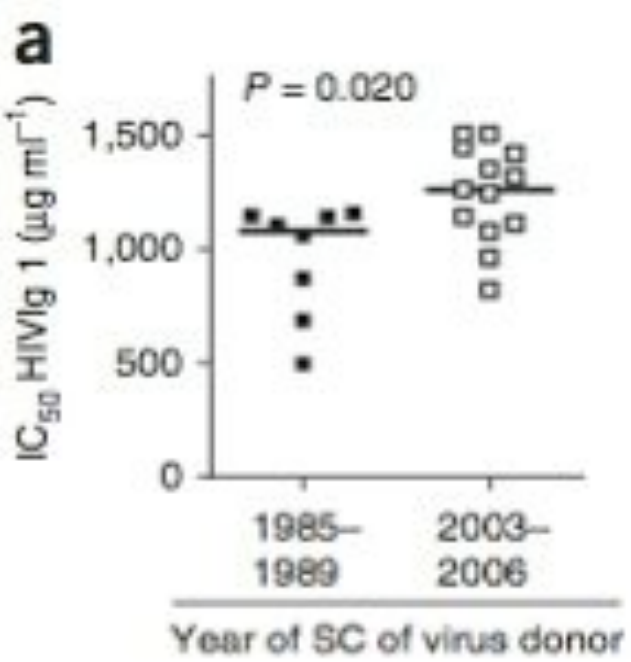
Conséquences de la pression de sélection exercée par les AcN sur l'espèce virale

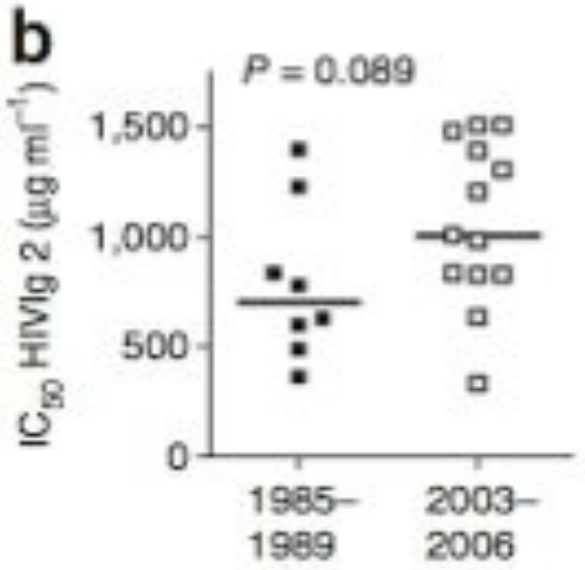


nature medicine

Adaptation of HIV-1 envelope gp120 to humoral immunity at a population level

Evelien M Bunnik[1], Zelda Euler[1,4], Matthijs R A Welkers[1,3,4], Brigitte D M Boeser-Nunnink[1], Marlous L Grijsen[2], Jan M Prins[2] & Hanneke Schuitemaker[1,3]



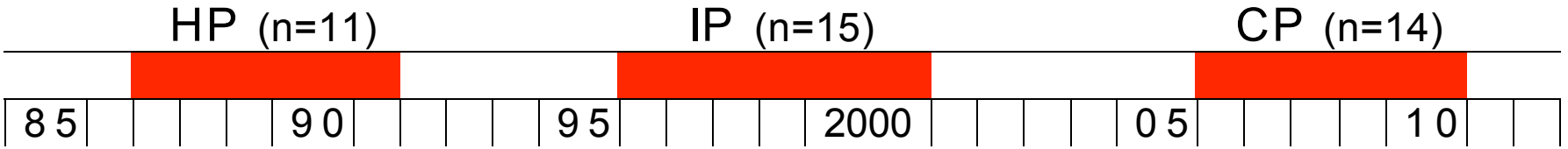


Les virus isolés au cours de la primo-infection (<4.5 mois) chez des sujets infectés au début de l'épidémie sont plus sensibles à la neutralisation que ceux isolés de sujets infectés récemment (virus sous-type B, cohorte Amsterdam)

Bunnik et coll., Nat Med 2010

Population

- Patients au stade de la primo-infection (or séroconversion précoce)
- Cohortes Seroco et Primo (ANRS)
- 3 périodes (1987-1991 / 1996-2000 / 2006-2010)
- MSM, caucasiens, non-traités.
- Clade B

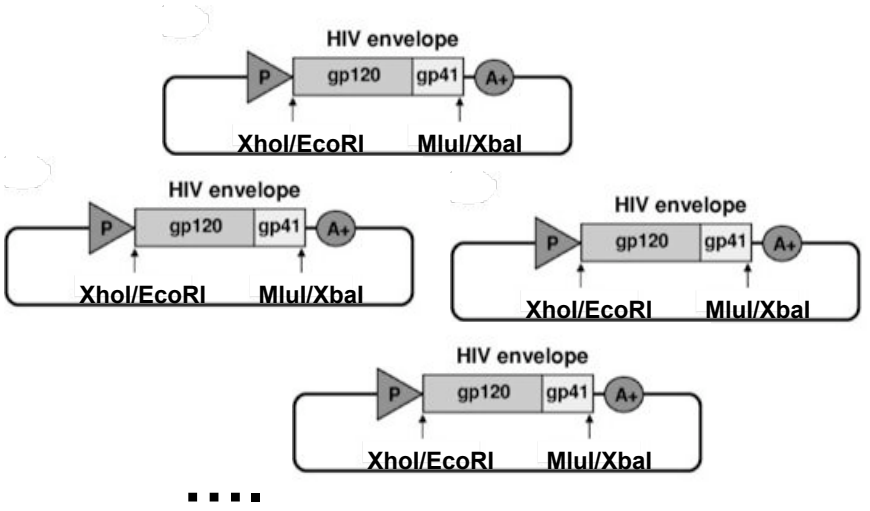


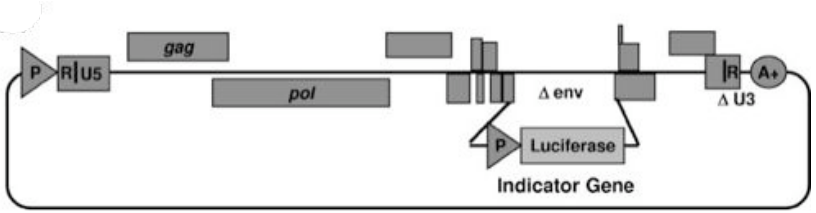
HP (n=11)	IP (n=15)	CP (n=14)
Delai* 1.8 (1.3-6.1)	Delai * 1.3 (0.9-3.3)	Delai * 1.4 (0.8-3.1)
VL 5.0 (4.5-6.1)	VL 5.1 (4.2-5.4)	VL 5.2 (4.1-5.9)
CD4 507 (260-1111)	CD4 619 (209-1542)	CD4 571 (170-1306)

* *Mois post-infection*

Méthodes

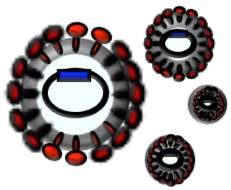
RT-PCR (full-length *env* gene)
Clonage en pCI
Librairie représentative de la population virale



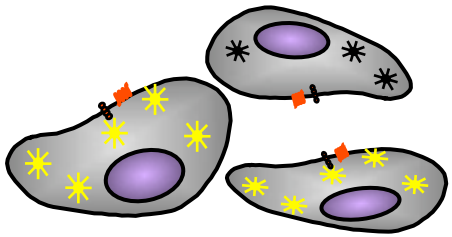


pNL4.3Δ*env*luc+

Co-transfection 293T
Virus pseudotypés



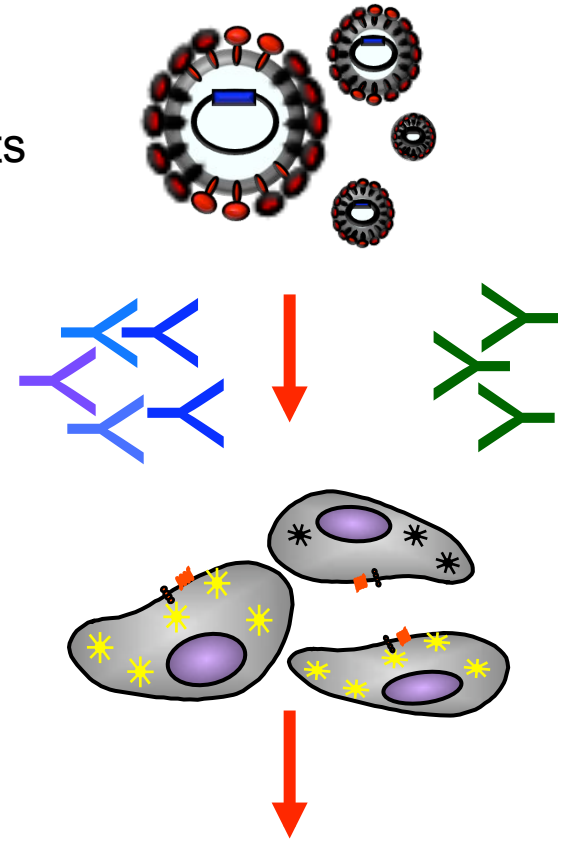
Infection des cellules TZM-bl (HeLa -CD4+CCR5+CXCR4+).
Mesure de l'activité Luciférase.



Méthodes: neutralisation

Pools de sérums de patients infectés

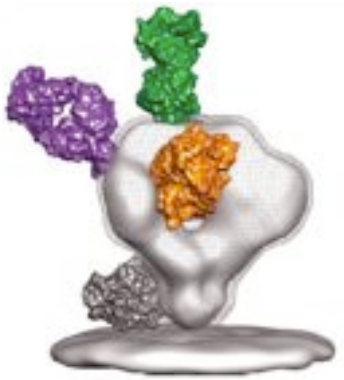
- Clade B
- MSM
- Caucasiens
- non-traités
- 35-52 mois post-infection
- 2 pools (87-91 / 03-07)



IC_{50}

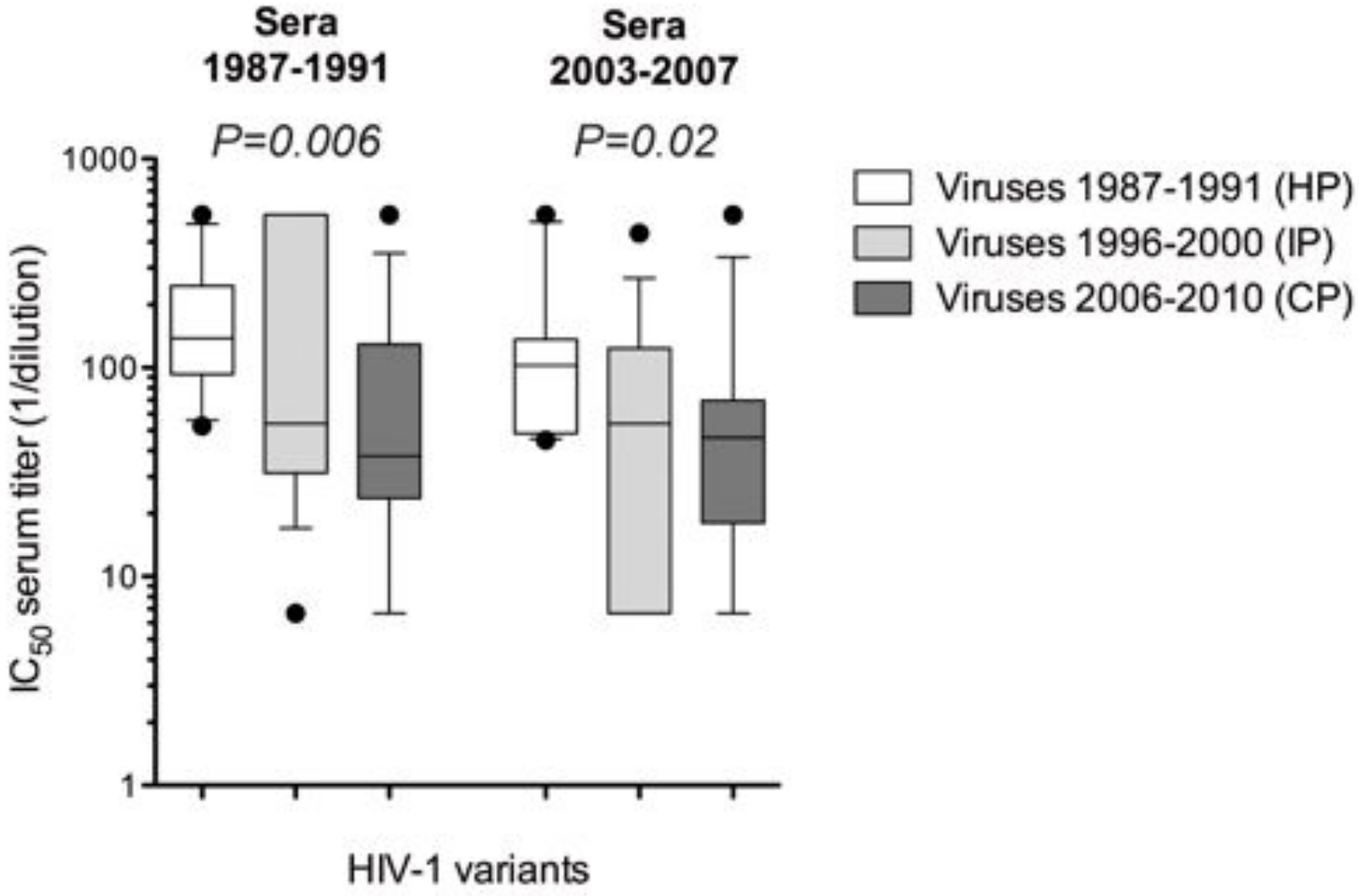
HuMoNAbs (n=13)

- CD4bs: b12, VRC01, VRC03, NIH45-46^{G54W}
- Glycan-dep. V1/V2: PG9, PG16, PGT145
- Glycan-dep. V3: PGT121, PGT128, PGT135, 2G12
- MPER: 2F5, 4E10



- Dilution du sérum permettant de réduire RLUs de 50%
- HuMoNAb concentration permettant de réduire RLUs de 50%

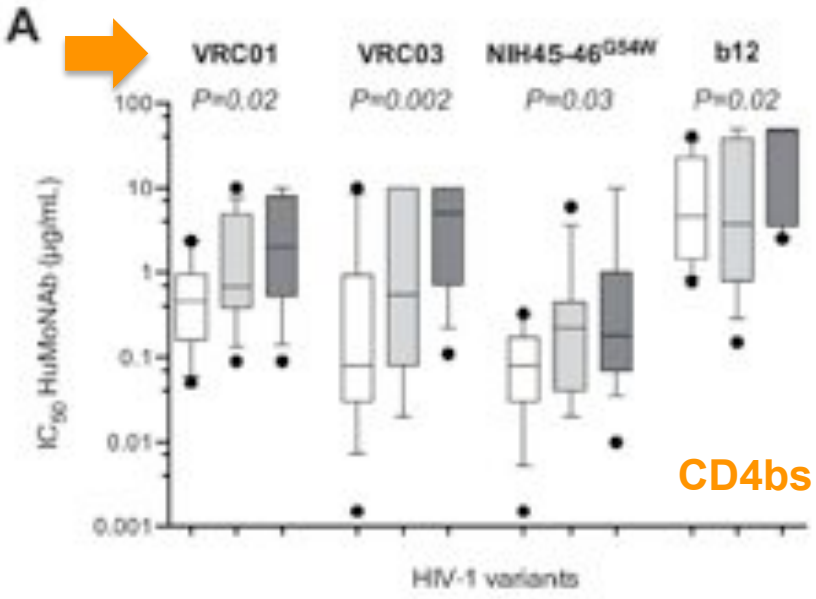
Résultats

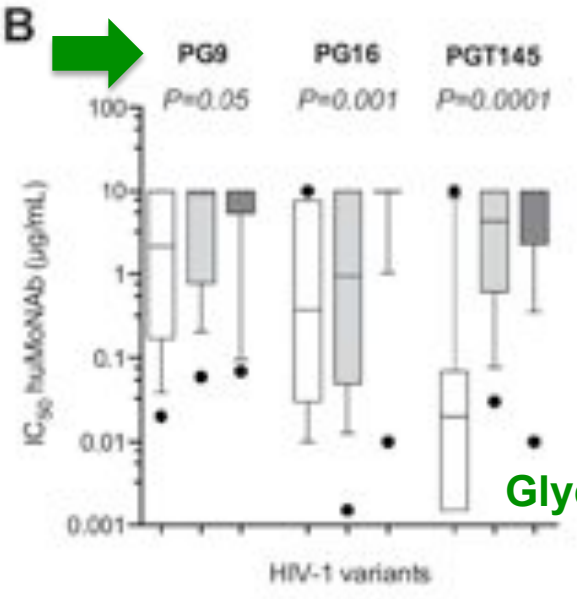


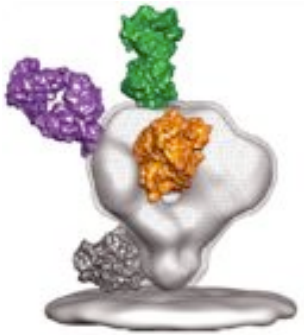
Bouvin-Pley et al.,
PLoS Pathogens 2013.

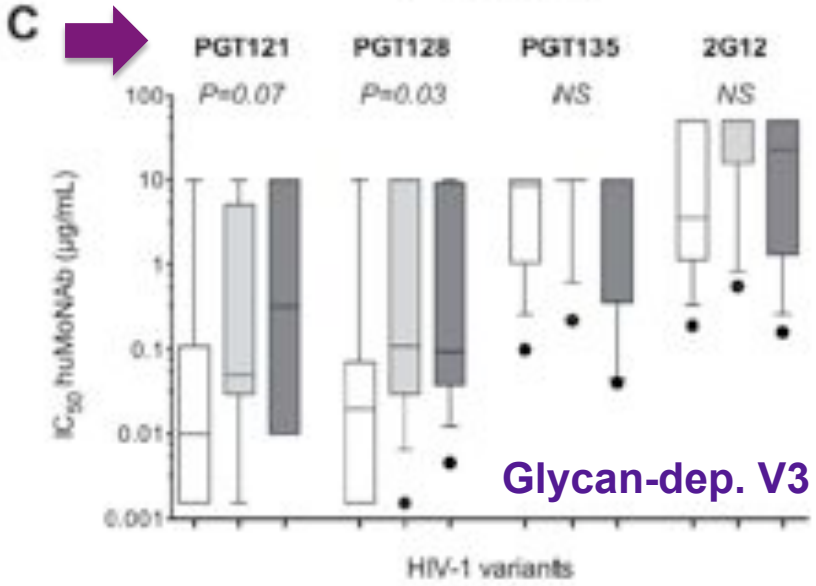
Jonckheere-Tersptra (JT) test for trend

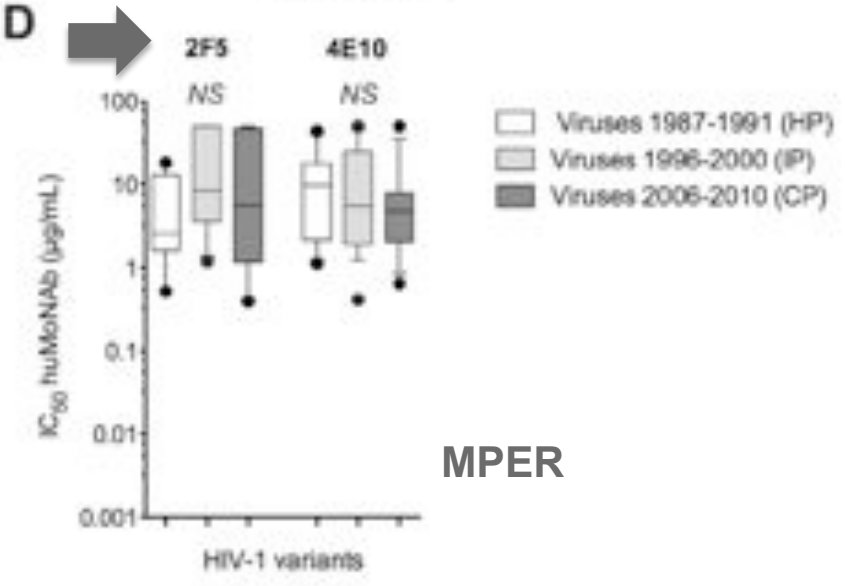
Résultats









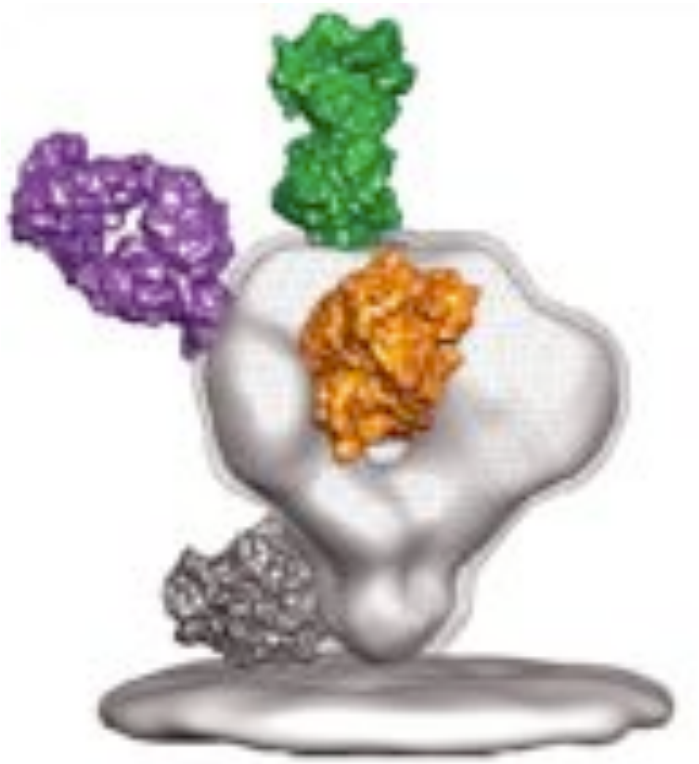


Bouvin-Pley et al., PLoS Pathogens 2013.

JT test for trend

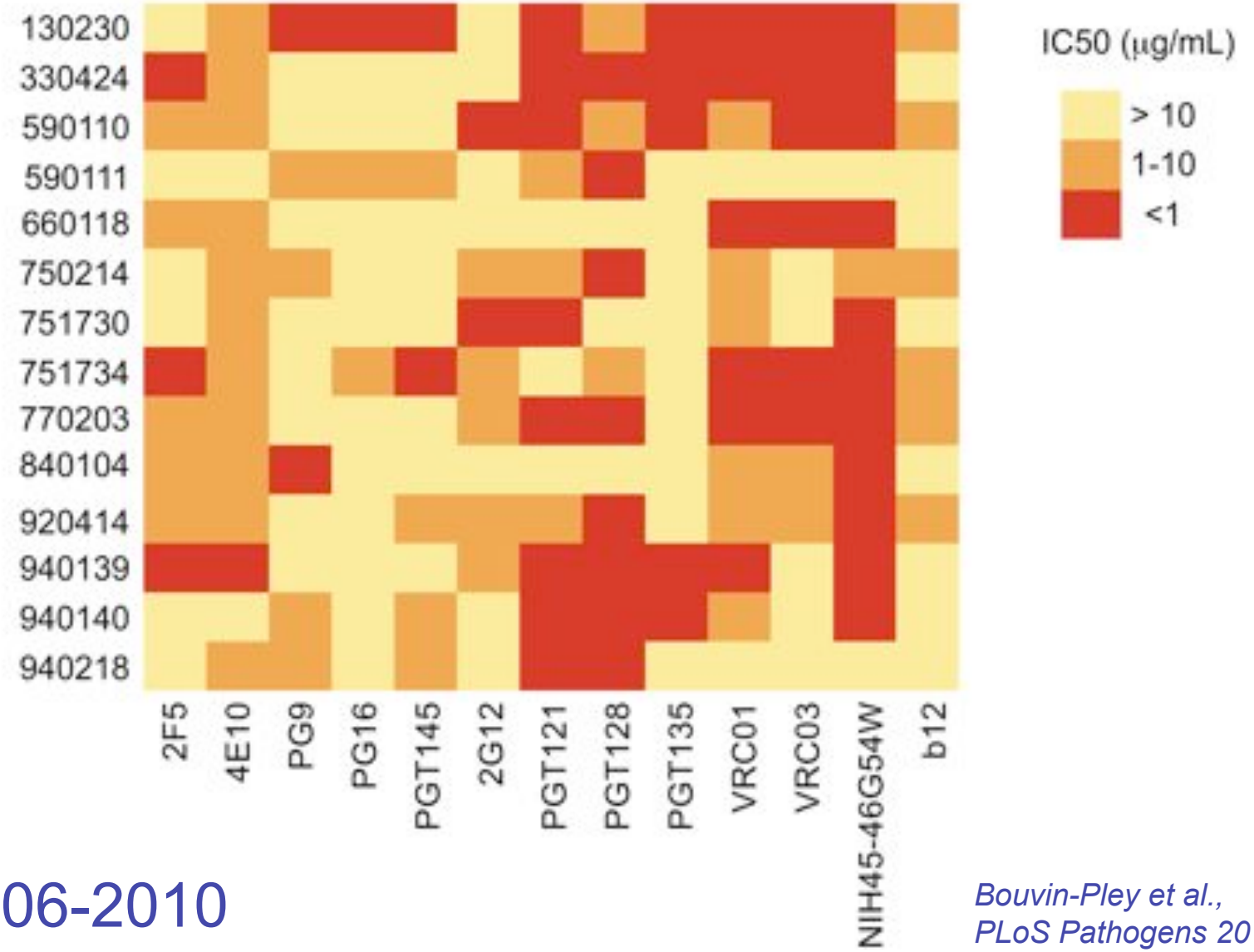
Résultats

- Le VIH-1 semble évoluer vers une plus grande résistance à la neutralisation au cours de l'épidémie.
- Cet effet est particulièrement observé avec les anticorps monoclonaux humains largement neutralisants qui ciblent le CD4bs et les épitopes glycanes-dépendants des boucles V1/ V2 et V3.



Bouvin-Pley et al.,
PLoS Pathogens 2013.

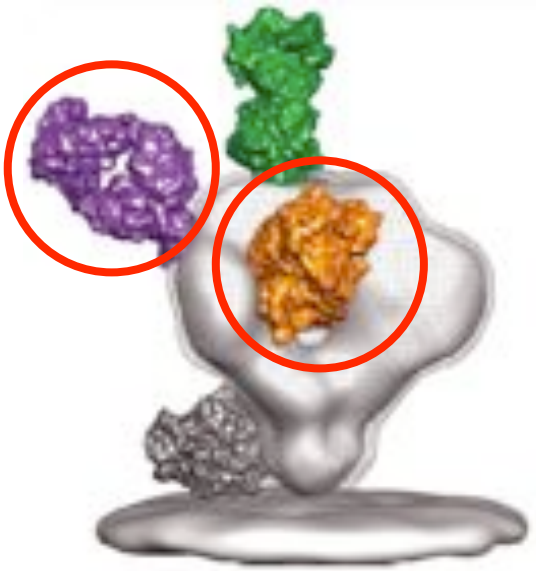
Résultats



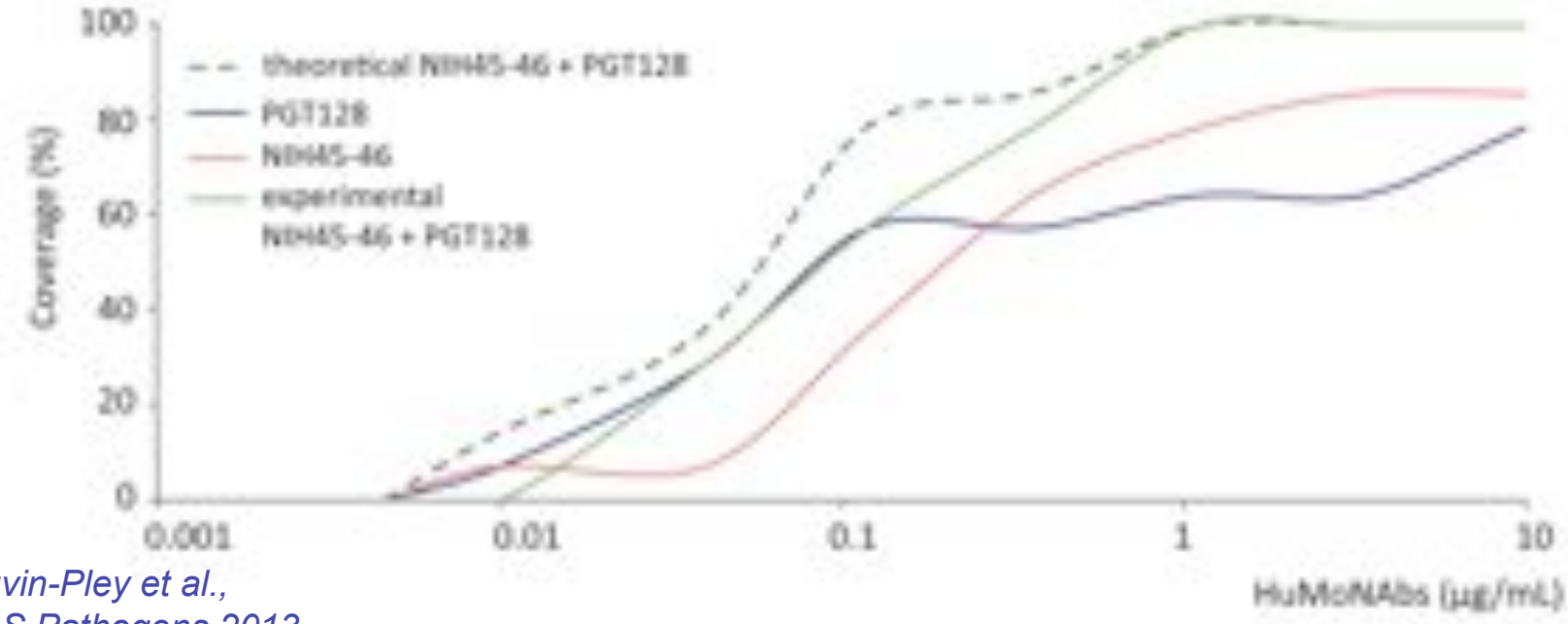
Virus 2006-2010

Bouvin-Pley et al.,
PLoS Pathogens 2013.

Résultats



Virus 2006-2010



Bouvin-Pley et al.,
PLoS Pathogens 2013.

Résultats

- 40 séquences *env* .
- 160 séquences *env* de VIH-1 clade B isolés lors de primo-infections (1990-2009, Los Alamos database):

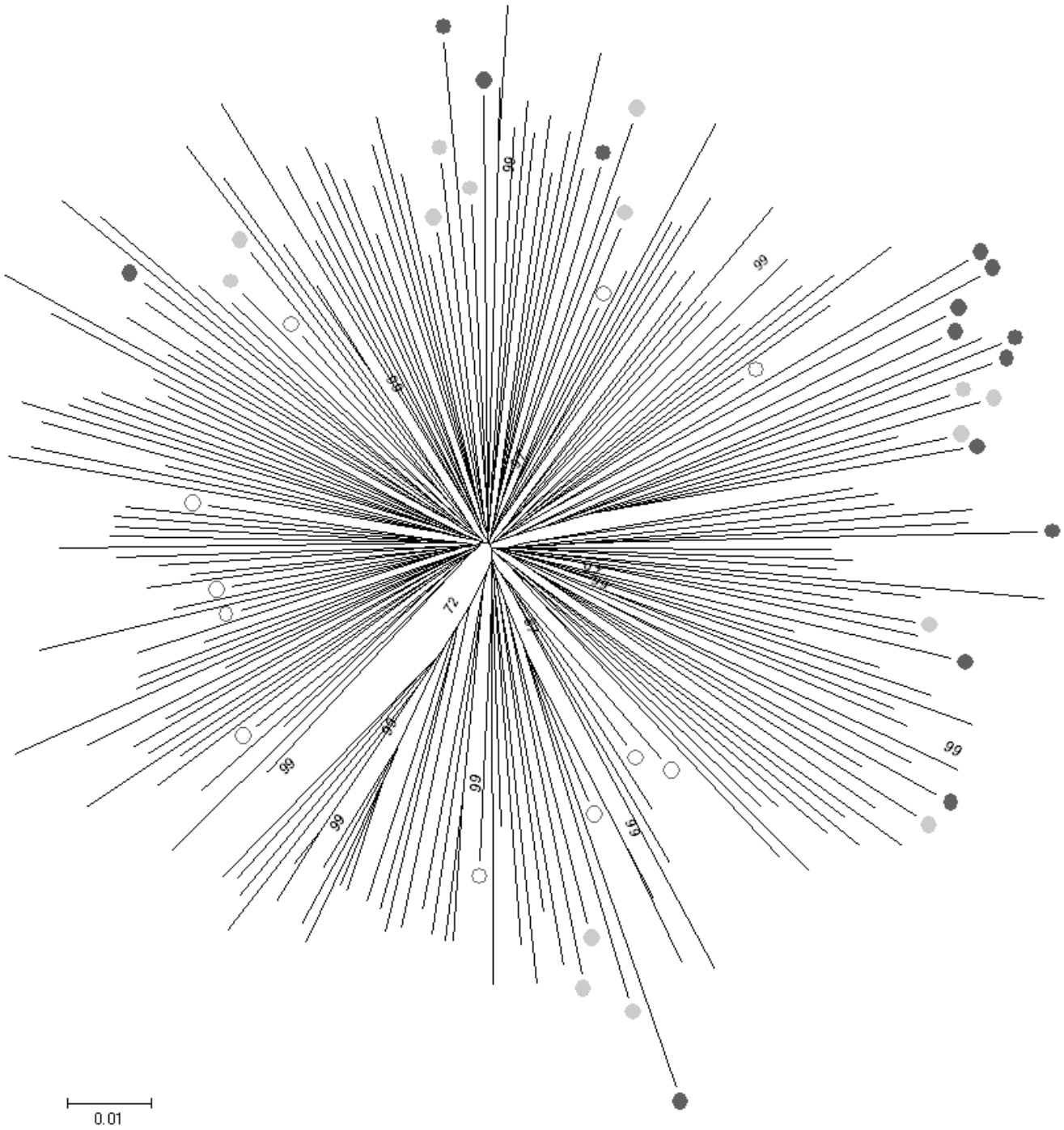
  113 USA,

  25 Europe,

  6 Australie,

  15 Trinidad,

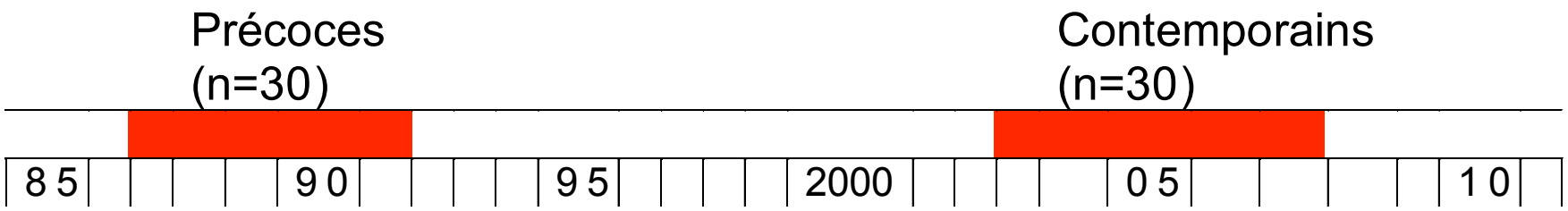
  1 Afrique.



Bouvin-Pley et al.,
PLoS Pathogens 2013.

Immunogénicité ?

- Patients ≥ 3 années post-infection
- Cohortes Seroco et Primo (ANRS)
- 2 périodes (1987-1991 / 2003-2007)
- MSM, caucasiens, non-traités.
- Clade B



Délai*
42.8 (34.7-51.6)

VL
4.2 (2.7-5.2)

CD4
468 (348-637)

Délai *
39 (36.2-50.9)

VL
4.4 (2.3-5.7)

CD4
464 (59-943)

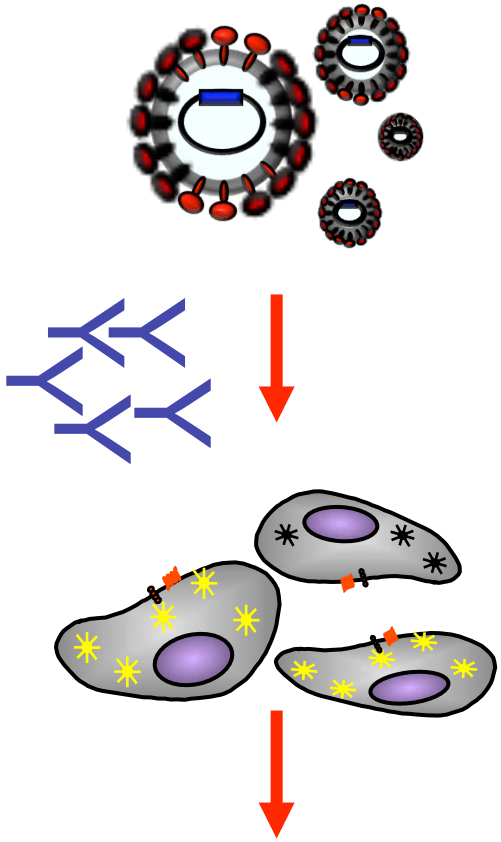
** Mois post-infection*

Méthodes: neutralisation

Tier 2 viruses
Clade B

- Virus pseudotypés
  SVPB6, SVPB13, SVPB14, SVPB16

- Isolats primaires
  BX08, 92BR020



- % de sérum ayant une activité neutralisante.

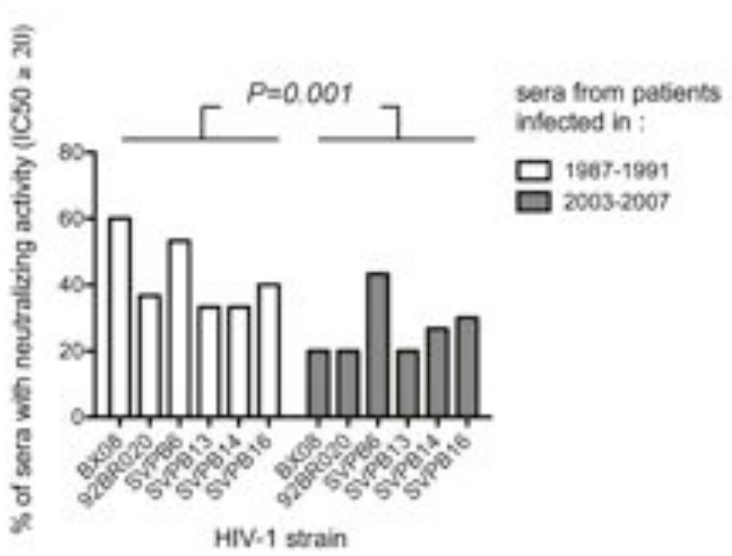
- Titres neutralisants.

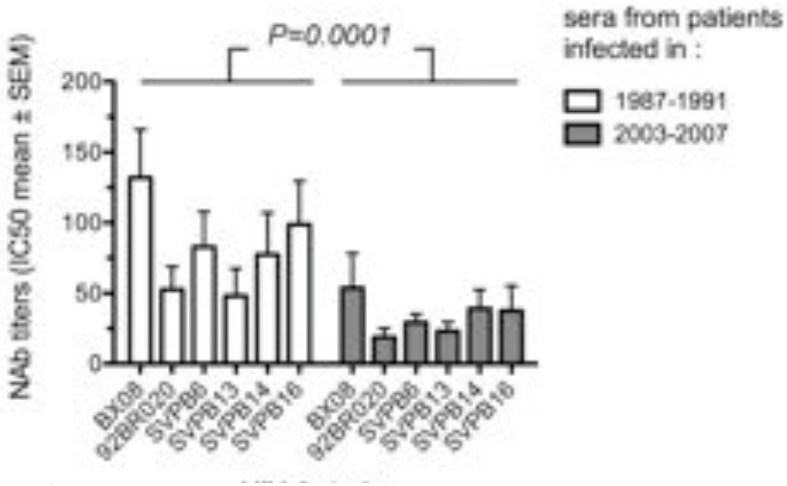
- Nombre de virus neutralisés.

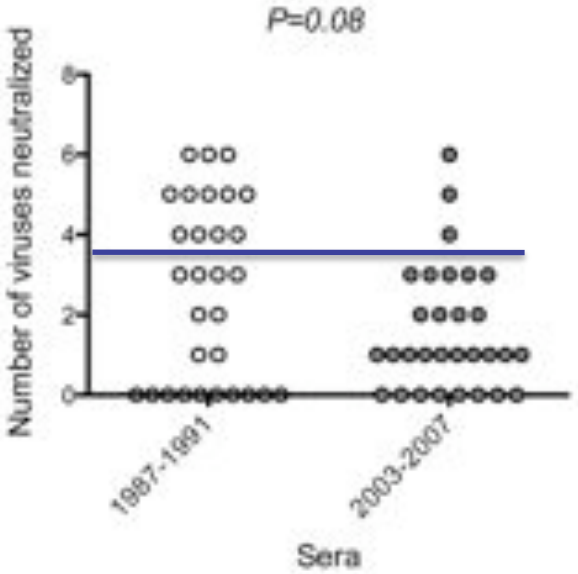
- Potency score (*Lynch et al., 2011*): spectre et efficacité.

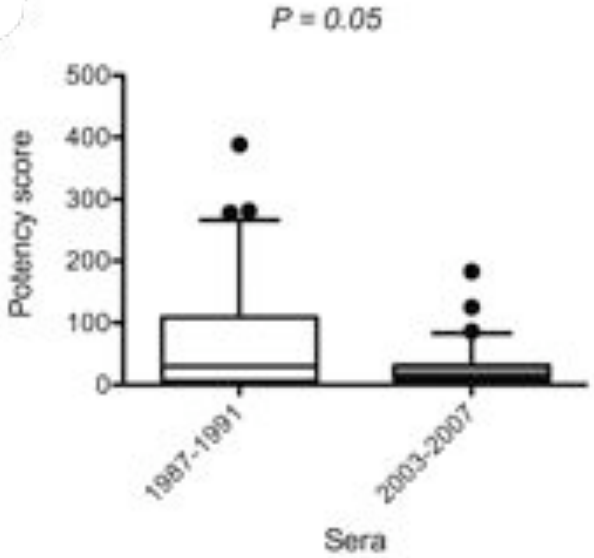
IC_{50}
Dilution de sérum permettant de réduire RLUs de 50%

Résultats









Bouvin-Pley et al., PLoS Pathogens 2013.

Conclusion

- Une diminution progressive de la sensibilité du VIH-1 (clade B) aux anticorps neutralisants est observée depuis le début de l'épidémie.
- Cette observation semble être associée à une diminution de l'immunogénicité du virus en terme de capacité à induire des anticorps neutralisants hétérologues.
- L'ensemble des données est en faveur d'une adaptation du VIH-1 en tant qu'espèce à la réponse humorale de la population humaine, ce qui pourrait être un obstacle supplémentaire au développement d'un vaccin efficace.
- Malgré cela, les virus « contemporains » de clade B demeurent sensibles à la neutralisation par une combinaison de deux HuMoNAbs, PGT128 et NIH45-46^{G54W}.

Questions -Perspectives

- Cette dérive antigénique est-elle similaire pour les autres sous-types prévalents (C, A, CRF02_AG, …) ?

- Cette adaptation de l'espèce virale, probable conséquence de la pression exercée par la réponse neutralisante au sein de la population humaine, a t'elle des répercussions fonctionnelles (capacité infectieuse, liaison aux récepteurs/corécepteurs, …) ?

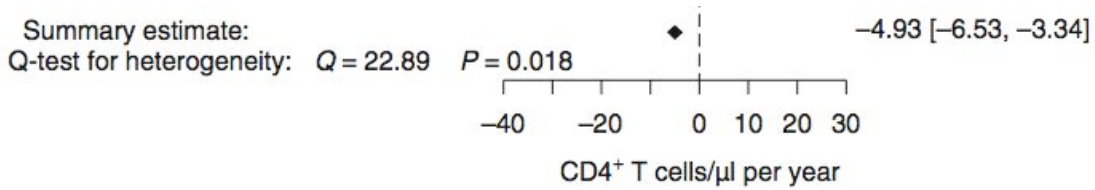
- Quelle place pour les anticorps monoclonaux largement neutralisants en prophylaxie voire en thérapeutique?

Is the virulence of HIV changing? A meta-analysis of trends in prognostic markers of HIV disease progression and transmission

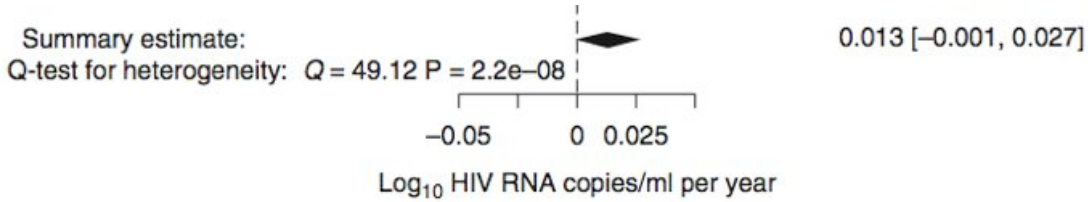
Joshua T. Herbeck[a], Viktor Müller[c], Brandon S. Maust[a], Bruno Ledergerber[d], Carlo Torti[e], Simona Di Giambenedetto[f], Luuk Gras[g], Huldrych F. Günthard[d], Lisa P. Jacobson[h], James I. Mullins[a,b] and Geoffrey S. Gottlieb[b]

12 studies of trends in baseline CD4+ T-cell counts (21 052 individuals), 1984-2010.
8 studies of trends in set point viral loads (10 785 individuals), 1984-2010.

Baseline $CD4^+$ T-cell:
Loss of 148 cells/μL over 30 years



Set point viral load:
Gain of 0.39 $\log_{10}$ copies/mL over 30 years



AIDS 2012, 26: 193-205

Questions -Perspectives

- Cette dérive antigénique est-elle similaire pour les autres sous-types prévalents (C, A, CRF02_AG, …) ?

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- Quelle place pour les anticorps monoclonaux largement neutralisants en prophylaxie voire en thérapeutique?

The Future Is Now

- La modification des gènes codant les anticorps monoclonaux humains largement neutralisants permet d'améliorer leur activité (élargissement du spectre et affinité).

- La dérive antigénique du VIH-1 nécessiterait de disposer d'une surveillance prospective de sa sensibilité à la neutralisation par ces anticorps.

JEM Article

Restricting HIV-1 pathways for escape using rationally designed anti–HIV-1 antibodies

Ron Diskin,[1] Florian Klein,[2] Joshua A. Horwitz,[2] Ariel Halper-Stromberg,[2] D. Noah Sather,[3] Paola M. Marcovecchio,[1] Terri Lee,[1] Anthony P. West Jr.,[1] Han Gao,[1] Michael S. Seaman,[4] Leonidas Stamatatos,[3,5] Michel C. Nussenzweig,[2,6] and Pamela J. Bjorkman[1,6]

R Diskin et al., JEM 2013

nature structural & molecular biology

Structural basis for diverse N-glycan recognition by HIV-1–neutralizing V1–V2–directed antibody PG16

Marie Pancera[1,11], Syed Shahzad-ul-Hussan[2,11], Nicole A Doria-Rose[1,11], Jason S McLellan[1], Robert T Bailer[1], Kaifan Dai[3], Sandra Loesgen[2], Mark K Louder[1], Ryan P Staupe[3], Yongping Yang[1], Baoshan Zhang[1], Robert Parks[3], Joshua Eudailey[3], Krissey E Lloyd[3], Julie Blinn[3], S Munir Alam[3], Barton F Haynes[3], Mohammed N Amin[4,5], Lai-Xi Wang[4,5], Dennis R Burton[6–9], Wayne C Koff[10], Gary J Nabel[1], John R Mascola[1], Carole A Bewley[2] & Peter D Kwong[1]

M Pancera et al., NSBM 2013

PNAS

Bispecific antibodies directed to CD4 domain 2 and HIV envelope exhibit exceptional breadth and picomolar potency against HIV-1

Craig S. Pace[a], Ruijiang Song[a], Christina Ochsenbauer[b], Chasity D. Andrews[a], David Franco[a], Jian Yu[a], Deena A. Oren[c], Michael S. Seaman[d], and David D. Ho[a,1]

[a]Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY 10016; [b]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL 35233; [c]The Rockefeller University, New York, NY 10016; and [d]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215

C Pace et al., PNAS2013

Nouveau concept: « vectored immunoprophylaxis »

Antibody-based protection against HIV infection by vectored immunoprophylaxis

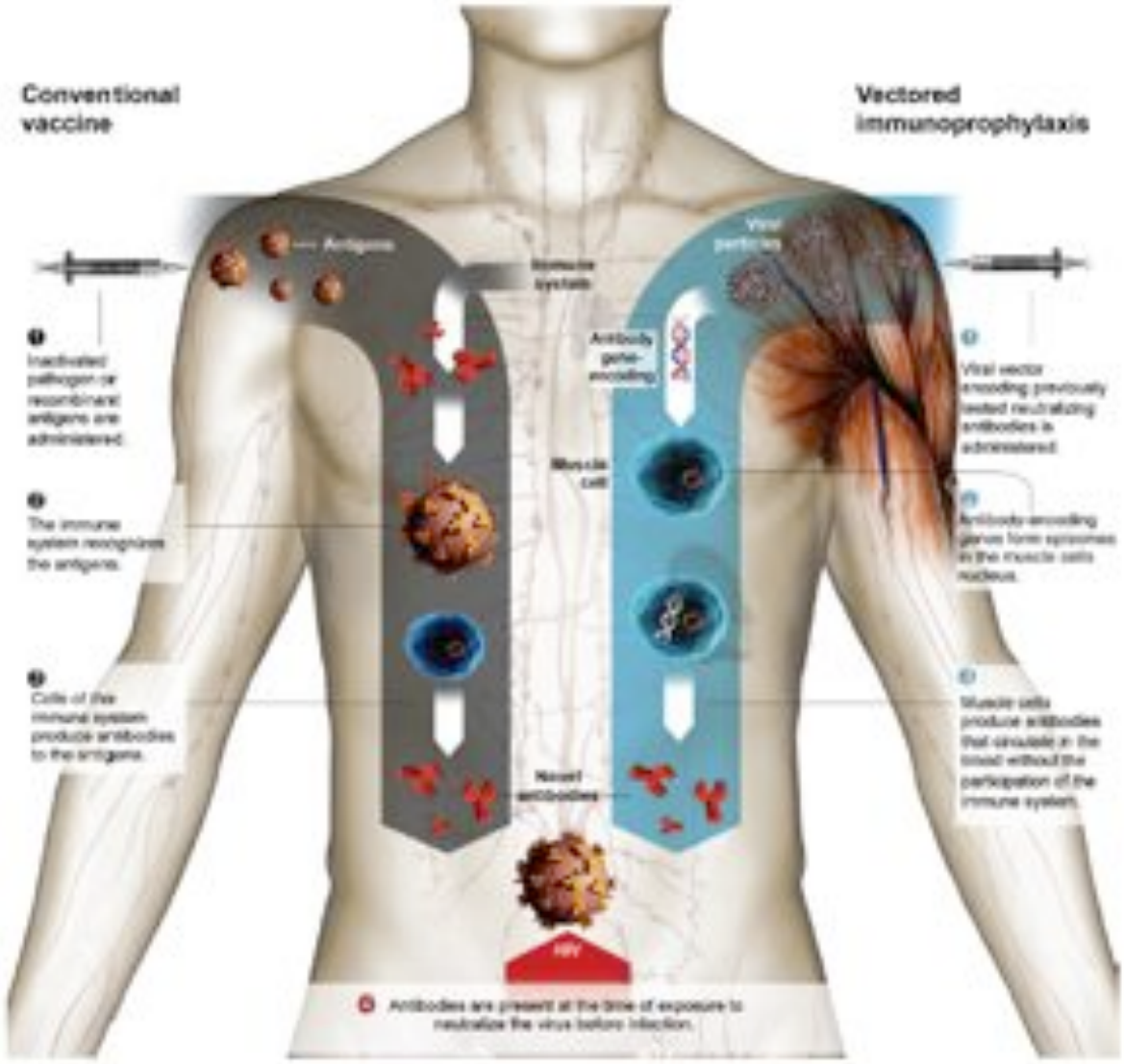
Alejandro B. Balazs[1], Joyce Chen[1], Christin M. Hong[1], Dinesh S. Rao[2], Lili Yang[1] & David Balti

A Balazs et al., Nature 2012

Antibody gene transfer for HIV immunoprophylaxis

Alejandro B Balazs & Anthony P West Jr

A Balazs & A West Jr., Nature Immunol 2013



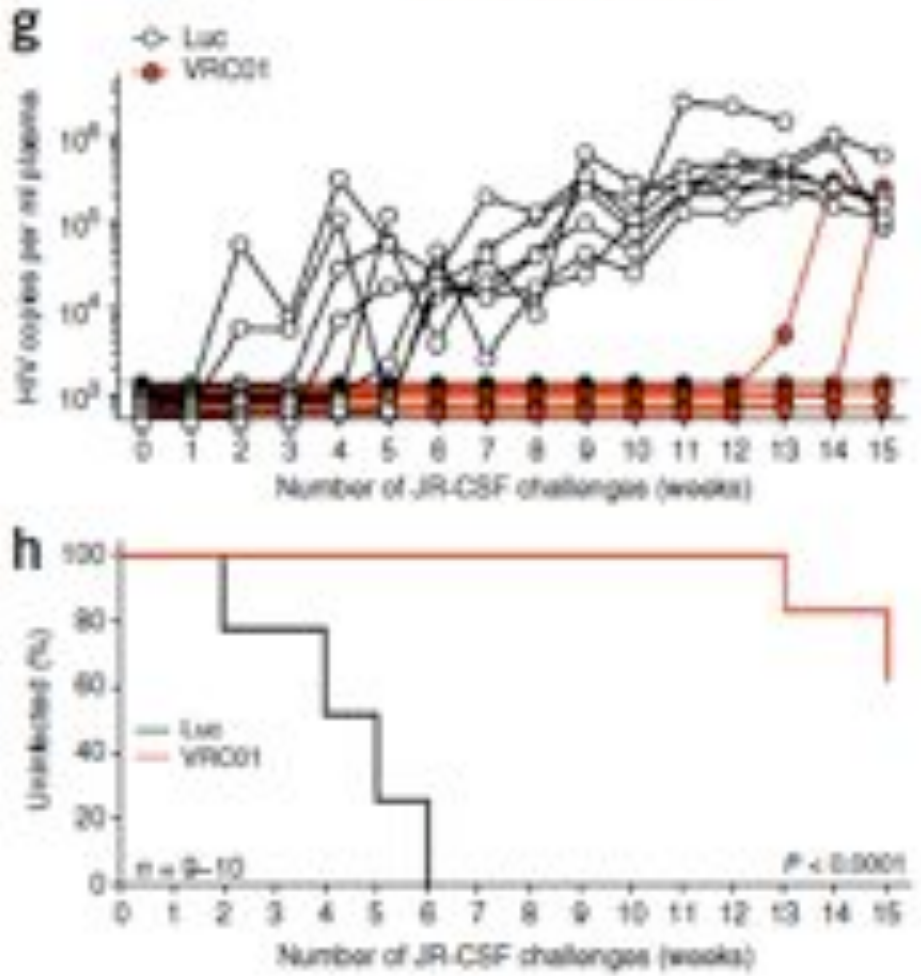
Nouveau concept: « vectored immunoprophylaxis »

Vectored immunoprophylaxis protects humanized mice from mucosal HIV transmission

Alejandro B Balazs[1,4], Yong Ouyang[1], Christin M Hong[1,4], Joyce Chen[1], Steven M Nguyen[1], Dinesh S Rao[2], Dong Sung An[3] & David Baltimore[1]

nature medicine

- Souris humanisées (BLT -*bone marrow-liver-thymus*- hu mice).
- AAV-VRC01 *vs* AAV-luc.
- [VRC01] à 4 semaines post -VIP: 100 µg/mL (sérum) et 100 ng/mL (lavages vaginaux)
- « Challenges » répétés par voie vaginale avec souche JR-CSF (isolat primaire R5).



A Balazs et al., Nature Medicine 2013, advance online pub.

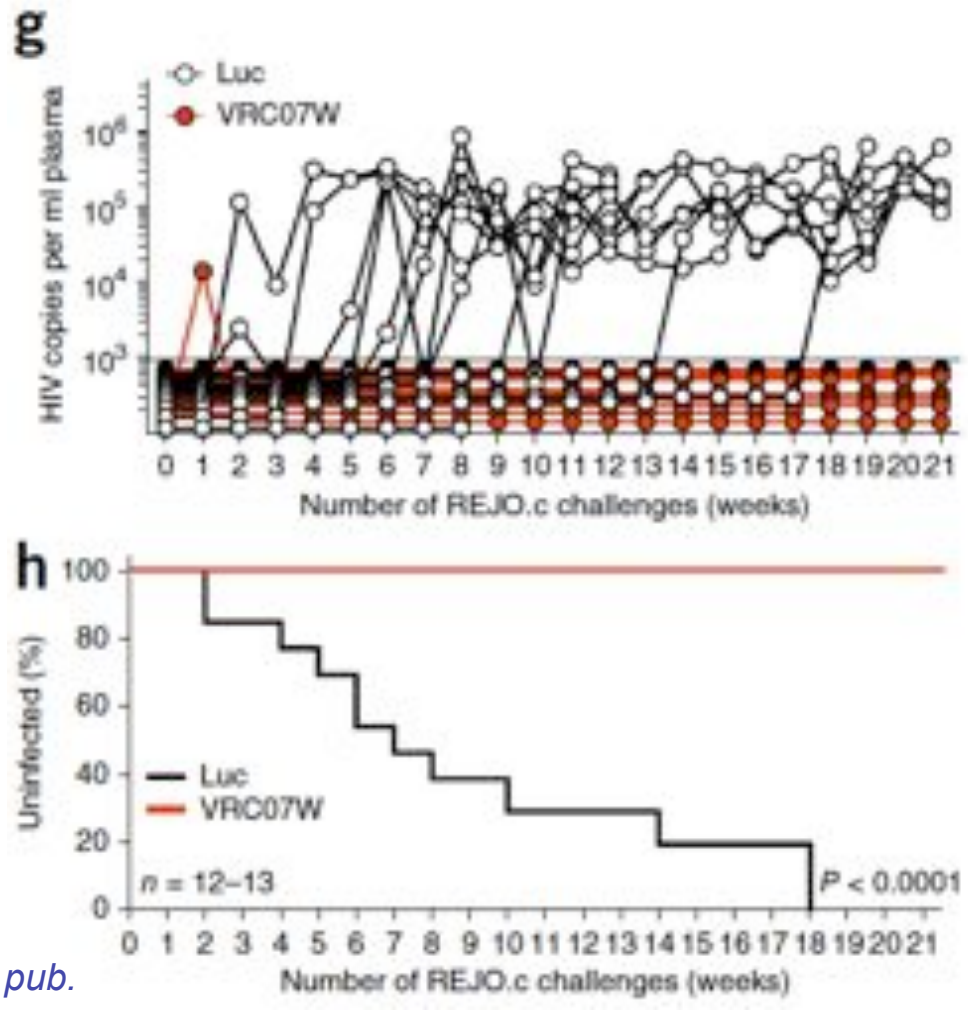
Nouveau concept: « vectored immunoprophylaxis »

Vectored immunoprophylaxis protects humanized mice from mucosal HIV transmission

Alejandro B Balazs[1,4], Yong Ouyang[1], Christin M Hong[1,4], Joyce Chen[1], Steven M Nguyen[1], Dinesh S Rao[2], Dong Sung An[3] & David Baltimore[1]

nature medicine

- Souris humanisées (BLT -*bone marrow-liver-thymus*- hu mice).
- AAV-VRC07W *vs* AAV-luc.
- « Challenges » répétés par voie vaginale avec souche REJO.c (clone moléculaire infectieux « Transmitted /Founder » R5 virus).



A Balazs et al., Nature Medicine 2013, advance online pub.

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Remerciements:
Cohortes SEROCO & PRIMO, *patients et cliniciens.*
Christine ROUZIOUX & Marie-Laure CHAIX
Brigitte AUTRAN & Henri AGUT (Cohorte ALT)
Pascal POIGNARD & IAVI
NIH AIDS Research and Reference Reagent Program, Division of AIDS, NIAID