Nuovi approcci diagnostico-terapeutici ai linfomi in HIV

Novità nella terapia CAR-T: presente e futuro

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DIPARTIMENTO DI FISIOPATOLOGIA
MEDICO-CHIRURGICA E DEI TRAPIANTI

CENTRE FOR MACH
MultidisciplinAry ResearCh in Health Science

Disclosures

AB received speaker’s honoraria and fees for attending advisory boards from bioMérieux, Gilead, Janssen-Cilag, Nordic Pharma, Pfizer, Qiagen, SOBI, Takeda, ViiV, and received research grants from Gilead

HIV infection: where are we today?

Global HIV data

	2000	2005	2010	2021	2022
People living with HIV	26.6 million [22.6 million - 31.2 million]	28.9 million [24.5 million - 33.8 million]	31.5 million [26.7 million - 36.8 million]	38.7 million [32.8 million - 45.2 million]	39.0 million [33.1 million - 45.7 million]
New HIV Infections	2.8 million [2.2 million - 3.8 million]	2.5 million [1.9 million - 3.3 million]	2.1 million [1.6 million - 2.8 million]	1.4 million [1.1 million - 1.8 million]	1.3 million [1.0 million - 1.7 million]
New HIV Infections (Adults, aged 15+)	2.3 million [1.7 million - 3.1 million]	2.0 million [1.5 million - 2.6 million]	1.8 million [1.4 million - 2.4 million]	1.3 million [950 000 - 1.7 million]	1.2 million [900 000 - 1.6 million]
New HIV Infections (Children, aged 0-14)	530 000 [360 000 - 830 000]	480 000 [330 000 - 750 000]	310 000 [210 000 - 490 000]	140 000 [96 000 - 220 000]	130 000 [90 000 - 210 000]
AIDS-related deaths	1.7 million [1.3 million - 2.4 million]	2.0 million [1.5 million - 2.7 million]	1.3 million [970 000 - 1.8 million]	660 000 [500 000 - 920 000]	630 000 [480 000 - 880 000]

Source: UNAIDS 2023 epidemiological estimates.

In 2022, there were 39 million people living with HIV:

- 37.5 million adults(15 years or older)
- 1.5 million children(0–14years).

53% of all people living with HIV were women and girls

At the end of December 2022, 29.8 million people (76% of all people living with HIV) were accessing antiretroviral therapy, up from 7.7 million in 2010.

New HIV infections have been reduced by 59% since the peak in 1995.

AIDS-related deaths have been reduced by 69% since the peak in 2004 and by 51% since 2010.

HIV infection: where are we today?

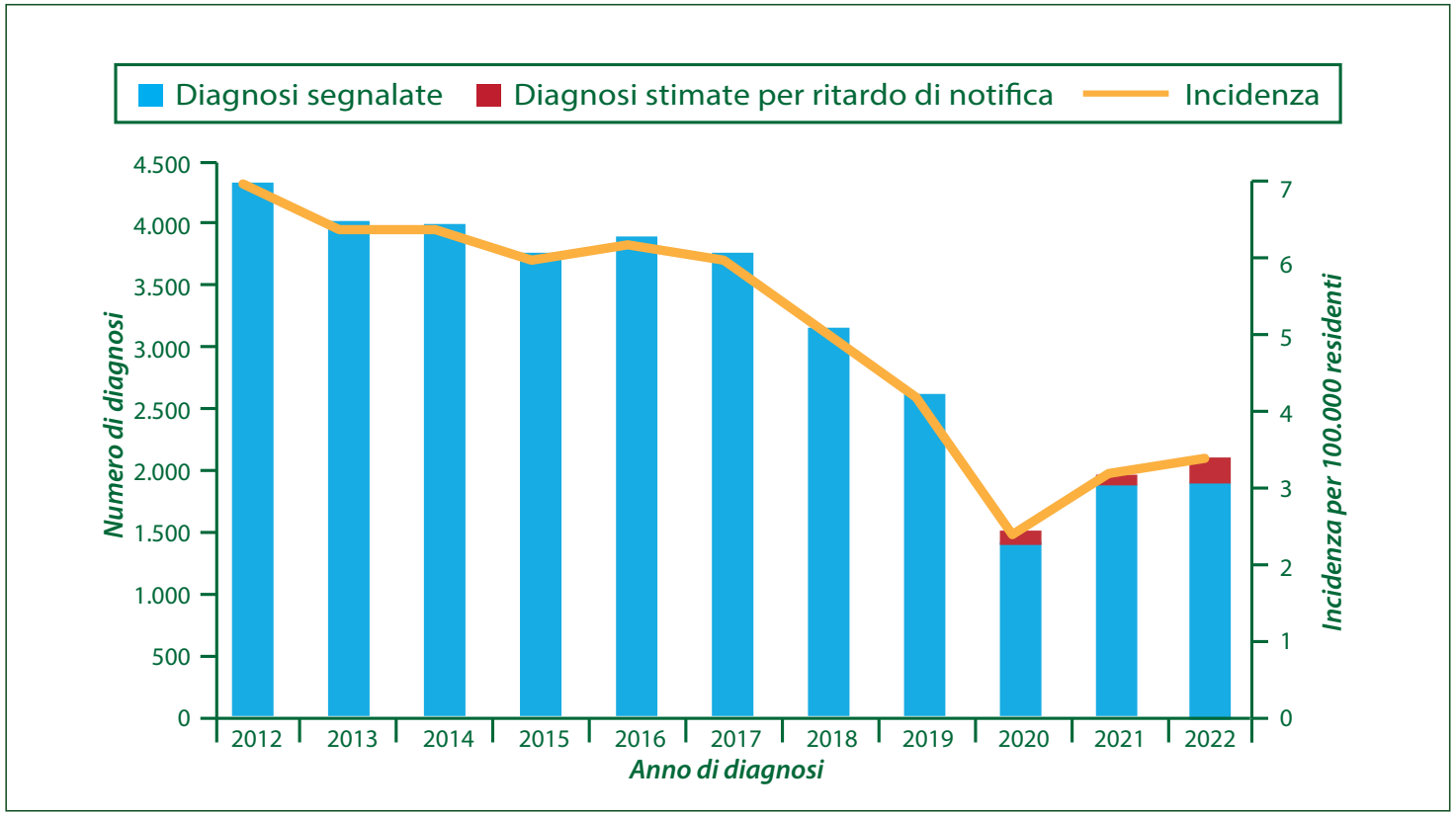
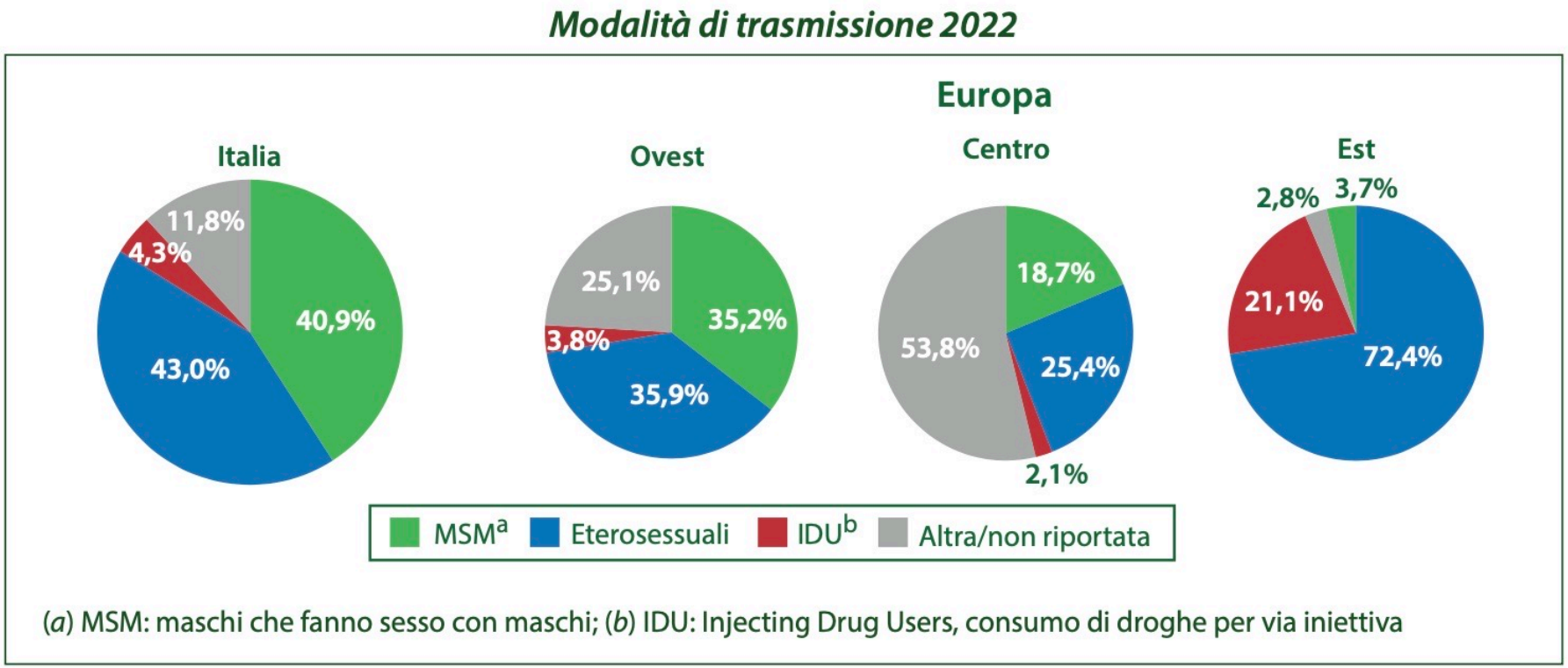


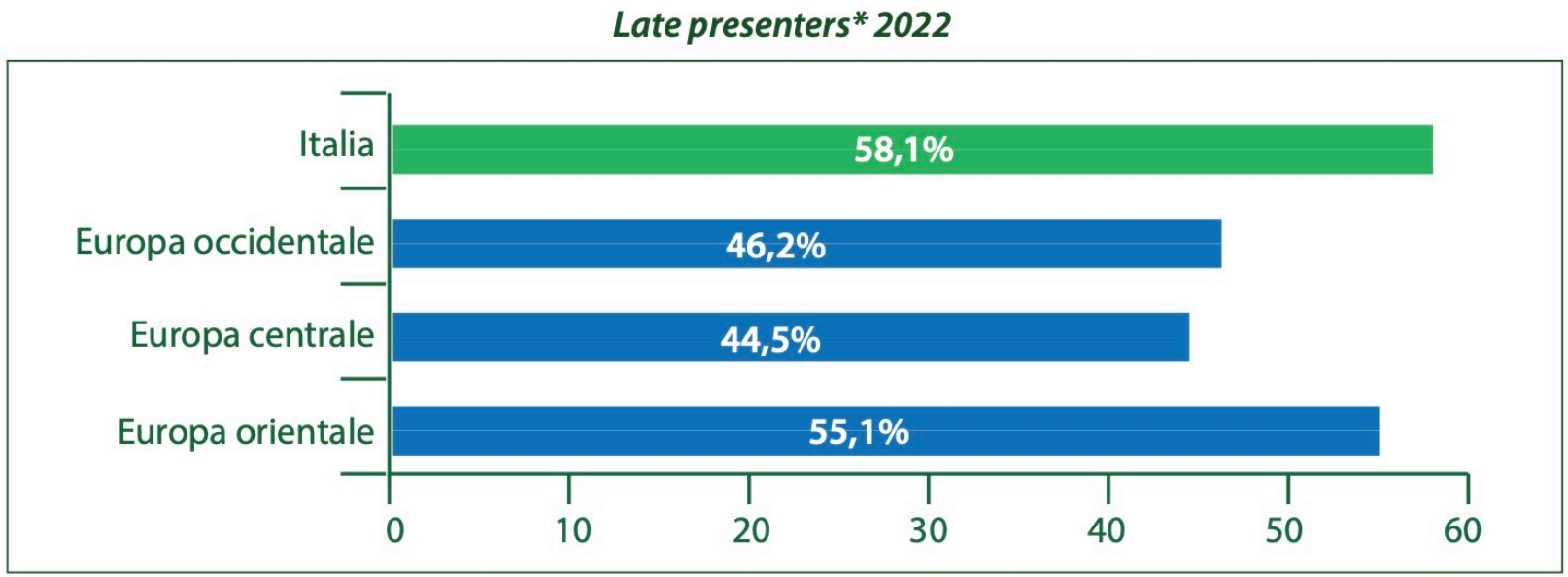
Figura 1 - Nuove diagnosi di infezione da HIV e incidenze corrette per ritardo di notifica (2012-2022)

HIV infection: where are we today?



Distribuzione percentuale delle nuove diagnosi di infezione da HIV per modalità di trasmissione 2022.
Fonti: Sistema di Sorveglianza HIV nazionale, *ECDC/WHO. HIV/AIDS Surveillance in Europe 2023-2022 data (1)*

HIV infection: where are we today?



(*) Late presenters: nuove diagnosi di infezione da HIV con numero di linfociti CD4 <350 cell/µl.
Fonti: Sistema di Sorveglianza HIV nazionale, *ECDC/WHO. HIV/AIDS Surveillance in Europe 2023-2022 data (1)*

Not Ist Super Sanità 2023;36(11)

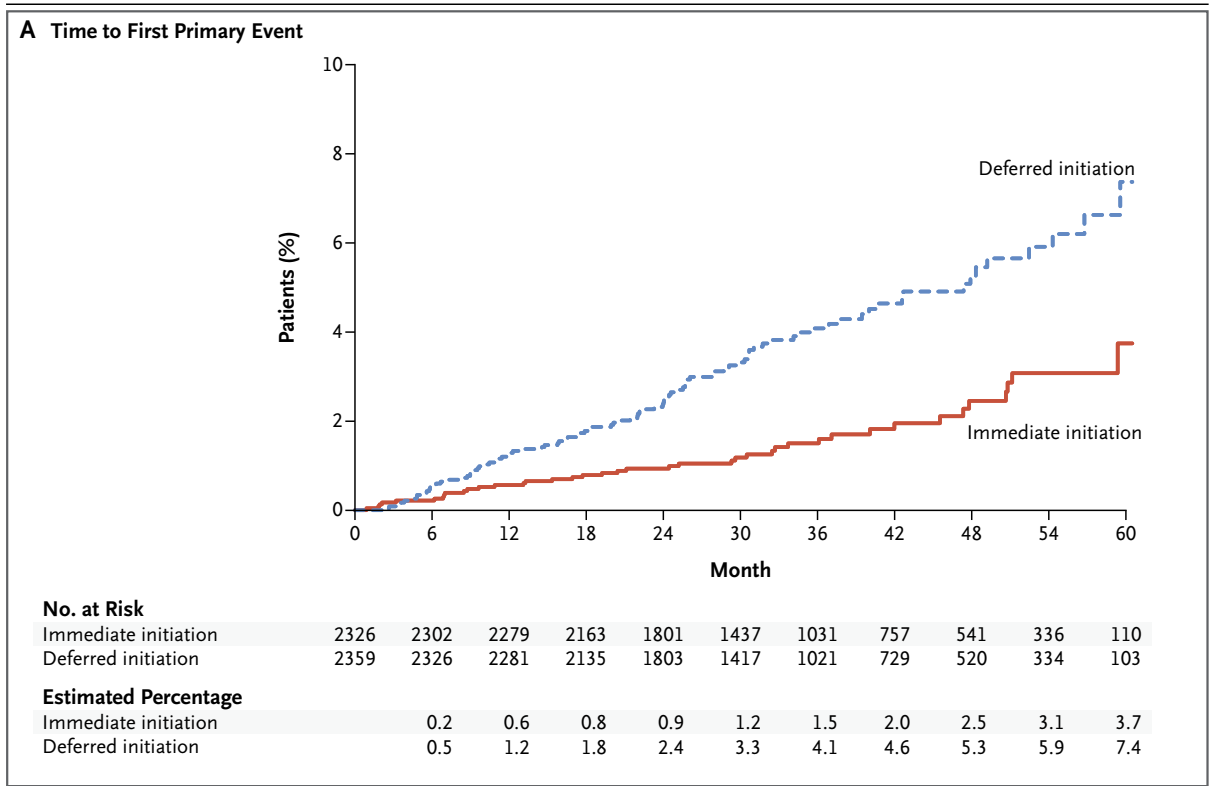
Management of HIV infection in 2024

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

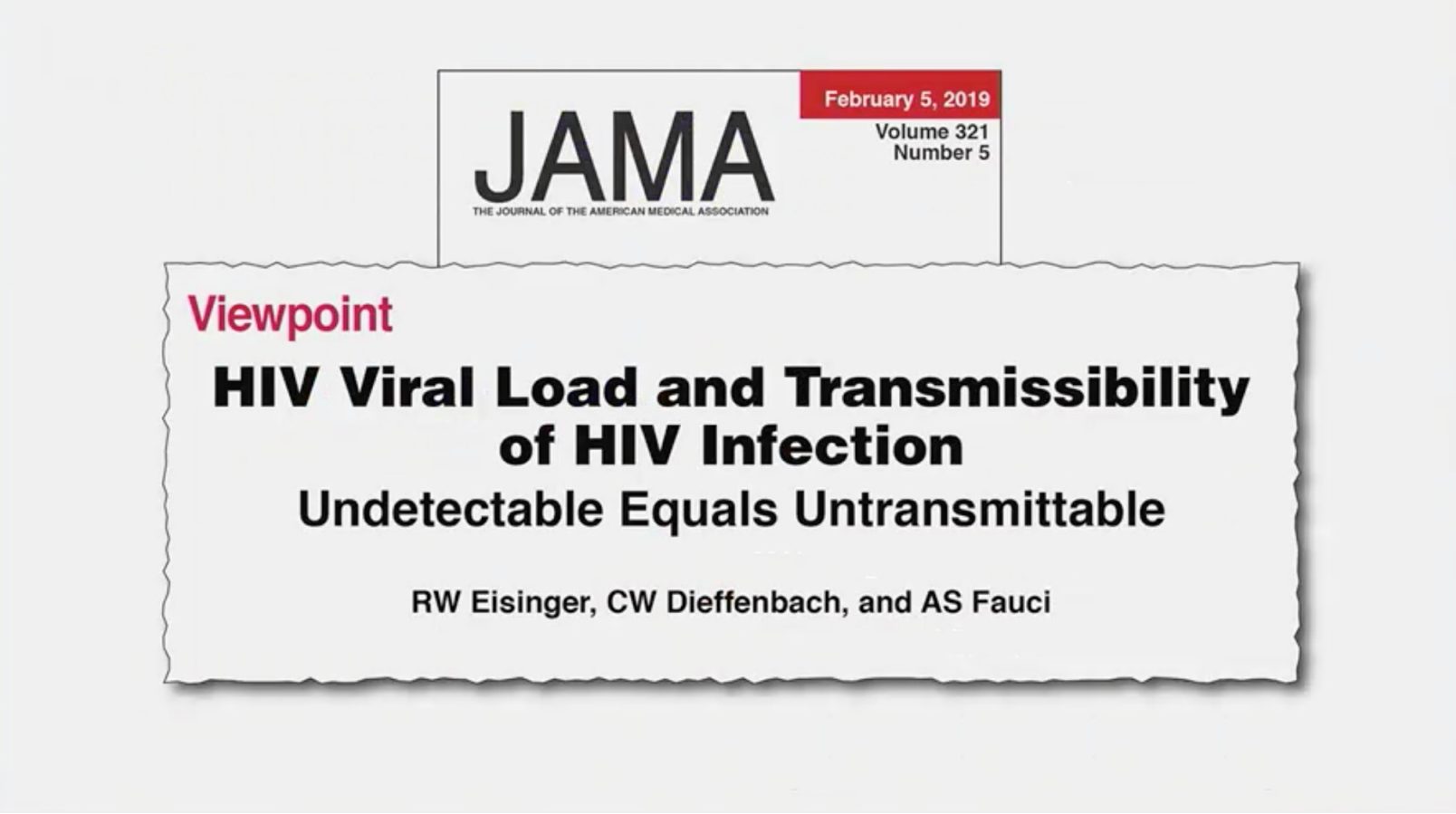


No. at Risk											
Immediate initiation	2326	2302	2279	2163	1801	1437	1031	757	541	336	110
Deferred initiation	2359	2326	2281	2135	1803	1417	1021	729	520	334	103
Estimated Percentage											
Immediate initiation		0.2	0.6	0.8	0.9	1.2	1.5	2.0	2.5	3.1	3.7
Deferred initiation		0.5	1.2	1.8	2.4	3.3	4.1	4.6	5.3	5.9	7.4

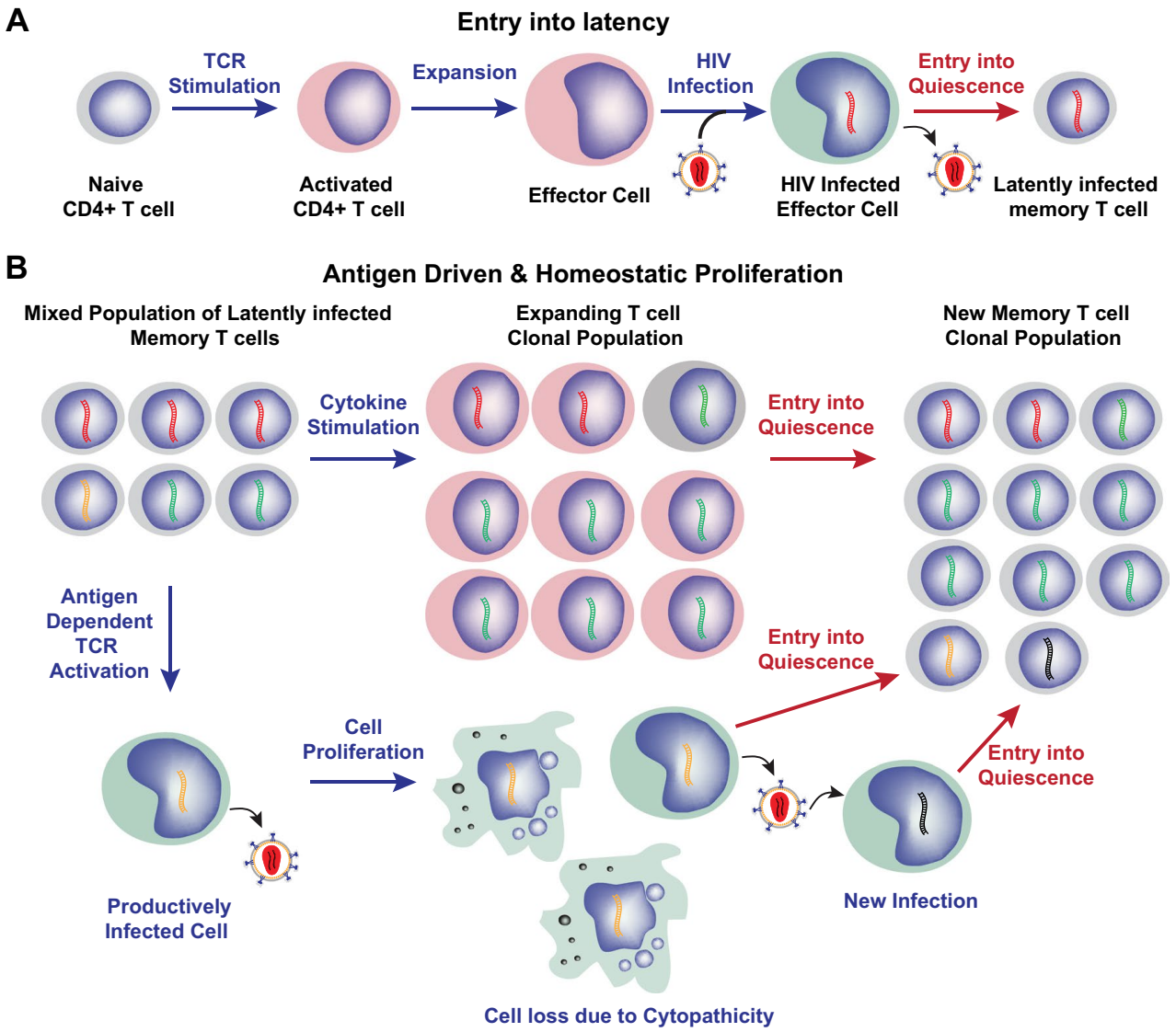
ART is the cornerstone of HIV care and should be initiated at or close to diagnosis.
There are 4 initial combination regimens for antiretroviral-naive patients and several others that can be used in certain clinical scenarios, which allows individualization of treatment.

Short- and long-term adverse effects and drug–drug interactions can be managed proactively.

Management of HIV infection in 2024

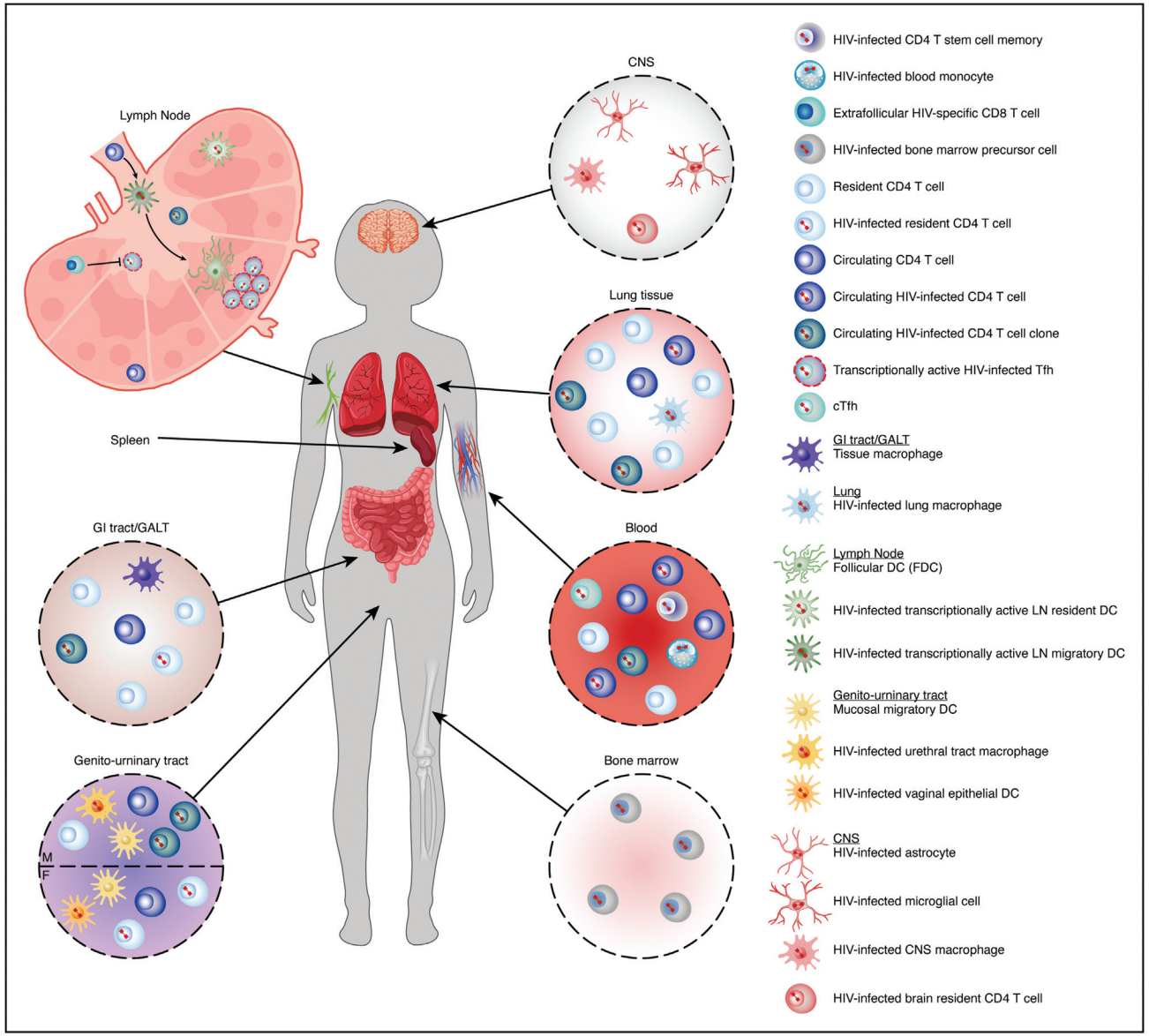


The cell biology of HIV-1 latency and rebound



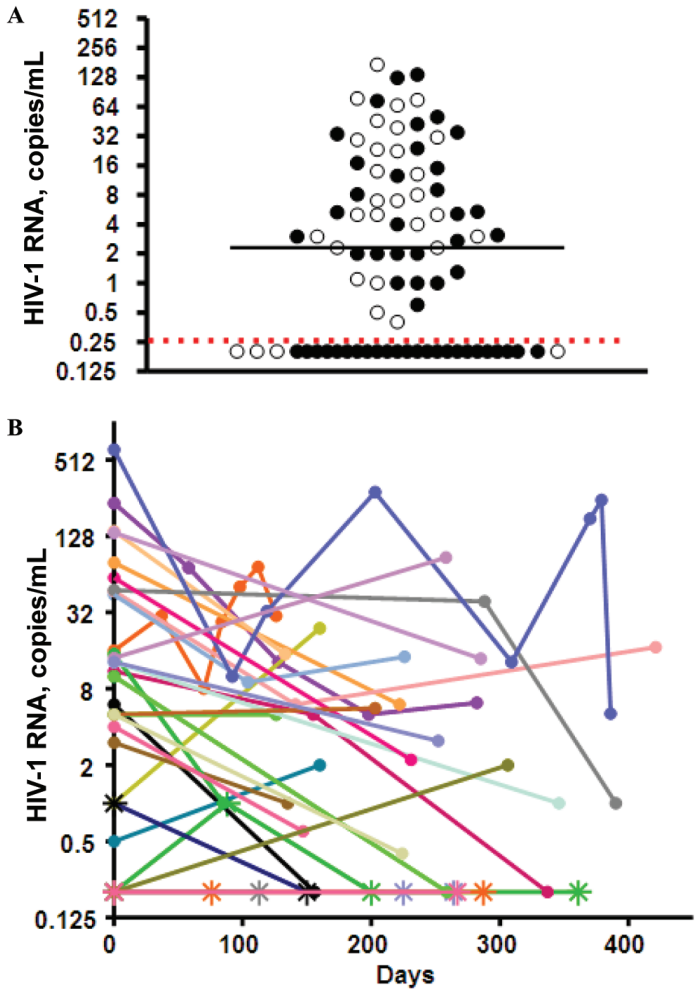
Mbonye, Retrovirology 2024

HIV tissue reservoirs

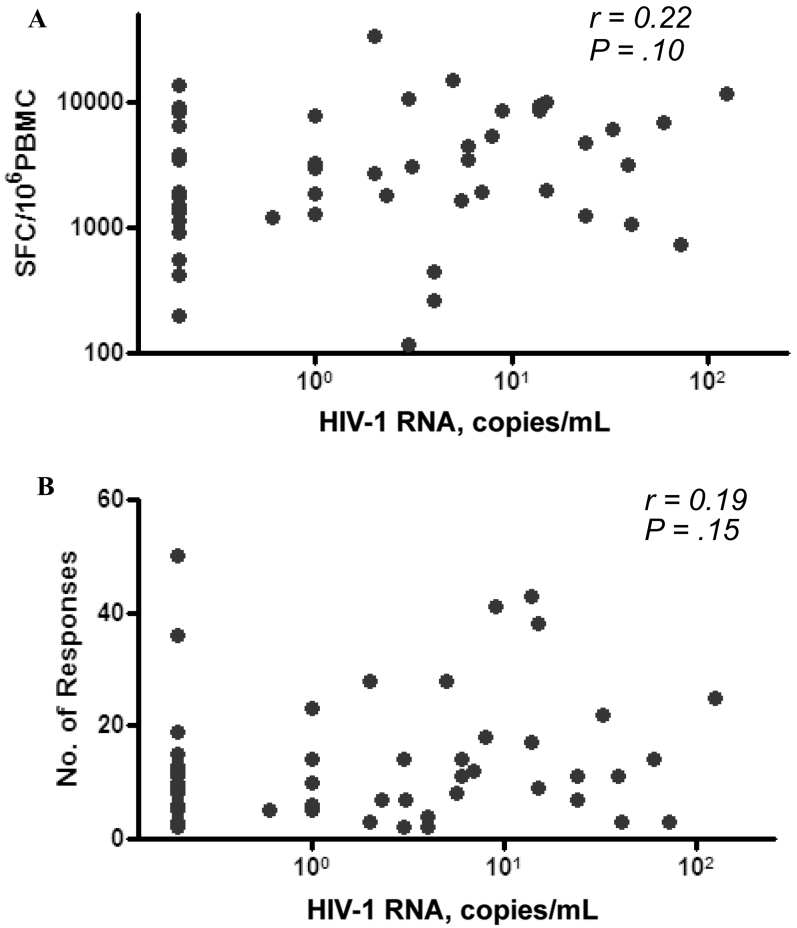


Banga R, Curr Opin HIV AIDS 2024

Models of HIV functional cure



Plasma HIV-1 RNA in elite controllers



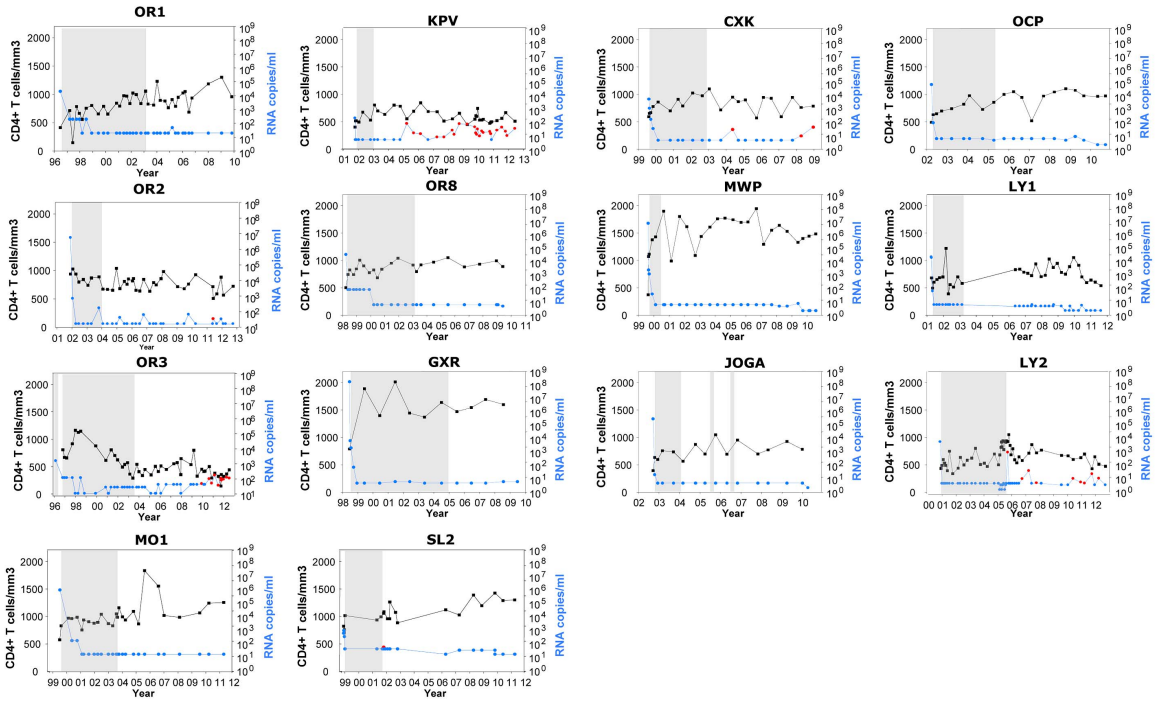
CD8+ T cell responses in elite controllers

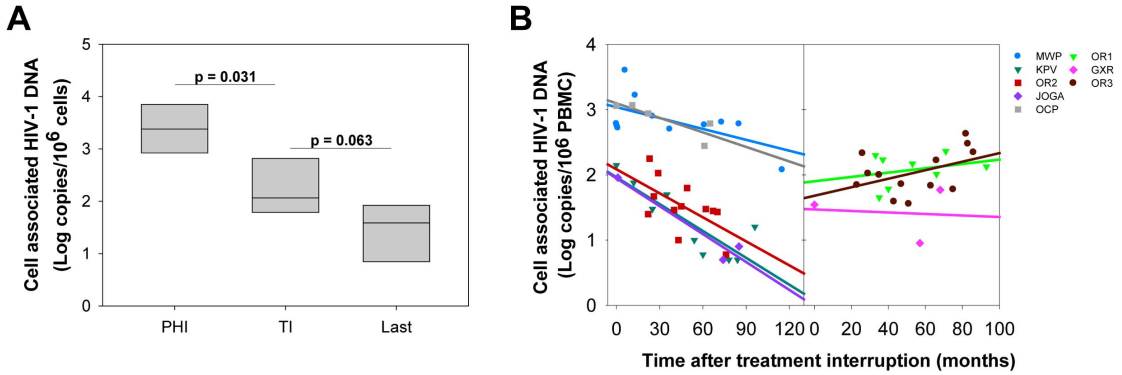
Pereyra F, J Infect Dis 2009

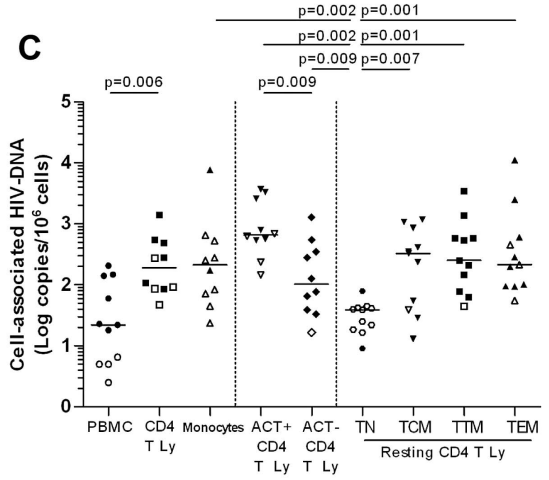
Models of HIV functional cure

Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

Asier Sáez-Cirión[1]*, Charline Bacchus[2], Laurent Hocqueloux[3], Véronique Avettand-Fenoel[4,5], Isabelle Girault[6], Camille Lecuroux[6], Valerie Potard[7,8], Pierre Versmisse[1], Adeline Melard[4], Thierry Prazuck[3], Benjamin Descours[2], Julien Guergnon[2], Jean-Paul Viard[5,9], Faroudy Boufassa[10], Olivier Lambotte[6,11], Cécile Goujard[10,11], Laurence Meyer[10,12], Dominique Costagliola[7,8,13], Alain Venet[6], Gianfranco Pancino[1], Brigitte Autran[2], Christine Rouzioux[4,5]*, the ANRS VISCONTI Study Group[¶]





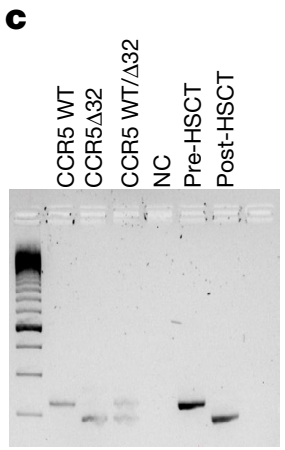


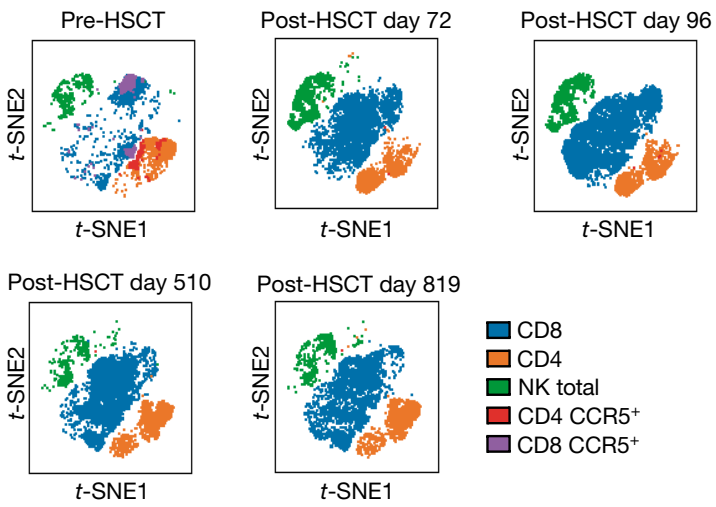
Plos Pahog 2013

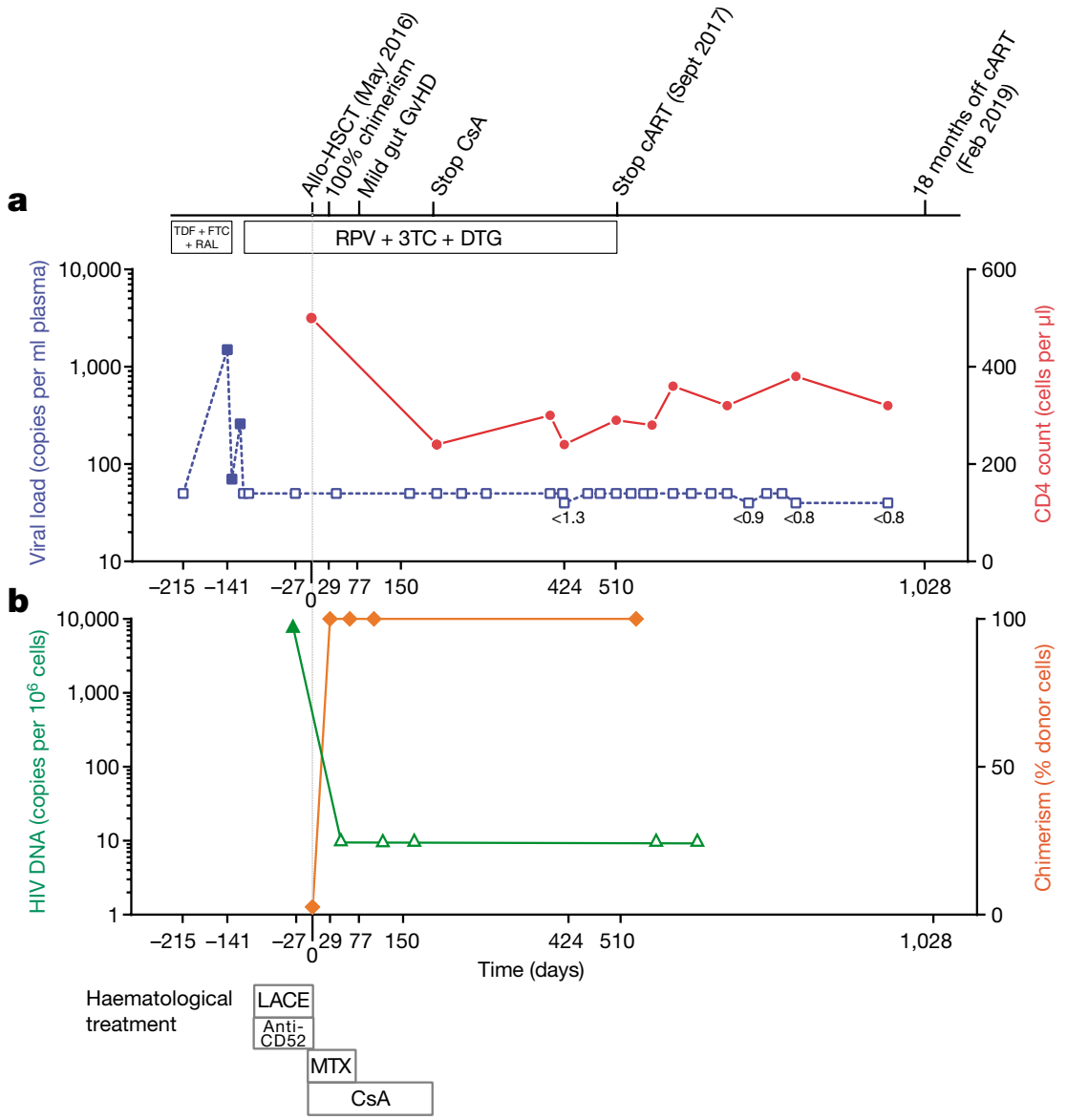
Models of HIV sterilizing cure

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

Ravindra K. Gupta[1,2,3,4,5]*, Sultan Abdul-Jawad[1], Laura E. McCoy[1], Hoi Ping Mok[4], Dimitra Peppa[3,6], Maria Salgado[7], Javier Martinez-Picado[7,8,9], Monique Nijhuis[10], Annemarie M. J. Wensing[10], Helen Lee[11], Paul Grant[12], Eleni Nastouli[12], Jonathan Lambert[13], Matthew Pace[6], Fanny Salasc[4], Christopher Monit[1], Andrew J. Innes[14,15], Luke Muir[1], Laura Waters[3], John Frater[6,16], Andrew M. L. Lever[4,17], Simon G. Edwards[3], Ian H. Gabriel[14,15,18,19] & Eduardo Olavarria[14,15,19]







Blood 2019

Models of HIV sterilizing cure

Timothy Brown

Adam Castillejo

Berlin/London HIV⁺ Malignancy Patients

↓

HLA-matched, **CCR5$^{\Delta 32/\Delta 32}$**
bone marrow donor

↓

Conditioning Regimen

↓

Allogeneic CCR5$^{\Delta 32/\Delta 32}$ stem cell transplant

↓

Withdrawal of ART

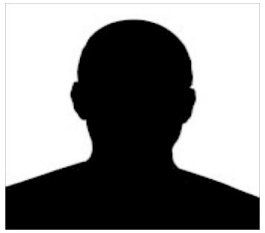
↓

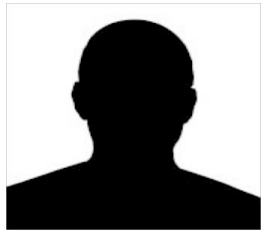
Sustained ART-free HIV remission

Düssel-dorf Patient

New York Patient

Gary Steinkohl





Boston/Minneapolis HIV⁺ Malignancy Patients

↓

HLA-matched, **CCR5$^{wt/wt}$**
bone marrow donor

↓

Conditioning Regimen

↓

Allogeneic CCR5$^{wt/wt}$ stem cell transplant

↓

Withdrawal of ART

↓

HIV-free for 12/32/41 weeks, followed by viral rebound

City of Hope Patient

Peterson, C.W. SHIV Reservoirs Persist Following CAR T Cell-Mediated Depletion of B Cell Follicles in Nonhuman Primates. In Proceedings of the AIDS 2022, Montreal, QC, Canada, 29 July–2 August 2022.

Models of HIV sterilizing cure

ORIGINAL RESEARCH

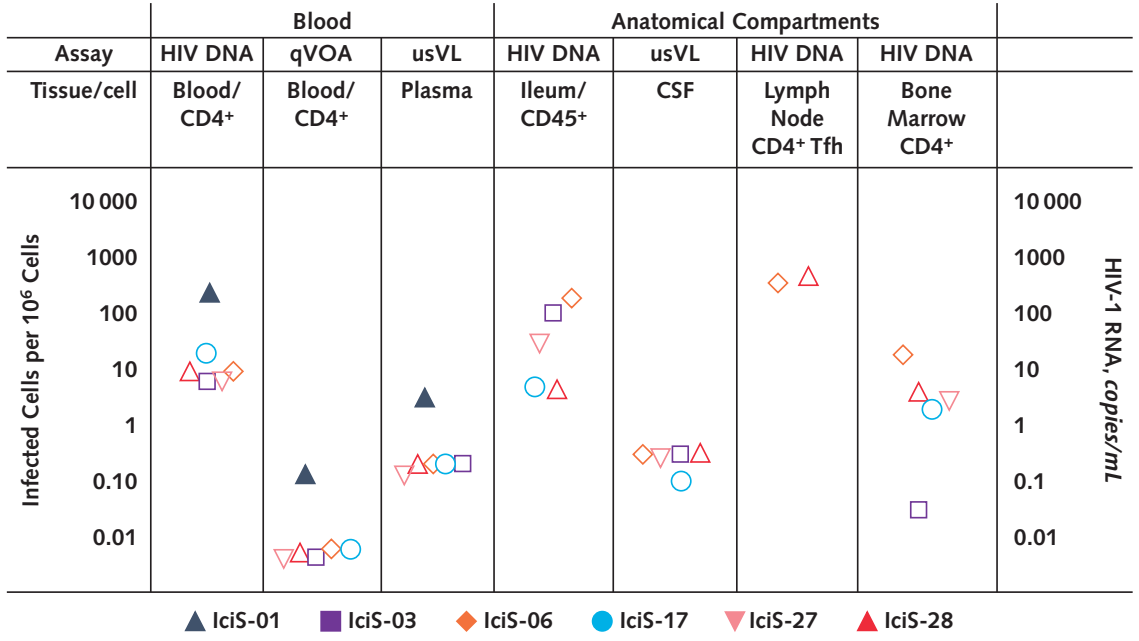
Annals of Internal Medicine

Mechanisms That Contribute to a Profound Reduction of the HIV-1 Reservoir After Allogeneic Stem Cell Transplant

Maria Salgado, PhD*; Mi Kwon, MD*; Cristina Gálvez, MS; Jon Badiola, MD; Monique Nijhuis, PhD; Alessandra Bandera, MD, PhD; Pascual Balsalobre, PhD; Pilar Miralles, MD; Ismael Buño, PhD; Carolina Martinez-Laperche, PhD; Cristina Vilaplana, MD, PhD; Manuel Jurado, MD, PhD; Bonaventura Clotet, MD, PhD; Annemarie Wensing, MD; Javier Martinez-Picado, PhD†; and Jose Luis Diez-Martin, MD, PhD†; for the IciStem Consortium‡

Ann Intern Med. 2018;

Figure 1. HIV reservoirs measured in blood and tissues after transplant.



Data are from the last collected sample for each patient. Open symbols represent undetectable values (only IciS-01 had detectable values). In those cases, the limit of detection for the sample varied on the basis of cell/volume input, and that value is represented. CSF = cerebrospinal fluid; qVOA = quantitative viral outgrowth assay; Tfh = T-follicular helper cells; usVL = ultrasensitive viral load.

Models of HIV sterilizing cure

ORIGINAL RESEARCH

Annals of Internal Medicine

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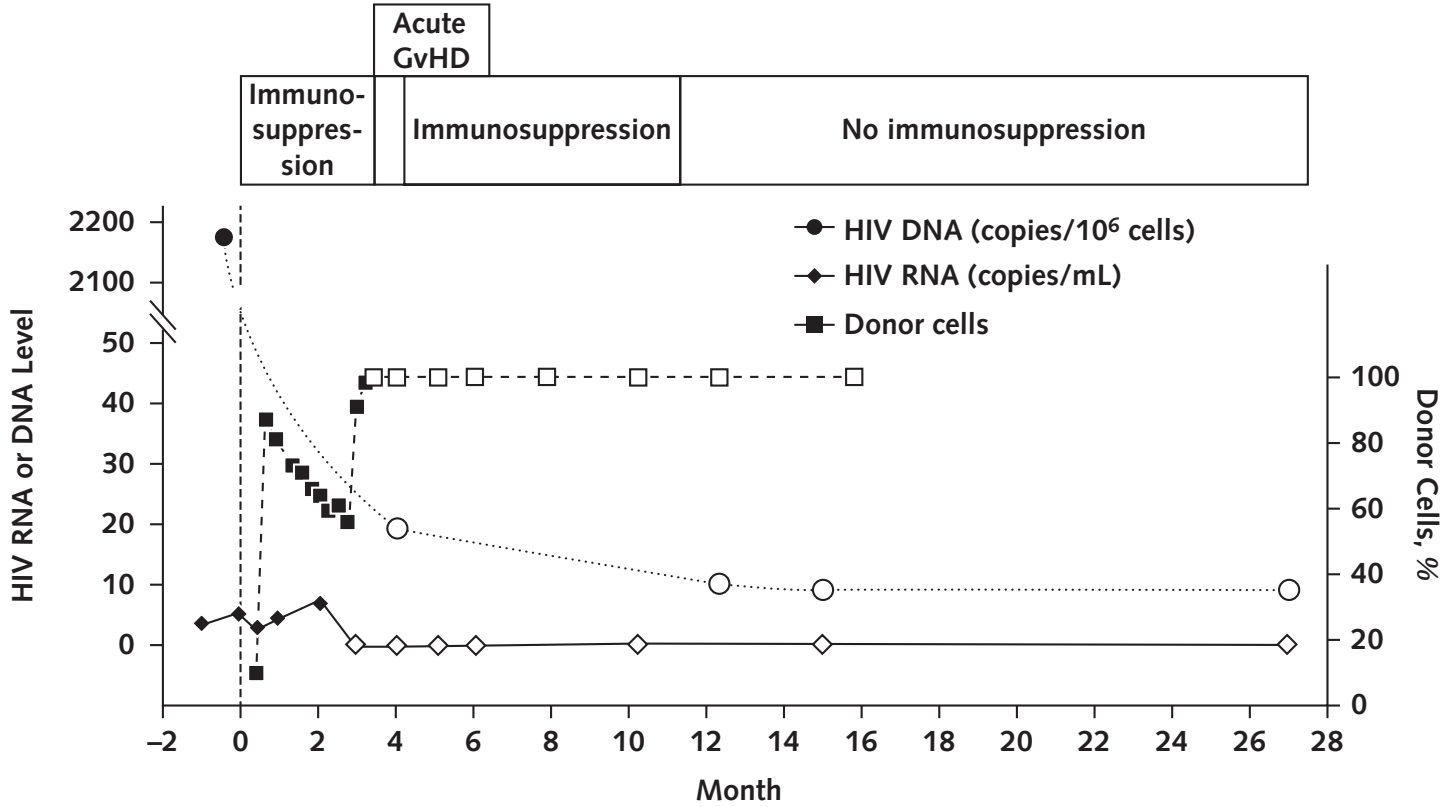

Models of HIV sterilizing cure

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Ann Intern Med. 2018;

«To achieve the goal of a sterilizing cure, therefore, an approach is needed that can mimic the alloreactivity that reduces the HIV reservoir but is implemented in a context outside of a high-risk procedure such as the allo-HSCT.»

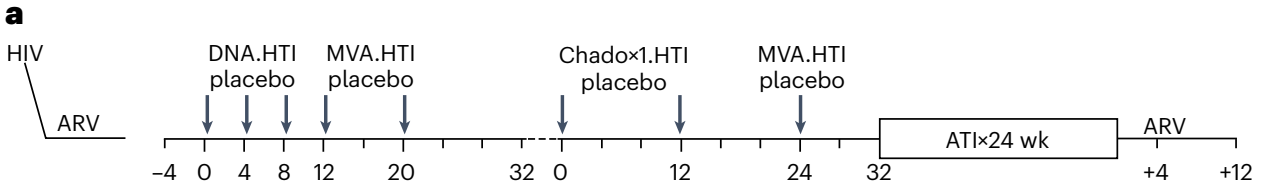
Therapeutic vaccination strategies

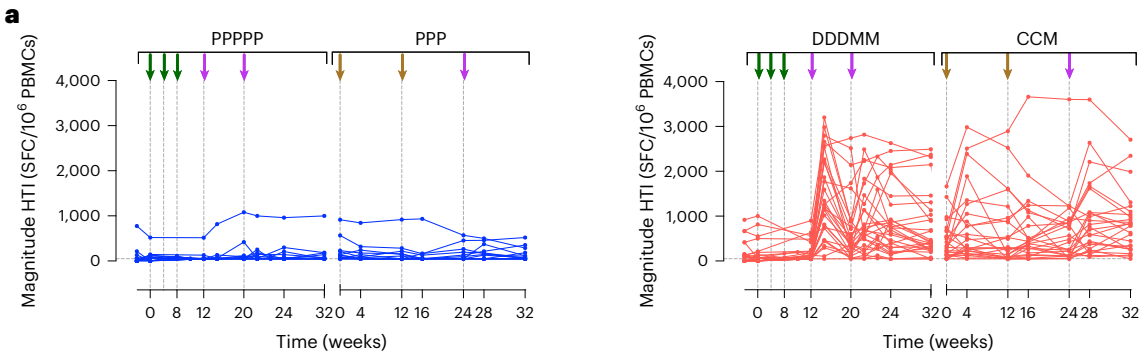
nature medicine

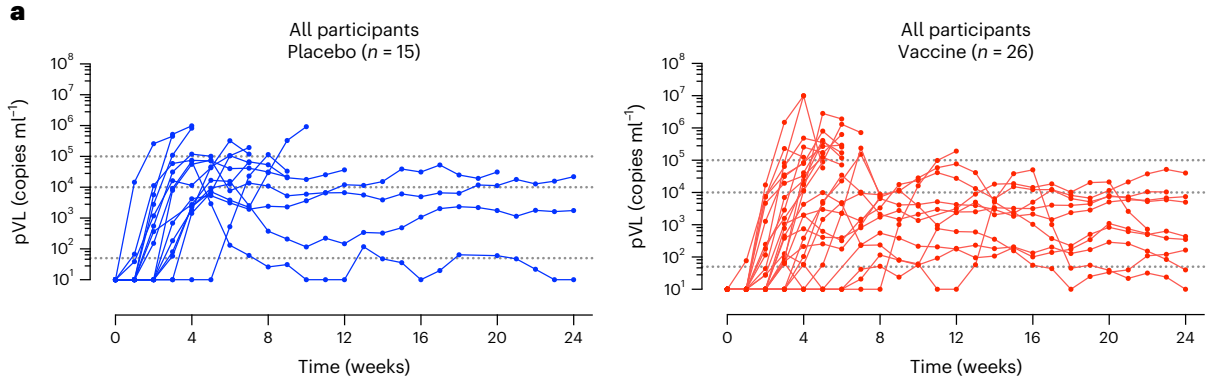
Article

https://doi.org/10.1038/s41591-022-02060-2

Safety, immunogenicity and effect on viral rebound of HTI vaccines in early treated HIV-1 infection: a randomized, placebo-controlled phase 1 trial







Immune checkpoint inhibitors in HIV

Article

Enhancement of Antiviral CD8+ T-Cell Responses and Complete Remission of Metastatic Melanoma in an HIV-1-Infected Subject Treated with Pembrolizumab

Oscar Blanch-Lombarte [1,2,†], Cristina Gálvez [1,2,†], Boris Revollo [3], Esther Jiménez-Moyano [1], Josep M. Llibre [3], José Luís Manzano [4], Aram Boada [2,5], Judith Dalmau [1], Daniel E. Speiser [6], Bonaventura Clotet [1,2,3,7], Julia G. Prado [1,8,*] and Javier Martinez-Picado [1,7,8,9,*]

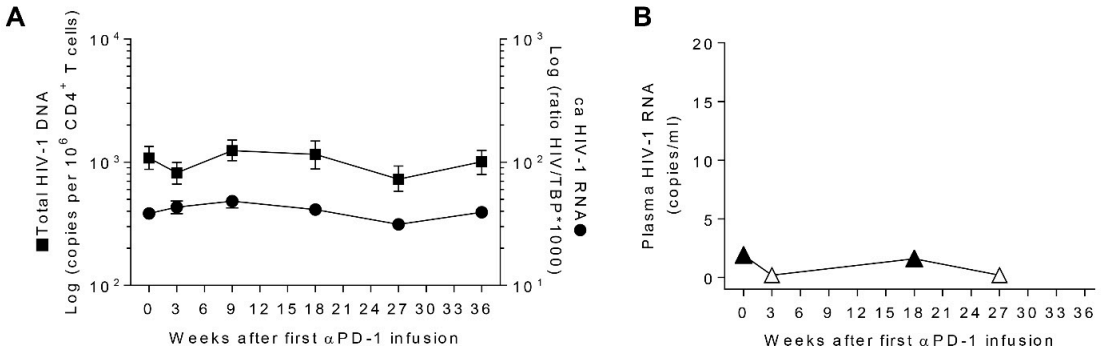
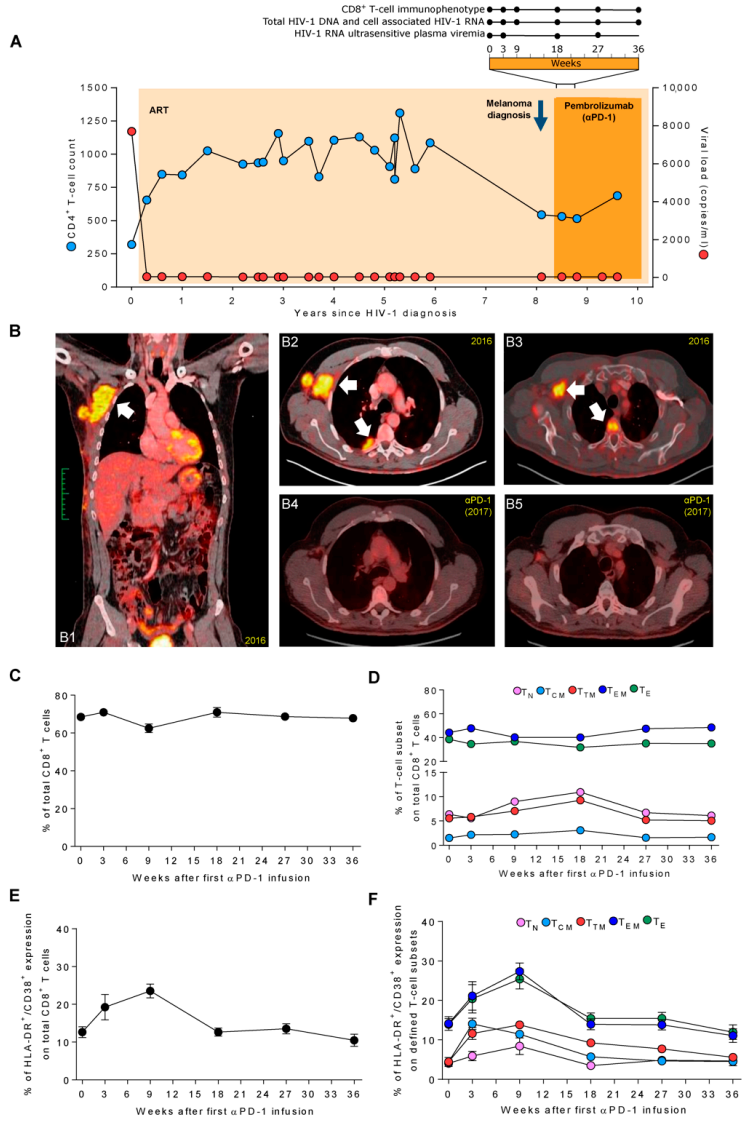
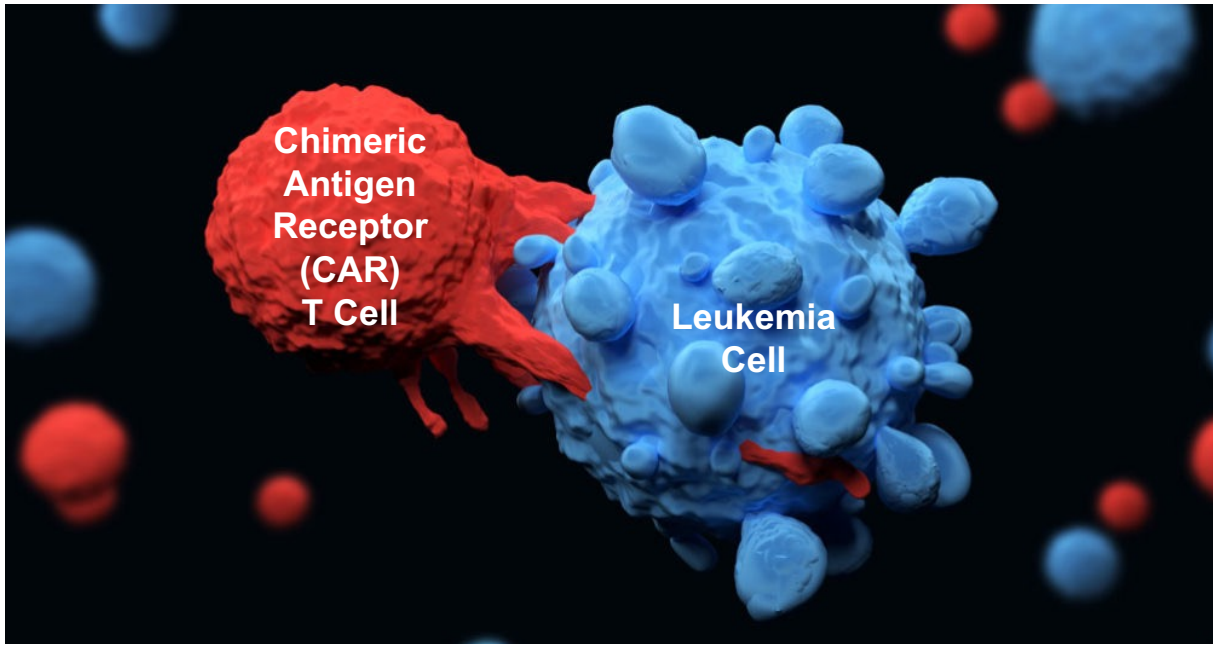


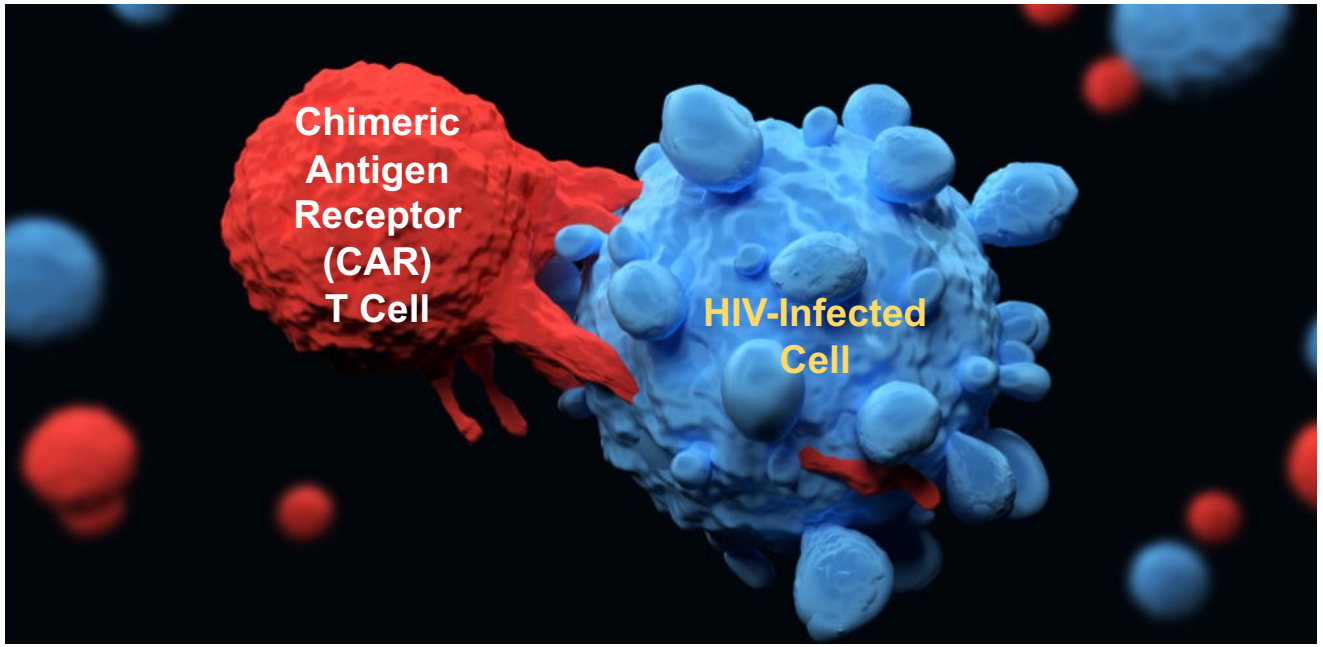
Figure 3. Longitudinal analysis of HIV-1 reservoir during pembrolizumab administration; (**A**) Total HIV-1 DNA (squares) and cell-associated HIV-1 RNA (circles) in CD4+ T cells, measured by ddPCR; (**B**) ultrasensitive viral load in plasma (triangles). Open symbols represent determinations below the limit of quantification.



J. Clin. Med. **2019**, *8*, 2089; doi:10.3390/jcm8122089

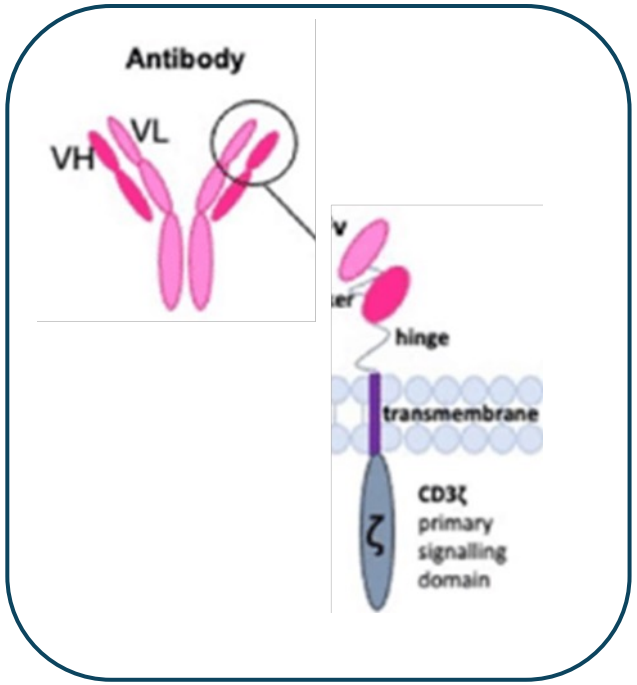
CAR T cells in HIV

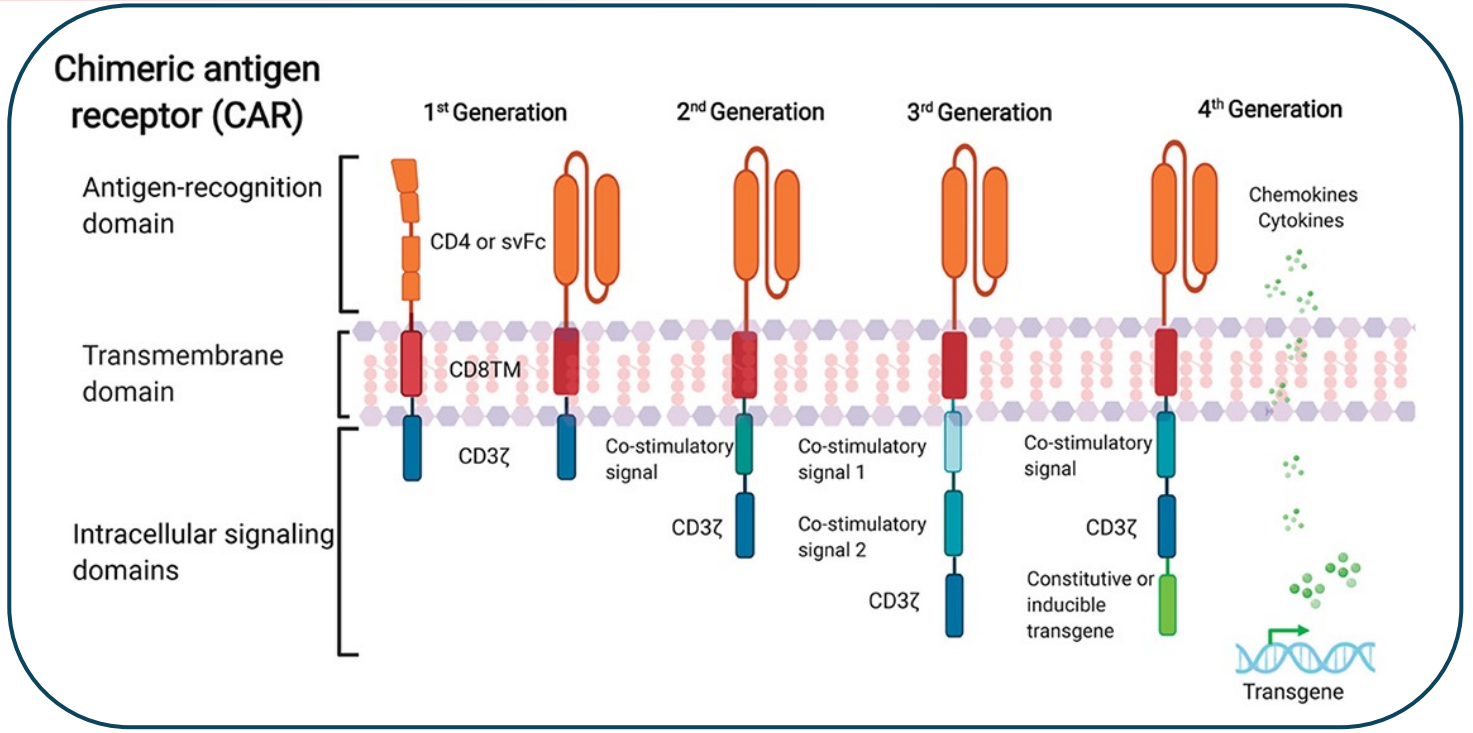


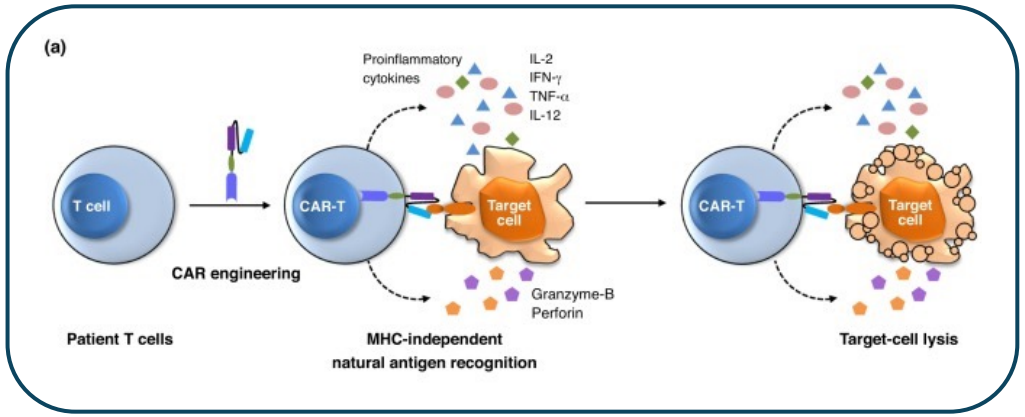


Peterson, C.W. SHIV Reservoirs Persist Following CAR T Cell-Mediated Depletion of B Cell Follicles in Nonhuman Primates. In Proceedings of the AIDS 2022, Montreal, QC, Canada, 29 July–2 August 2022.

CAR T cells in HIV







Bingfeng Liu, 2019; Mu W, 2020

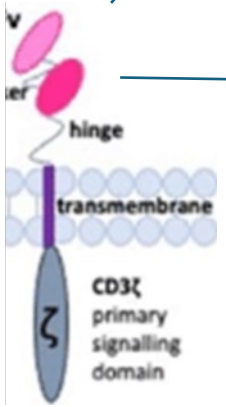
CAR T cells in HIV

CD4-based

extracellular domain of CD4 → Viral mutants are unlikely to escape CD4-based CAR because of a substantial replicative fitness cost

Failure

CD4z-CAR cells can be infected by HIV-1 → Co-expression of HIV-1 fusion inhibitors



scFv-based

single-chain variable fragments (scFvs) derived from bNAbs → HIV-1 bNAb-derived scFvs have a **stronger binding affinity** to gp120 subunit than the CD4 moiety

→ the interaction between the bNAb-derived scFv and gp120 did not lead to fusion of viral membrane with cell membrane, **thus reducing the ability of the virus to enter the modified CD8+ T lymphocytes**

Failure

A single infusion of bNAb-based CAR T cells only resulted in transient viral suppression for a few weeks, associated with the **relatively rapid emergence of escape variants** in HIV-infected individuals

to improve their efficacy → **Multispecific CAR**

Courtesy of Chiara Agrati

S.G. Deeks, B. 2002; R.T. Mitsuyasu, P.A. 2000; M. Hale, 2017; A. Ali, 2016; M.S. Pampusch, 2022; C.R. Maldini, 2020; M. Guan, 2022; B. Liu, 2021; L. Liu, 2015; K. Anthony-Gonda, 201
E.K. Cartwright, M.S. 2022;

CAR-T cells immunotherapy in HIV cure

A Phase II Randomized Study of HIV-Specific T-Cell Gene Therapy in Subjects with Undetectable Plasma Viremia on Combination Antiretroviral Therapy

Steven G. Deeks,[1] Bridget Wagner,[2] Peter A. Anton,[3] Ronald T. Mitsuyasu,[3] David T. Scadden,[4] Christine Huang,[5] Catherine Macken,[6] Douglas D. Richman,[7] Cindy Christopherson,[8] Carl H. June,[9] Richard Lazar,[10] David F. Broad,[10] Sayeh Jalali,[10] and Kristen M. Hege[10,*]

Phase II randomized trial of CD4 gene–modified versus unmodified T cells in 40 HIV-infected subjects on HAART with plasma viral loads < 50 copies/ml.
Serial analyses of residual blood and tissue HIV reservoirs were done for 6 months postinfusion.

No significant between-group differences were noted in viral reservoirs following therapy.
Infusion of gene-modified, but not unmodified, T cells was associated with a decrease from baseline in HIV burden in two of four reservoir assays and a trend toward fewer patients with recurrent viremia

TABLE 1: Baseline characteristics of patients in HIV-specific T-cell gene therapy study groups

Characteristic	Gene modified (n = 20)	Unmodified (N = 20)	P[a]
Gender			
Male	20	20	
Female	0	0	
Age (years)			
Mean	39	43	0.18
Range	(28, 54)	(28, 59)	
HIV infection (Years)			
Mean	7.2	6.8	0.76
Range	(1.2, 15)	(1.5,18)	
HAART therapy (Years)			
Mean	1.5	1.7	0.27
Range	(0.4, 3.0)	(0.6, 3.0)	
$CD4^+$ count ($cells/mm^3$)			
Mean	409	435	0.60
95% CI[b]	(345, 474)	(366,505)	
HIV coculture (log_{10} IUPM[c])			
Mean	1.67	1.65	0.91
95% CI	(1.44, 1.90)	(1.49, 1.82)	
Percentage detectable at baseline	75	100	
HIV DNA blood (log_{10} copies/μg DNA)			
Mean	–0.79	–0.77	0.92
95% CI	(–1.08, –0.51)	(–0.96, –0.59)	
Percentage detectable at baseline	90	100	
HIV DNA rectal (log_{10} copies/10^6 cells)			
Mean	2.48	2.36	0.59
95% CI	(2.21, 2.75)	(2.03, 2.69)	
Percentage detectable at baseline	100	90	
HIV RNA rectal (log_{10} copies/μg mRNA)			
Mean	1.41	1.40	0.97
95% CI	(1.10, 1.72)	(1.14, 1.66)	
Percentage detectable at baseline	65	65	

[a] P, test of significance (Wilcoxon).
[b] CI, confidence interval.
[c] IUPM, infectious units per million.

Mol Ther 2002

Avoiding CAR-T cells infection by HIV

Broadly neutralizing antibody–derived CAR T cells reduce viral reservoir in individuals infected with HIV-1

Bingfeng Liu,[1,2] Wanying Zhang,[1] Baijin Xia,[1] Shuliang Jing,[1] Yingying Du,[1] Fan Zou,[1,3] Rong Li,[1] Lijuan Lu,[1] Shaozhen Chen,[2] Yonghong Li,[2] Qifei Hu,[3] Yingtong Lin,[1] Yiwen Zhang,[1] Zhangping He,[1] Xu Zhang,[1] Xiejie Chen,[2] Tao Peng,[4] Xiaoping Tang,[2] Weiping Cai,[2] Ting Pan,[1] Linghua Li,[2] and Hui Zhang[1]

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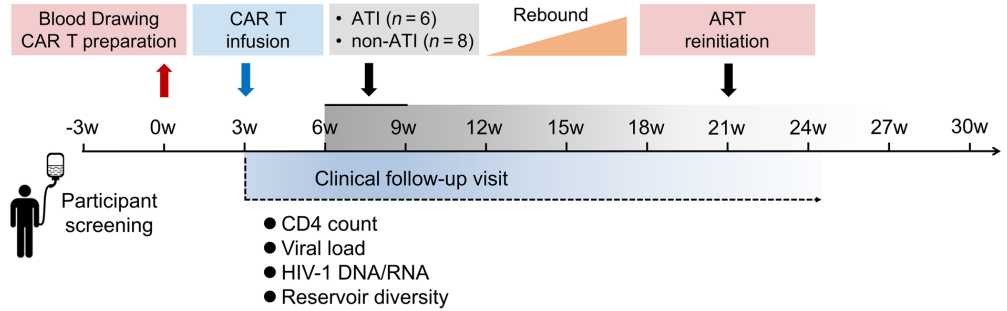
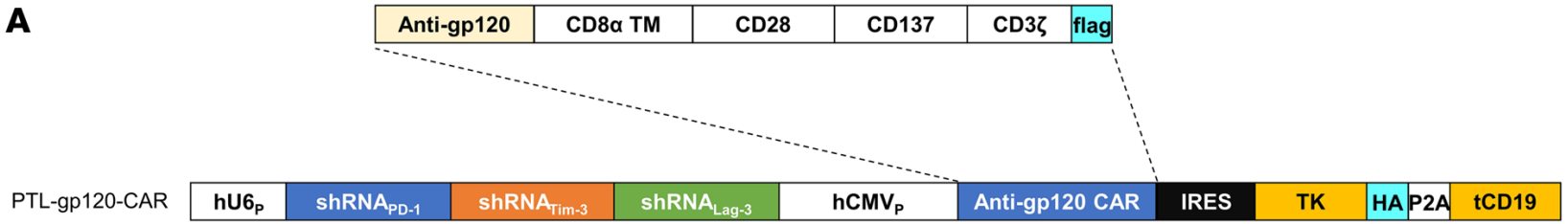
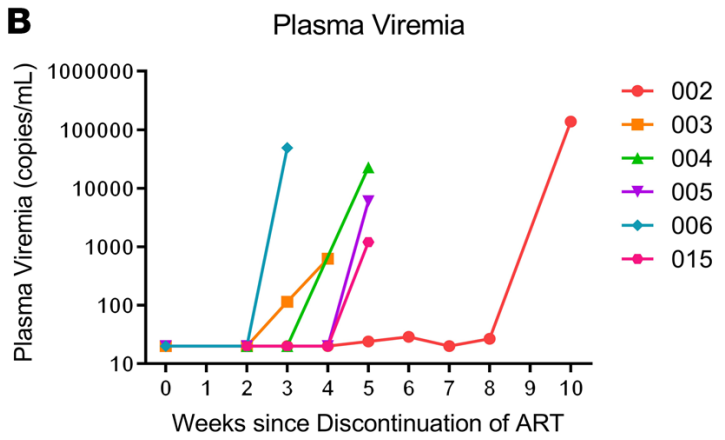
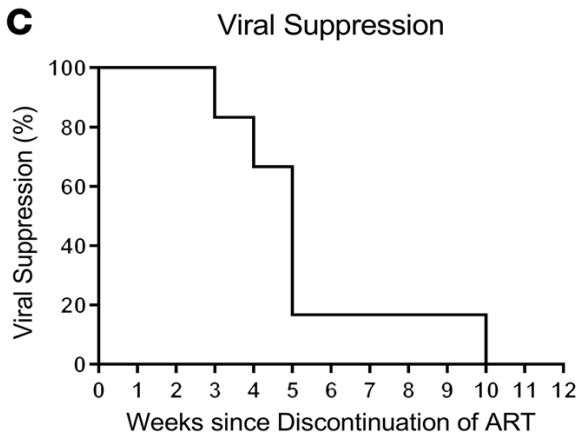








J Clin Invest. 2021;131(19):e150211

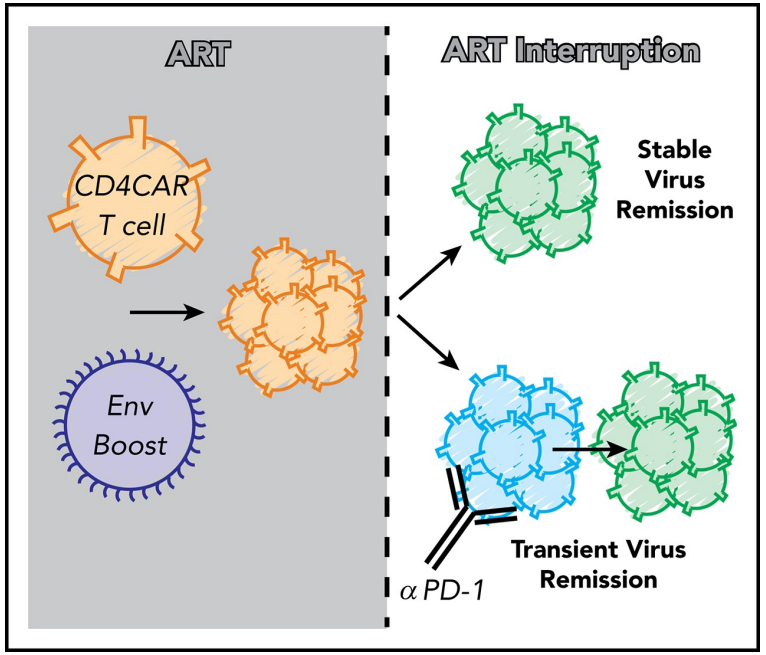
Avoiding CAR-T cells infection by HIV

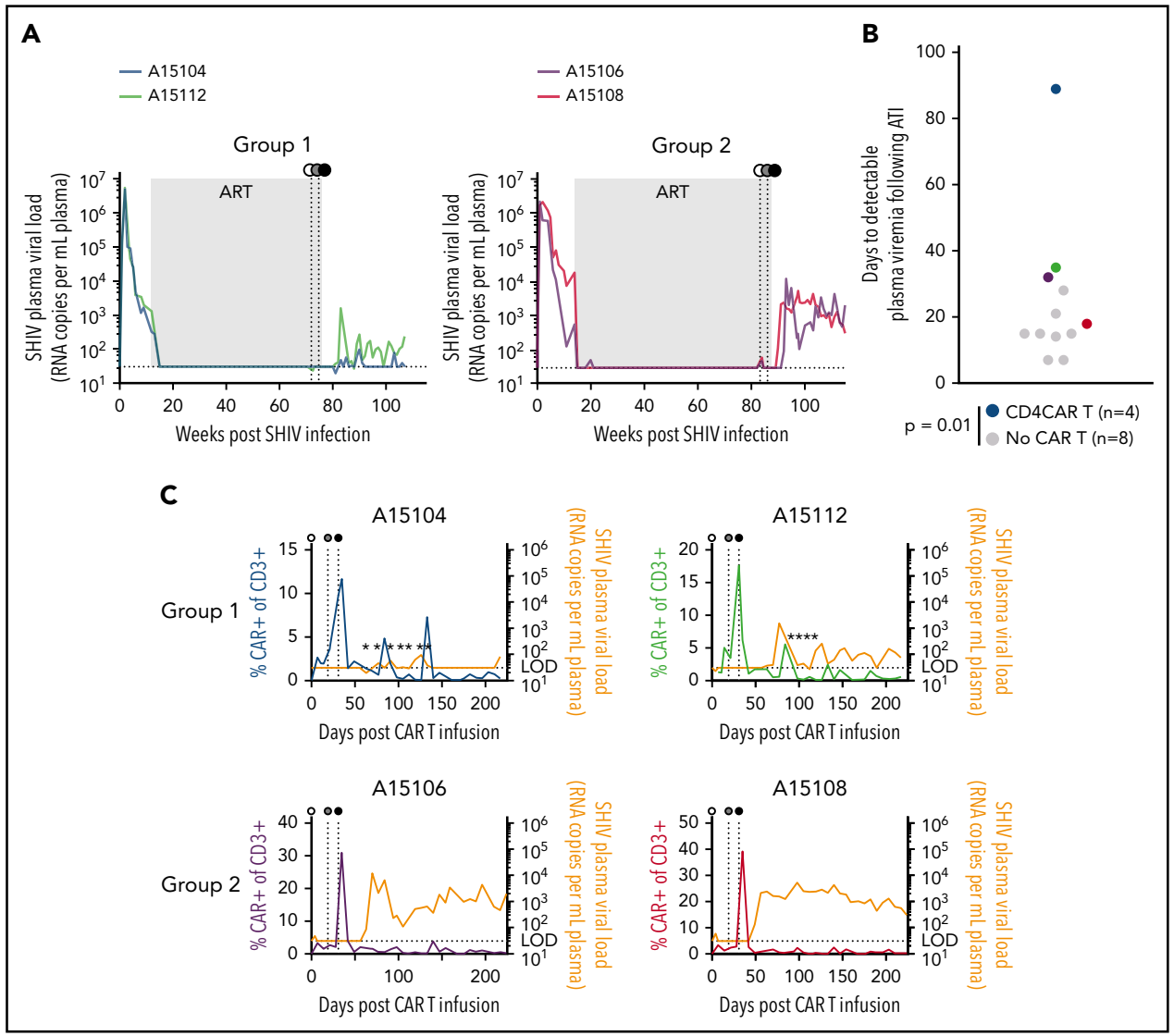
GENE THERAPY

Robust expansion of HIV CAR T cells following antigen boosting in ART-suppressed nonhuman primates

Blake J. Rust,[1] Leslie S. Kean,[2] Lucrezia Colonna,[1] Katherine E. Brandenstein,[1] Nikhita H. Poole,[1] Willimark Obenza,[1] Mark R. Enstrom,[1] Colby R. Maldini,[3] Gavin I. Ellis,[3] Christine M. Fennessey,[4] Meei-Li Huang,[5] Brandon F. Keele,[4] Keith R. Jerome,[5,6] James L. Riley,[3] Hans-Peter Kiem,[1,6,7] and Christopher W. Peterson[1,7]

In an in vivo assay using nonhuman primates, CD4+ CAR-T cells were genetically modified to knock out the *CCR5* gene in order to protect the CAR-T cells from simian HIV (SHIV) infection





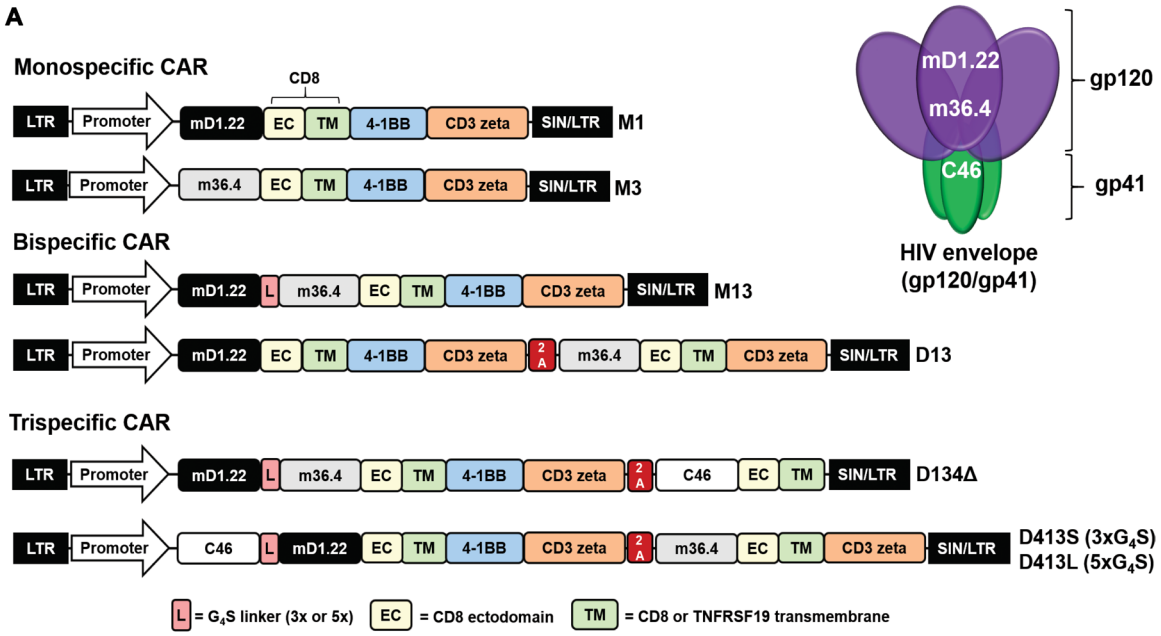
Blood 2020

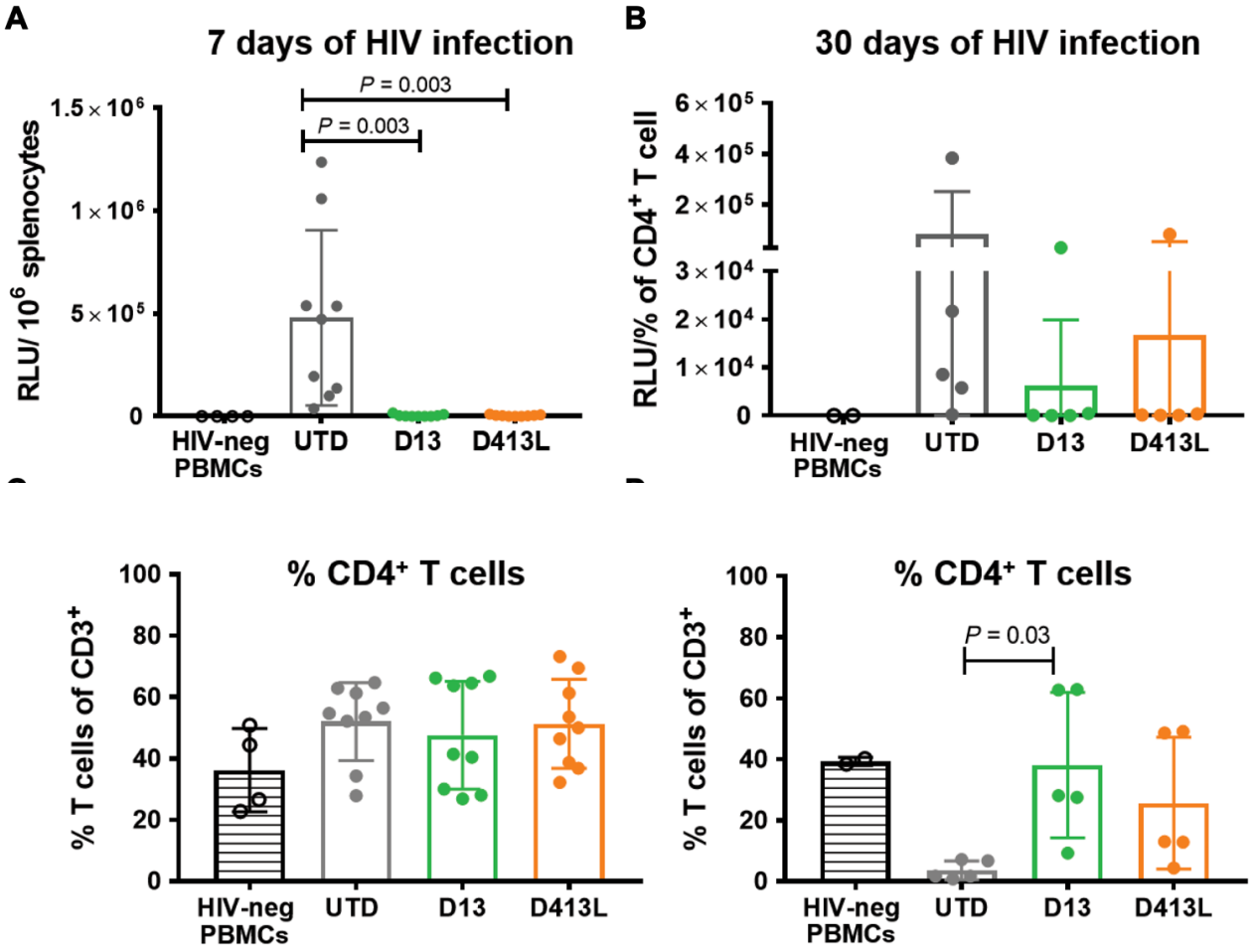
Reducing viral escape

HIV

Multispecific anti-HIV duoCAR-T cells display broad in vitro antiviral activity and potent in vivo elimination of HIV-infected cells in a humanized mouse model

Kim Anthony-Gonda[1]*, Ariola Bardhi[2]*, Alex Ray[2], Nina Flerin[2], Mengyan Li[2], Weizao Chen[3], Christina Ochsenbauer[4], John C. Kappes[4,5], Winfried Krueger[1], Andrew Worden[1], Dina Schneider[1], Zhongyu Zhu[1], Rimas Orentas[1†], Dimiter S. Dimitrov[6‡], Harris Goldstein[2‡], Boro Dropulić[1‡]





Targeting HIV infected cells

A key factor makes CAR-T cell therapies more successful in the blood cancer scenario.

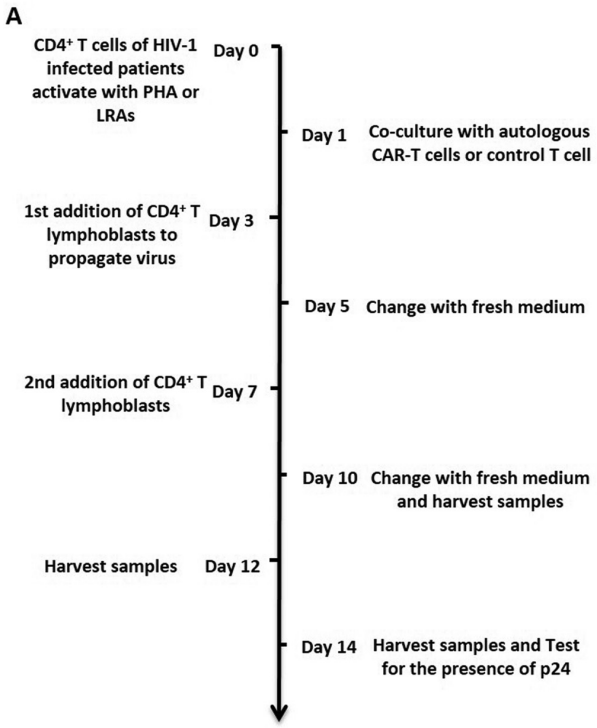
Blood malignancies are characterized by uncontrolled multiplication of the target cell, which translates into an enormous amount of antigen, and this makes the cell more easily accessible for the CAR-T cells to elicit a cytotoxic response.

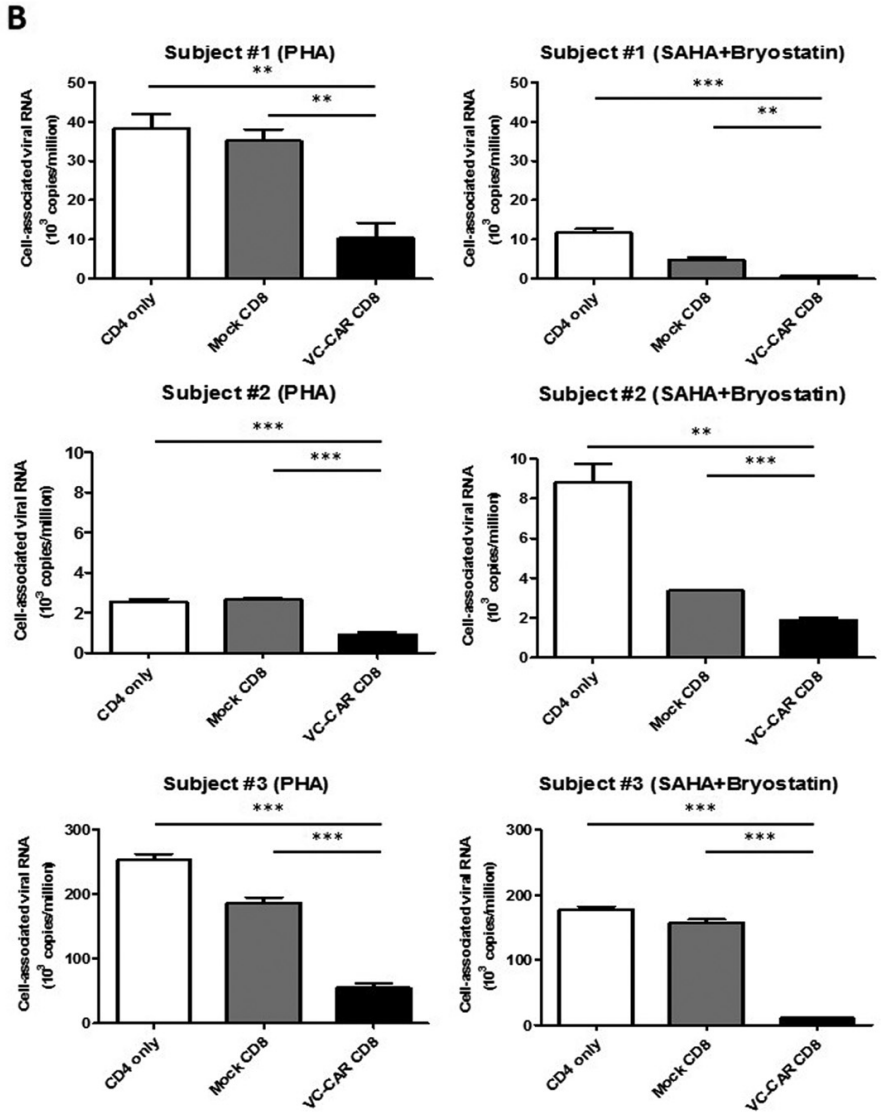
In contrast, the fact that the amount of antigen in people with HIV on cART is lower requires a more greatly target-specific approach to CAR-T cell therapy. In a context of suppressive cART therapy, HIV-infected cells are mostly transcriptionally silent, and this translates into minimal amounts of available targets for CAR-T cells.

Targeting HIV infected cells

Chimeric Antigen Receptor T Cells Guided by the Single-Chain Fv of a Broadly Neutralizing Antibody Specifically and Effectively Eradicate Virus Reactivated from Latency in CD4$^+$ T Lymphocytes Isolated from HIV-1-Infected Individuals Receiving Suppressive Combined Antiretroviral Therapy

Bingfeng Liu,[a,b,c] Fan Zou,[a,b,c] Lijuan Lu,[a,b,c] Cancan Chen,[a,b,c] Dalian He,[a,b,c] Xu Zhang,[a,b,c] Xiaoping Tang,[d] Chao Liu,[a,b,c] Linghua Li,[d] Hui Zhang[a,b,c]





J Virol 2016

Targeting HIV infected cells

Latently infected cells from the reservoir are mostly resting memory CD4+ T cells, presenting a low proliferation rate, mainly by homeostatic proliferation through IL-7 and found in several anatomical locations such as the lymph nodes, gut-associated lymph tissue (GALT), genital tract, and brain.

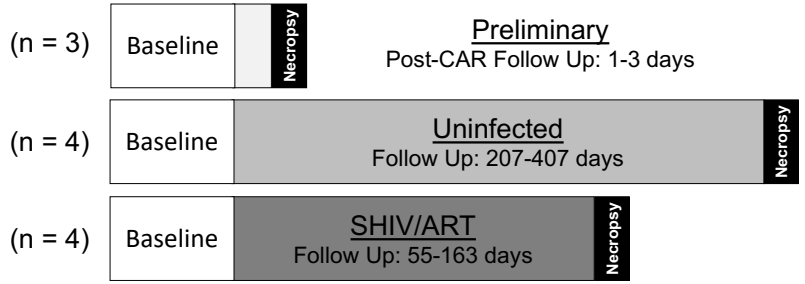
The brain and the lymph node B cell germinal centres are sanctuaries, meaning that the cells inside are protected from cART or CTL penetration, thereby hindering the complete eradication of the reservoir.

Hence, it is important to both ensure efficient transport of the CAR-T cells to the tissue sanctuaries and to maintain their potent antiviral effect once the effector cells make contact with the reservoir.

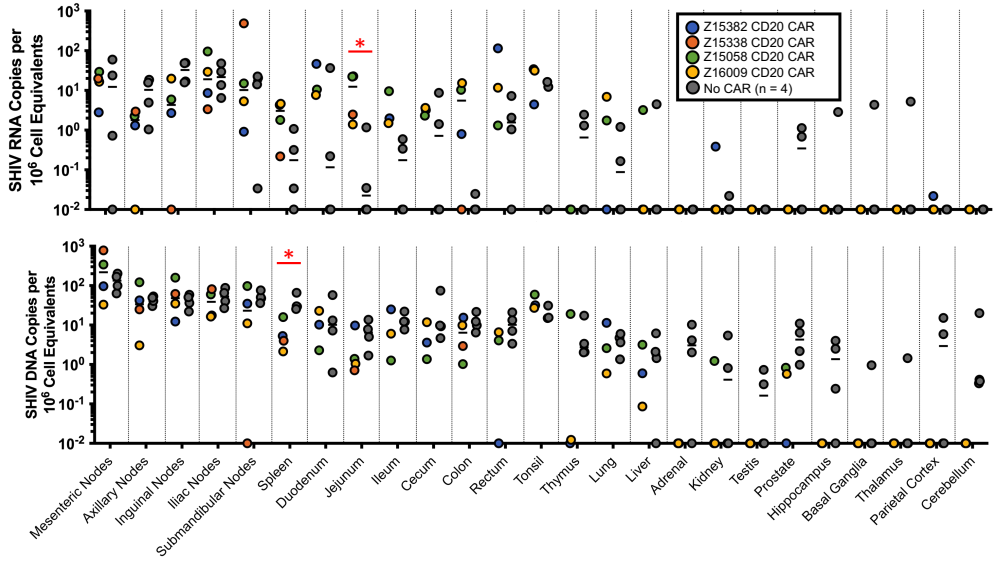
Targeting HIV infected cells

SHIV Reservoirs Persist Following CAR T Cell-Mediated Depletion of B Cell Follicles in Nonhuman Primates

Quantifying CD20 CAR T Cell Function and Trafficking in Naïve and SHIV-Infected, ART-Suppressed Macaques



CD20 CAR T Cell Therapy Does Not Systemically Impact SHIV Reservoir Size



Peterson, C.W. SHIV Reservoirs Persist Following CAR T Cell-Mediated Depletion of B Cell Follicles in Nonhuman Primates. In Proceedings of the AIDS 2022, Montreal, QC, Canada, 29 July–2 August 2022.

CAR-T cells immunotherapy in HIV cure

Trial Registration	Study Title	Start Date	Phase	Country	CAR Generation	Type of CAR	Outcome	Reference
-	Prolonged survival and tissue trafficking following adoptive transfer of CD4ζ gene-modified autologous $CD4^+$ and $CD8^+$ T cells in human immunodeficiency virus–infected subjects	1999 *	Phase II	USA	First	CD4ζ-based	Validation of the feasibility and antiviral activity	Mitsuyasu et al. *Blood* **2000**. [28]
-	Long-term in vivo survival of receptor-modified syngeneic T cells in patients with human immunodeficiency virus infection	1999 *	Phase I	USA	First	CD4ζ-based	Prove that administration is safe	Walker et al. *Blood* **2000**. [24]
-	A phase II randomized study of HIV-specific T-cell gene therapy in subjects with undetectable plasma viremia on combination antiretroviral therapy	2002 *	Phase II Randomized	USA	First	CD4ζ-based	Confirmed safety and feasibility, but no effect on HIV reservoirs	Deeks et al. *Mol. Ther*. **2002**. [29]
NCT01013415	A phase I/II study of the safety, survival, and trafficking of autologous CD4-ζ gene-modified T cells with and without extension Interleukin-2 in HIV infected patients	2001	Phase I Non-Randomized	USA	First	CD4ζ-based	Safety and long term persistence of modified T cells	Scholler et al. *Sci. Trasl. Med*. **2012**. [30]

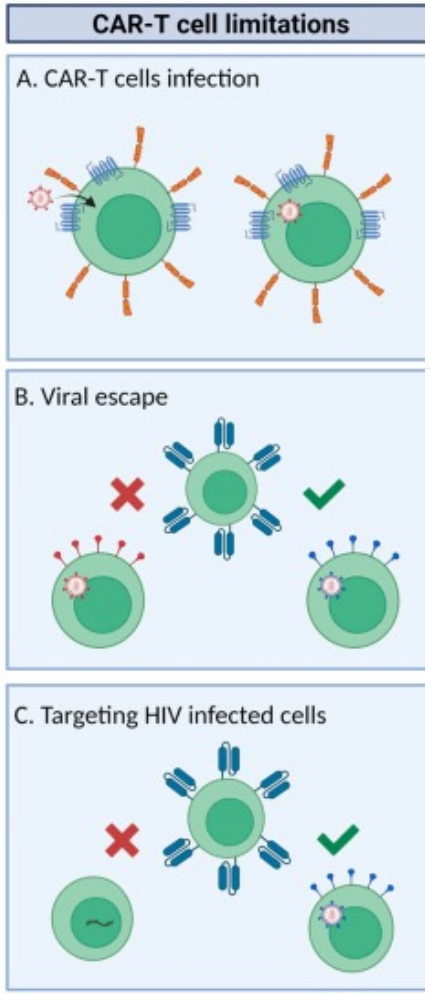
Campos-Gonzales, Viruses 2023

CAR-T cells immunotherapy in HIV cure

Trial Registration	Study Title	Start Date	Phase	Country	CAR Generation	Type of CAR	Outcome	Reference
NCT03240328	The effect of CAR-T cell therapy on the reconstitution of HIV-specific immune function	2017	Phase I	China	Third	bNAb-based	Long term in vivo persistence and no safety concerns	Liu et al. *J. Clin. Invest.* **2021**. [31]
NCT03617198	A pilot study of T cells genetically modified by Zinc Finger Nucleases SB-728mR and CD4 chimeric antigen receptor in HIV-infected subjects	2019	Phase I Randomized	USA	Second	*CCR5* ZFN-treated $CD4^+$	Ongoing	-
NCT04648046	Safety and anti-HIV activity of autologous $CD4^+$ and $CD8^+$ T cells transduced with a lentiviral vector encoding bi-specific anti-gp120 CAR molecules (LVgp120duoCAR-T) in anti-retroviral drug-treated HIV-1 infection	2021	Phase I/IIa Non-Randomized	USA	Second	CD4-based duoCAR	Ongoing	-

Campos-Gonzales, Viruses 2023

CAR T cells in HIV

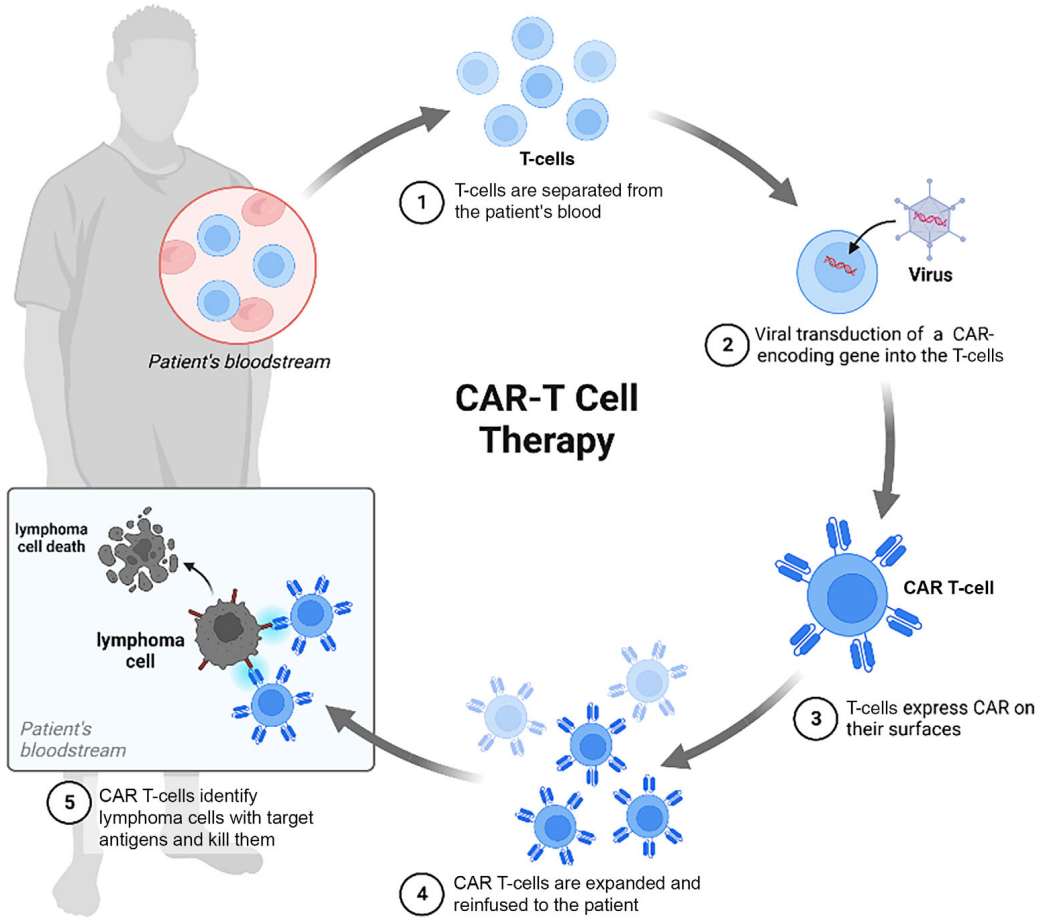


- **Ectopic expression of CXCR5**: to promote their homing to lymph nodes to target latently infected TFH cells
- **Blockade of check-points** may decrease the exhaustion state and maintain the cytolytic function

CAR T-cells therapies for HIV-lymphomas

Enabling CAR T-cell therapies for HIV-positive lymphoma patients – A call for action

Tessa Hattenhauer[1] | Rebekka Mispelbaum[1] | Marcus Hentrich[2] | Christoph Boesecke[3,4] | Malte Benedikt Monin[3,4]



HIV Med. 2023;24:957–964.

T cell status

A sufficient number of apheresed CD4+ T-cells is a critical aspect for successful CAR T-cell production and for CAR T-cell function, and presumably for long-term effects

TABLE 1 Use of CAR T-cell therapy in patients with HIV ($n = 6$).

Case	References	Age (years)	Sex	Combined ART	$CD4^+$ T-cells (cells/μL)	T-cells (cells/μL)	Viral load (copies/mL)	Lymphoma	CAR product	Side effects (grade)/ therapy	Response (follow up)
1	[33]	47	m	Yes	52	n.s.	67	DLBCL	Axicabtagene ciloleucel	CRS (grade 2)/ tocilizumab, steroid ICANS (grade 3)/ steroid	CR (1 year)
2	[33]	n.s.	m	Bictegravir/ emtricitabine/ tenofovir alafenamide	127	n.s.	Undetectable	DLBCL	Axicabtagene ciloleucel	no CRS no ICANS	CR (at least 28 days)
3	[31]	n.s.	n.s.	n.s.	127	n.s.	Undetectable	DLBCL	Axicabtagene ciloleucel	n.s.	CR (n.s.)
4	[32]	49	m	Yes	170	847	Undetectable	DLBCL	Axicabtagene ciloleucel	CRS (grade 1)/steroid ICANS (grade 2)/ steroid	PR (PD after 2 months)
5	[36]	66	f	n.s.	629	n.s.	Undetectable	DLBCL	Axicabtagene ciloleucel	CRS (grade 1)/steroid ICANS (grade 2)/ steroid	PD (isolated CNS recurrence after 4 months with systemic CR)
6	[34]	53	m	Yes	n.s.	n.s.	n.s.	DLBCL	Axicabtagene ciloleucel	CRS (grade 1)/ anakinra, steroid ICANS (grade 3)/ anakinra, steroid	PD (after 15 days)

Abbreviations: ART, antiretroviral therapy; CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; CRS, cytokine releasing syndrome; DLBCL, diffuse large B-cell lymphoma; f, female; ICANS, immune effector cell-associated neurotoxicity syndrome; m, male; n.s., not stated; PD, progressive disease (including recurrent disease); PR, partial response.

Low-level viraemia and blips

In patients with cancer, especially when receiving chemotherapy, blips must be expected.

The occurrence of both conditions, low-level viraemia and/or blips, is considered a controlled HIV infection and is not a reason to exclude people living with HIV from CAR T-cell therapy.

Drug-drug interactions

Current combined ART is mainly based on integrase inhibitors (particularly in people living with HIV undergoing cancer treatment), so the potential for drug–drug interactions between combined ART and chemotherapy is low.

No interactions between ART and fludarabine/cyclo-phosphamide (standard lymphodepleting chemotherapy) have been described

With regard to the pharmacology of CAR-T cells, an interaction with or direct influence of combined ART on CAR-T cells is not expected.

Cytokine-release syndrome

Interleukin (IL)-6, a proinflammatory cytokine, is assumed to induce a proinflammatory signalling pathway, which leads to CRS.

Elevated IL-6 levels have been observed in people living with HIV.

Since higher IL-6 levels have been shown to predict CRS, the higher cytokine levels of people living with HIV might be associated with an increased risk for CRS.

The available case reports do not show a higher rate or grade of CRS in this patient group.
However, low or undetectable viral loads are associated with lower IL-6 levels, a group the case reports are limited to.
For a final evaluation of side effects of CAR T-cell treatment in people living with HIV, more data are urgently needed.

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