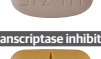
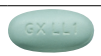
I farmaci antiretrovirali nell'anziano

Innovazione farmaceutica

Generic name	Trade name		Formulation	Standard adult dose
Single-tablet regimens				
Efavirenz / emtricitabine / tenofovir disoproxil	*Atripla*		Tablet comprising 600mg efavirenz, 200mg emtricitabine and 245mg tenofovir disoproxil	One tablet once a day
Rilpivirine / emtricitabine / tenofovir disoproxil	*Eviplera*		Tablet comprising 25mg rilpivirine, 200mg emtricitabine and 245mg tenofovir disoproxil	One tablet once a day
Rilpivirine / tenofovir alafenamide / emtricitabine	*Odefsey*		Tablet comprising 25mg rilpivirine, 25mg tenofovir alafenamide, 200mg emtricitabine	One tablet once a day
Elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide	*Genvoya*		Tablet comprising 150mg elvitegravir, 150mg cobicistat, 200mg emtricitabine, 10mg tenofovir alafenamide	One tablet once a day
Elvitegravir /cobicistat / emtricitabine / tenofovir disoproxil	*Stribild*		Tablet comprising 150mg elvitegravir, 150mg cobicistat, 200mg emtricitabine, 245mg tenofovir disoproxil	One tablet once a day
Dolutegravir / abacavir / lamivudine	*Triumeq*		Tablet comprising 50mg dolutegravir, 600mg abacavir and 300mg lamivudine	One tablet once a day
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)				
Abacavir	*Ziagen*		300mg tablet	300mg twice a day **or** 600mg once a day
Emtricitabine	*Emtriva*		200mg capsule	200mg once a day
Lamivudine	*Epivir*		150* and 300mg tablets	150mg twice a day **or** 300mg once a day
Zidovudine	*Retrovir*		100 and 250mg* capsules	250mg twice a day
Tenofovir disoproxil	*Viread*		245mg tablet	245mg once a day
NRTI fixed-dose combinations				
Abacavir / lamivudine	*Kivexa*		Tablet comprising 600mg abacavir and 300mg lamivudine	One tablet once a day
Abacavir / lamivudine / zidovudine	*Trizivir*		Tablet comprising 300mg abacavir, 150mg lamivudine and 300mg zidovudine	One tablet twice a day
Emtricitabine / tenofovir disoproxil	*Truvada*		Tablet comprising 200mg emtricitabine and 245mg tenofovir disoproxil	One tablet once a day
Emtricitabine / tenofovir alafenamide	*Descovy*		Tablet comprising 200mg emtricitabine and 10mg or 25mg* tenofovir alafenamide	One tablet once a day. The 10mg version is recommended for use in combination with some boosted protease inhibitors.
Lamivudine / zidovudine	*Combivir*		Tablet comprising 150mg lamivudine and 300mg zidovudine	One tablet twice a day

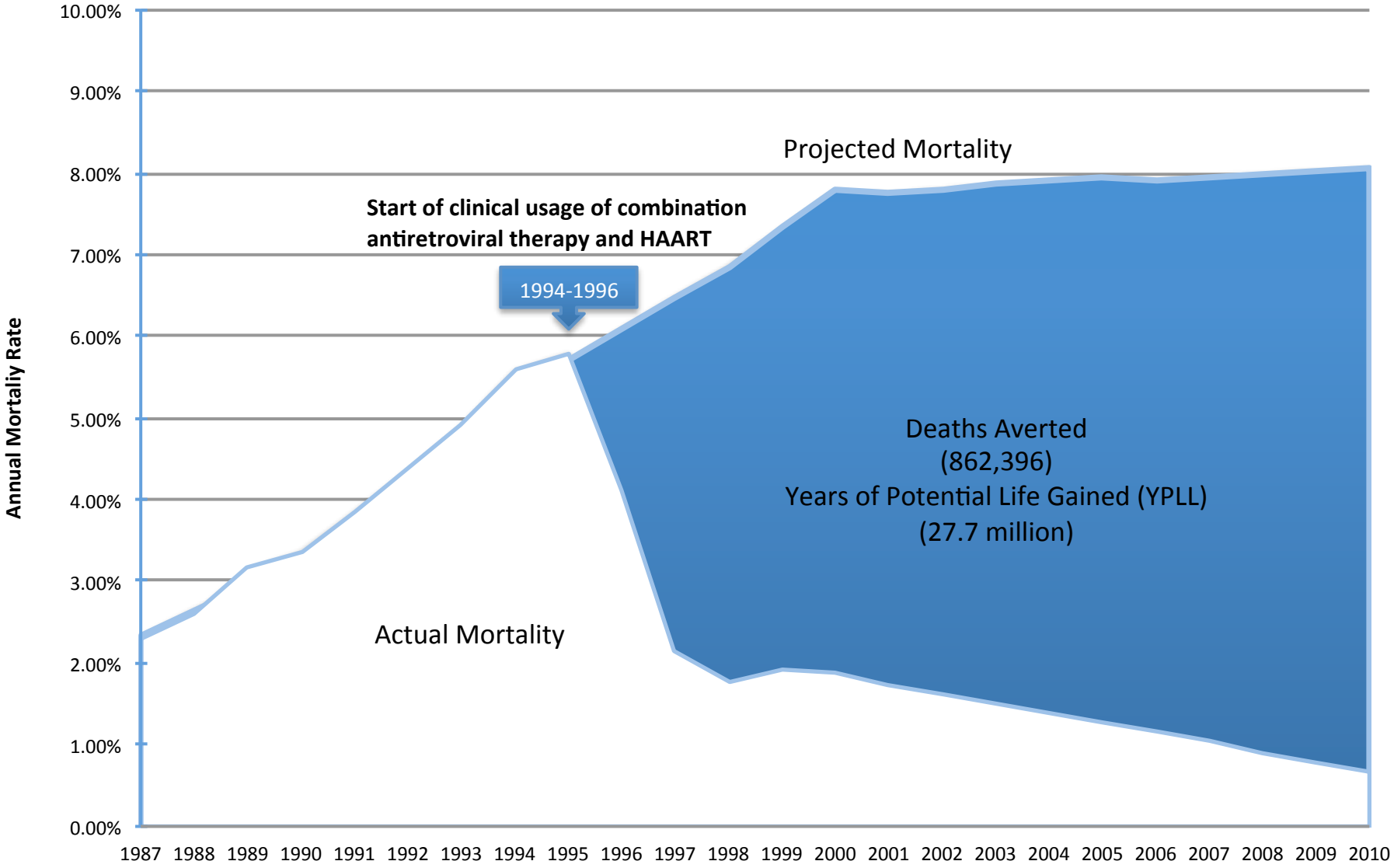
Integrase inhibitors				
Dolutegravir	*Tivicay*		50mg tablet	50mg once a day **or** 50mg twice a day if taken with efavirenz, nevirapine or tipranavir, or for HIV known to be resistant to integrase inhibitors
Raltegravir	*Isentress*		400mg tablet	400mg twice a day
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)				
Efavirenz	*Sustiva Stocrin*		600mg tablet* and 200mg capsule	600mg once a day
Etravirine	*Intelence*		100 and 200mg* tablet	200mg twice daily
Nevirapine	*Viramune*		200mg tablet	200mg once a day for two weeks **then** 200mg twice a day
Nevirapine	*Viramune prolonged-release*		400mg tablet	400mg once a day after introductory period on non-extended-release nevirapine
Rilpivirine	*Edurant*		25mg tablet	25mg once a day
Protease inhibitors				
Atazanavir	*Reyataz*		150, 200 and 300mg* capsule	300mg with 100mg ritonavir once a day
Darunavir	*Prezista*		600, and 800mg* tablet	800mg with 100mg ritonavir once a day **or** 600mg with 100mg ritonavir twice a day
Darunavir / cobicistat	*Rezolsta*		Tablet comprising 800mg darunavir and 150mg cobicistat	One tablet once a day
Fosamprenavir	*Telzir*		700mg tablet	700mg with 100mg ritonavir twice a day
Lopinavir / ritonavir	*Kaletra*		Tablet comprising 200mg lopinavir and 50mg ritonavir	Two tablets twice a day **or** four tablets once a day
Atazanavir / cobicistat	*Evotaz*		Tablet comprising 300mg atazanavir, 150mg cobicistat	One tablet once a day
CCR5 inhibitor				
Maraviroc	*Celsentri*		150* and 300mg tablets	300mg twice a day **or** 150mg twice a day with ritonavir-boosted PI except tipranavir and fosamprenavir or 600mg twice a day with efavirenz **or** etravirine without a ritonavir-boosted PI
Booster drugs				
Cobicistat	*Tybost*		150mg tablet	One tablet once a day
Ritonavir	*Norvir*		100mg tablet	**To 'boost' other PIs:** 100 – 200mg once or twice a day

G. Sava

SOCIETÀ ITALIANA DI FARMACOLOGIA

LA TERAPIA ANTINFETTIVA NELL'ANZIANO Verona- 21 APRILE 2017

Figure 5. Age-adjusted death rates rates for HIV disease in the US 1987-2010, Actual versus Projected



Source: Actual Mortality Rates. Table 31. Death rates for human immunodeficiency virus (HIV) disease, by sex, race, Hispanic origin, and age: United States, selected years 1987-2010. Health United States, 2013. Projected Mortality Rates based on projection model

Published in final edited form as:

JAMA. 2016 July 12; 316(2): 191–210. doi:10.1001/jama.2016.8900.

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults:

2016 Recommendations of the International Antiviral Society–USA Panel

CONCLUSIONS AND RELEVANCE— Antiretroviral agents remain the cornerstone of HIV treatment and prevention. ,,,. When used effectively, currently available ARVs can sustain HIV suppression and can prevent new HIV infection. With these treatment regimens, **survival rates among HIV-infected adults who are retained in care can approach those of uninfected adults**.

THEN AND NOW

Since HIV/AIDS was first recognized in 1981, advances in medicines have helped lower the death rate by 83%. Prior to 1995, when the first antiretroviral treatment was approved by the FDA, an HIV diagnosis was a death sentence. Now, thanks to medicines developed by biopharmaceutical scientists and their research partners, it is a chronic condition with manageable costs and patients are able to reach nearly a full life expectancy.

ARTHUR ASHE

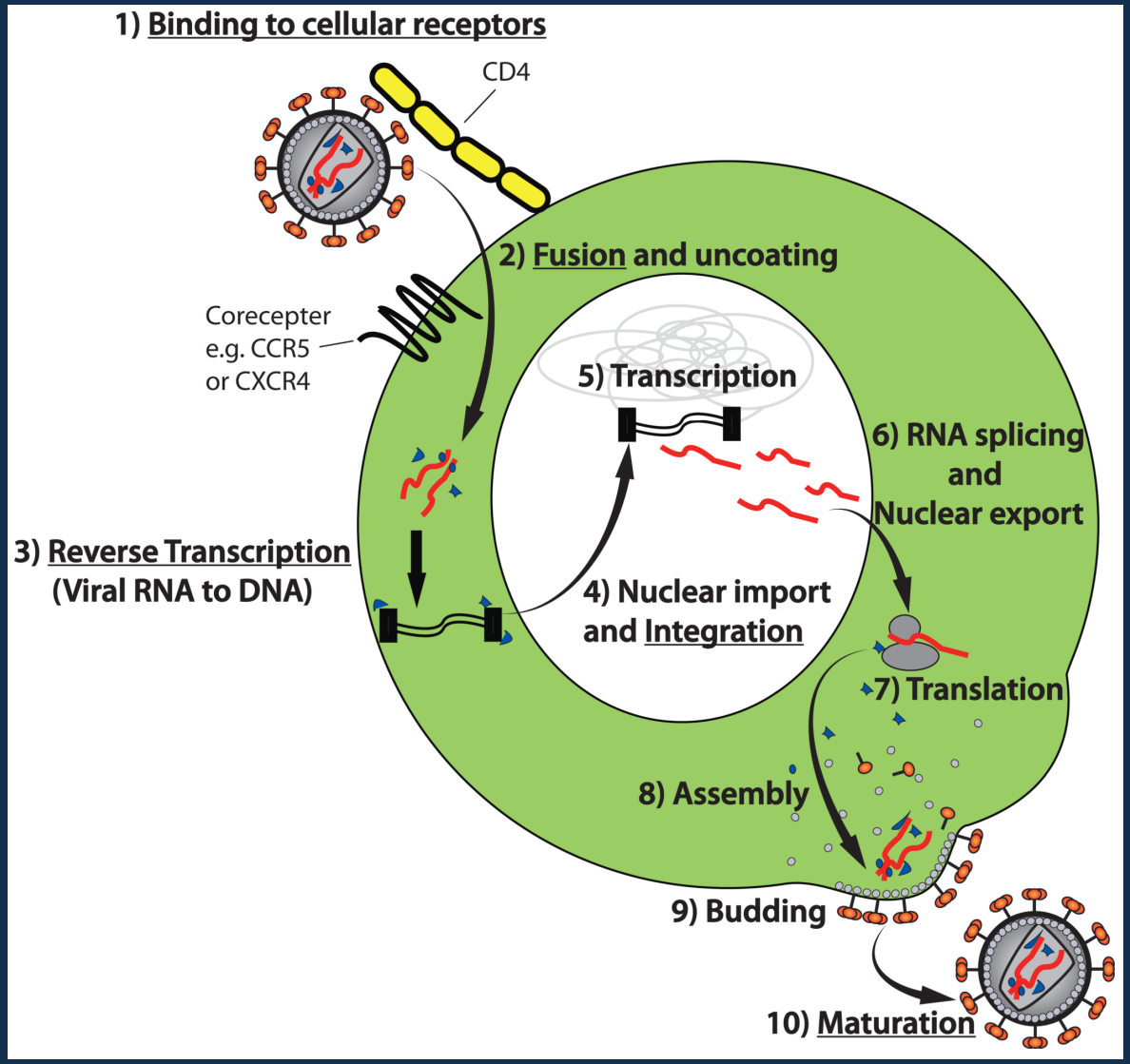
Due to the lack of effective medicines, Arthur Ashe succumbed to AIDS-related pneumonia at 50 years old in 1993, just 10 years after he contracted the disease and 5 years after diagnosis

MAGIC JOHNSON

Despite being diagnosed with HIV/AIDS in 1991, Magic is expected to meet his full life expectancy due to the treatments available at the outset of his diagnosis

Source: Magic Johnson Foundation, Arthur Ashe Learning Center (AALC).

Essential steps in the HIV life cycle and targets of currently available antiretroviral drugs



Bioorg Med Chem Lett. 2013 July 15; 23(14): 4003–4010

HIV Treatment

FDA–Approved HIV Medicines

(Last updated 2/27/2017; last reviewed 2/27/2017)

Nucleoside Reverse Transcriptase Inhibitors

Zidovudine, 19/3/1987 – Emtricitabine, 2/7/2003

Protease Inhibitors

Saquinavir, 6/12/1995 – Darunavir, 23/6/2006

Non-Nucleoside Reverse Transcriptase Inhibitors

Nevirapine, 21/6/1996 – Rilpivirine, 20/5/2011

Fusion Inhibitors

Enfuvirtide, 13/3/2003 –

Entry Inhibitors

Maraviroc, 6/8/2007 –

Integrase Inhibitors

Raltegravir, 12/10/2007 – Elvitegravir, 24/9/2014

Enhancers

Cobicistat, 24/9/2014 –

Combination HIV medicines contain two or more HIV drugs

HIV Treatment

FDA–Approved HIV Medicines
(Last updated 2/27/2017; last reviewed 2/27/2017)

lamivudine and zidovudine 27, 9, 1997

lopinavir and ritonavir 15, 9, 2000

abacavir and lamivudine 2, 8, 2004

abacavir, lamivudine, and zidovudine 14, 11, 2000

abacavir, dolutegravir, and lamivudine 22, 8, 2014

emtricitabine and tenofovir disoproxil fumarate 2, 8, 2004

efavirenz, emtricitabine, and tenofovir disoproxil fumarate 12, 7, 2006

emtricitabine, rilpivirine, and tenofovir disoproxil fumarate 10, 8, 2011

elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate 27, 8, 2012

atazanavir and cobicistat 29, 1, 2015

darunavir and cobicistat 29, 1, 2015

elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate 5, 11, 2015

emtricitabine, rilpivirine, and tenofovir alafenamide 1, 3, 2016

emtricitabine and tenofovir alafenamide 4, 4, 2016

Older people represent a growing share of the HIV population.

The number of **people over 50 with HIV or AIDS is growing** rapidly (40% of people with AIDS in the USA are over age 50).

Older people have to deal with other health issues. These can complicate the selection of anti-HIV medications. They can also be confused with some of the side effects of HIV drugs.

HIV drugs seem to **work as well in older people as in younger people**, although their CD4 cell counts may be lower.

hepatic metabolism and renal elimination are the major routes of clearance of ARV drugs.

…liver and kidney functions decrease with age and current ARV dosing recommendations are based on PK and pharmacodynamic data derived from participants with normal organ function.

… drug accumulation in the older patient may lead to greater incidence and severity of adverse effects than seen in younger patients.

… efficacy, PKs, adverse effects, and drug interaction potentials of ART in the older adult have not been studied systematically.

Genvoya:
Elvitegravir, cobicistat/emtricitabina/tenofovir alafenamide

-alfuzosina (**ipertrofia prostatica**)
-amiodarone, chinidina (**aritmie**)
-carbamazepina, oxcarbazepina, fenobarbital, fenitoina, topiramato (**epilessia e convulsioni**)
-rifampicina, rifabutina (tubercolosi)
-diidroergotamina, ergometrina, ergotamina (**emicrania**)
-cisapride (**digerente**)
-prodotti contenenti l'erba di S. Giovanni (**depressione/ansia**)
-lovastatina, simvastatina (**colesterolo**)
-pimozide (alterazioni del pensiero)
-sildenafil (**ipertensione arteriosa polmonare**)
-vardenafil (**impotenza**)
-midazolam somministrato per via orale, triazolam, clorazepato, diazepam, furazepam (**sonno e/o ansia**)
-desametasone (infiammazioni e immunità)
-dabigatran (sangue)
-bosentan (**ipertensione arteriosa polmonare**)

Several research studies have measured **how much adherence is "enough"**.

For the best viral load results, **people had to take over 90% of their pills correctly**, even if some studies suggest that adherence levels to regimens based on (NNRTIs) may be lower than 90%.

The fewer doses you miss, the better the chances of keeping HIV under control and the lower the risk of developing viral resistance.

As the world moves towards adopting the WHO 2015 guidelines, **advances in technology**, including **the introduction of lower-cost, highly effective antiretroviral regimens may prove to be "game changers"** that allow more people to be on ART with the resources available.

Journal of Medicinal Chemistry

Perspective

pubs.acs.org/jmc

Anti-HIV Drug Discovery and Development: Current Innovations and Future Trends

An ideal follow-on anti-HIV drug (namely, a new antiretroviral for a known target) **should meet rigorous requirements**:

(i) **improved activity** against WT and resistant virus;

(ii) favorable **oral bioavailability** and metabolic stability;

(iii) minimal **side effects** and good safety profile;

(iv) lack of **drug–drug interactions** (ability to interact beneficially with other drugs);

(v) ease of preparation and **formulation**

J. Med. Chem. 2016, 59, 2849−2878

Tenofovir disoproxil fumarato (TDF) vs Tenofovir alafenamide fumarato (TAF)

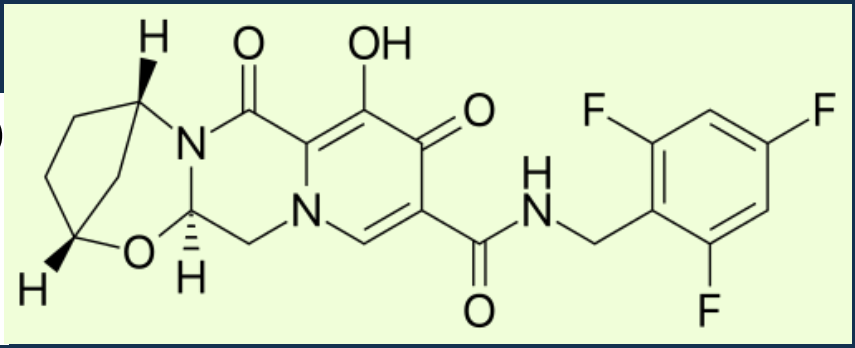
CROI
Conference on Retroviruses and Opportunistic Infections

Cabotegravir+Rilpivirine as Long-Acting Maintenance Therapy: LATTE-2 Week 32 Results

Q8W and Q4W CAB LA + RPV LA as 2-drug injectable maintenance therapy demonstrated comparable antiviral activity to daily oral CAB + ABC/3TC through 32 weeks in virologically suppressed pts. Injectable CAB LA + RPV LA were generally well tolerated.

CROI
Conference on Retroviruses and Opportunistic Infections

Hiv, promettente il nuovo inibitore dell'integrasi bictegravir (BIC; formerly GS-9883)



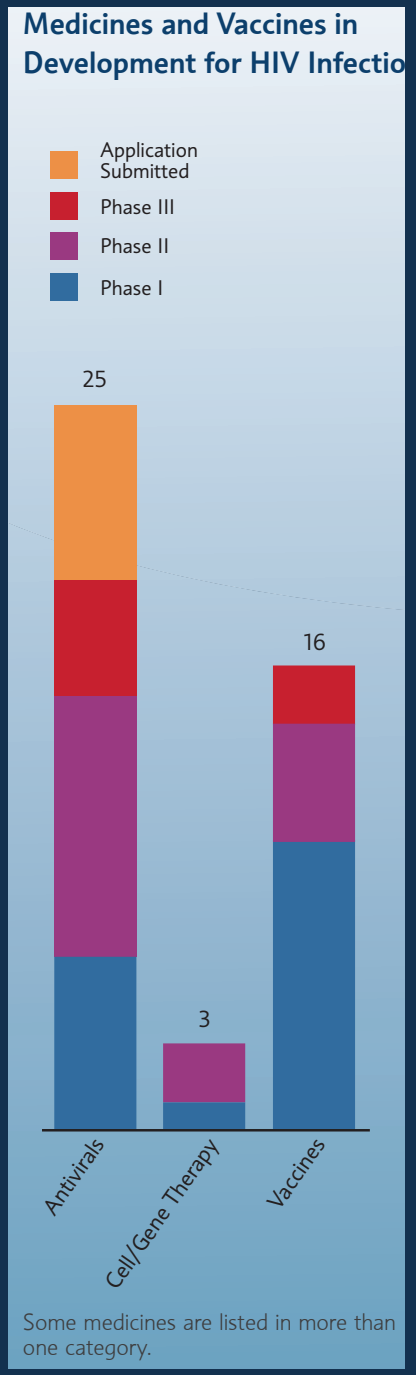
44 MEDICINES & VACCINES IN DEVELOPMENT for HIV infection

25 Antivirals

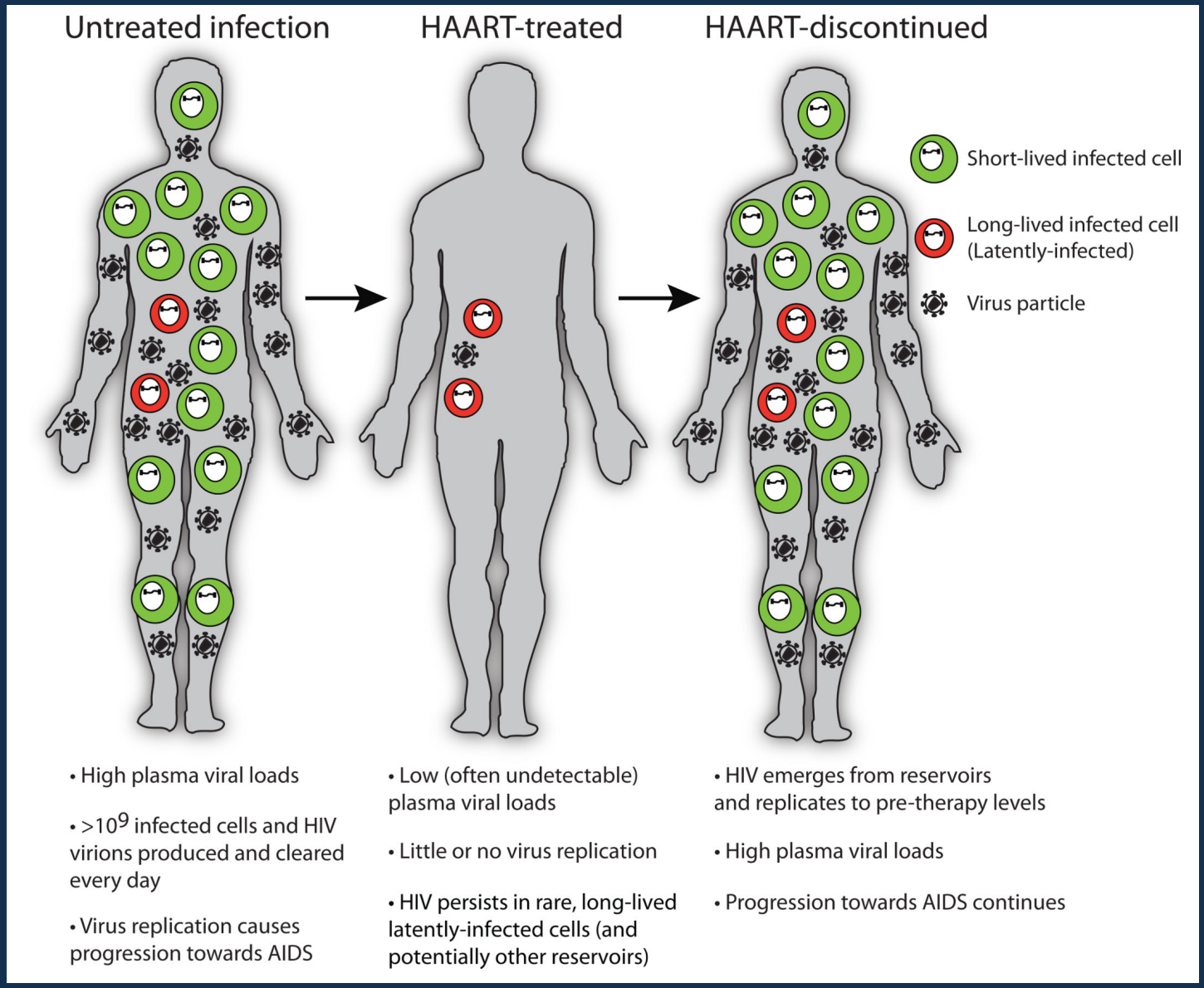
3 Cell/Gene Therapy

16 Vaccines

Source: 2014 PhRMA Medicines in Development for HIV/AIDS, PhRMA.

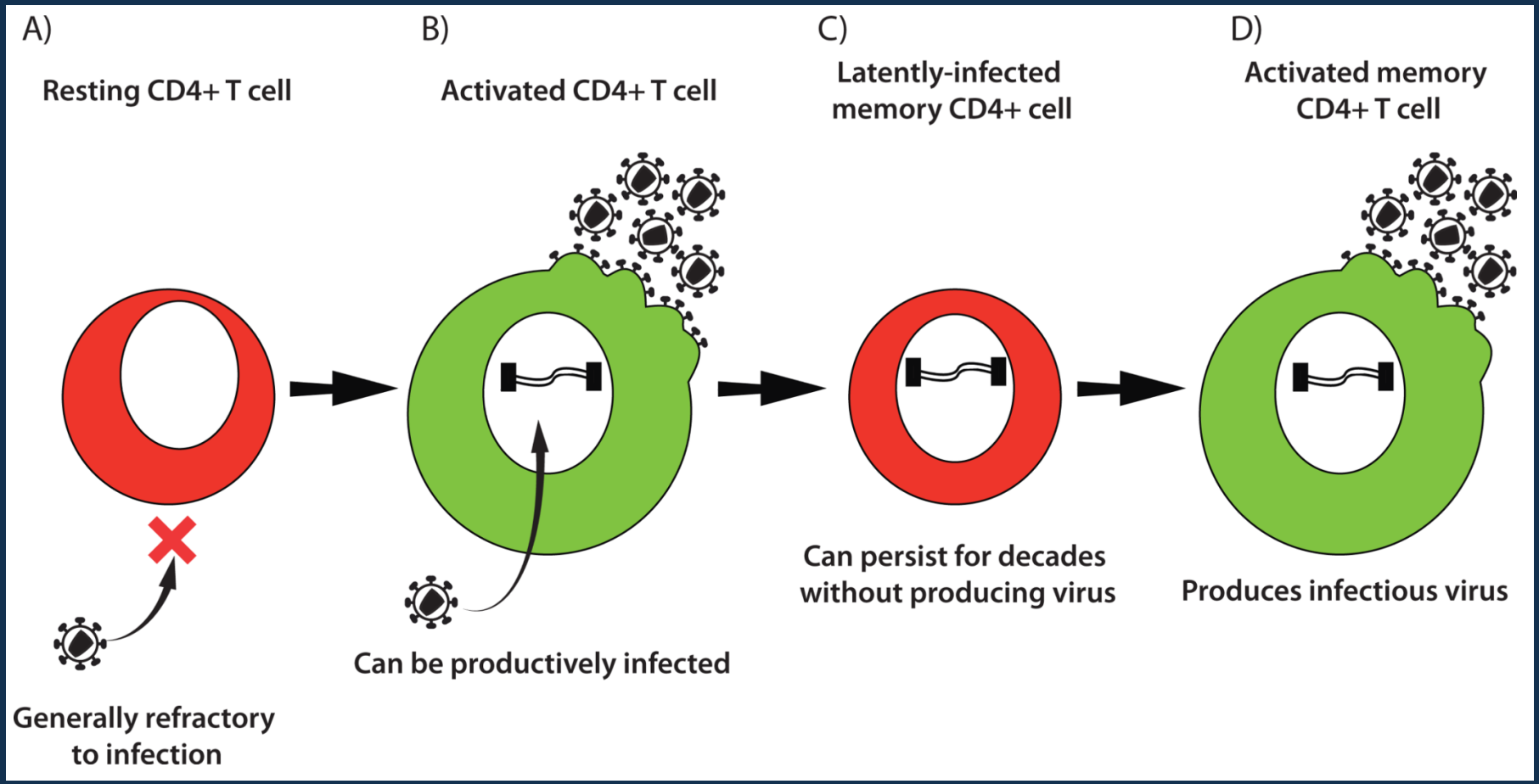


Suppression of HIV replication during therapy



Bioorg Med Chem Lett. 2013 July 15; 23(14): 4003–4010

Generation of HIV latency



Bioorg Med Chem Lett. 2013 July 15; 23(14): 4003–4010

Timothy Ray Brown

"paziente di Berlino"

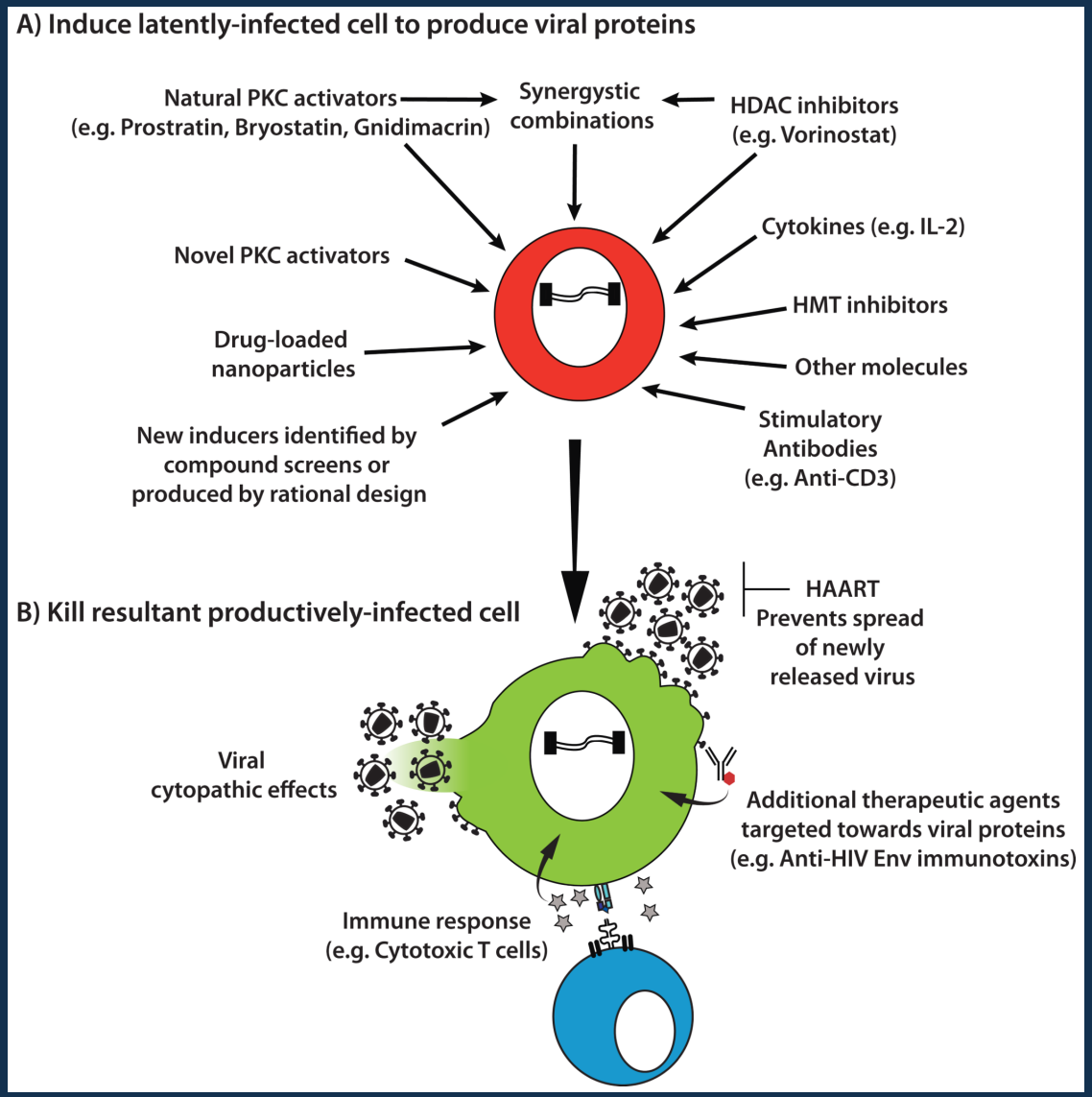
AIDS 1995; leucemia linfoide 2006; "curato" da entrambi con trapianto midollo

Ipotesi a: effetto citotossico di Chemioterapia e Radiazioni

Ipotesi b: effetto della mutazione del gene per CCR5 nel midollo trapiantato

Ipotesi c: GVHD

Activation/elimination approaches to purge the latent HIV reservoir



Bioorg Med Chem Lett. 2013 July 15; 23(14): 4003–4010

RIVER: Research In Viral Eradication of HIV Reservoirs

The "Kick and Kill" approach

A new way to reduce the size of the HIV reservoir. Vorinostat, a HDAC inhibitor, is the "kick" and the boosted immune response is the "kill"

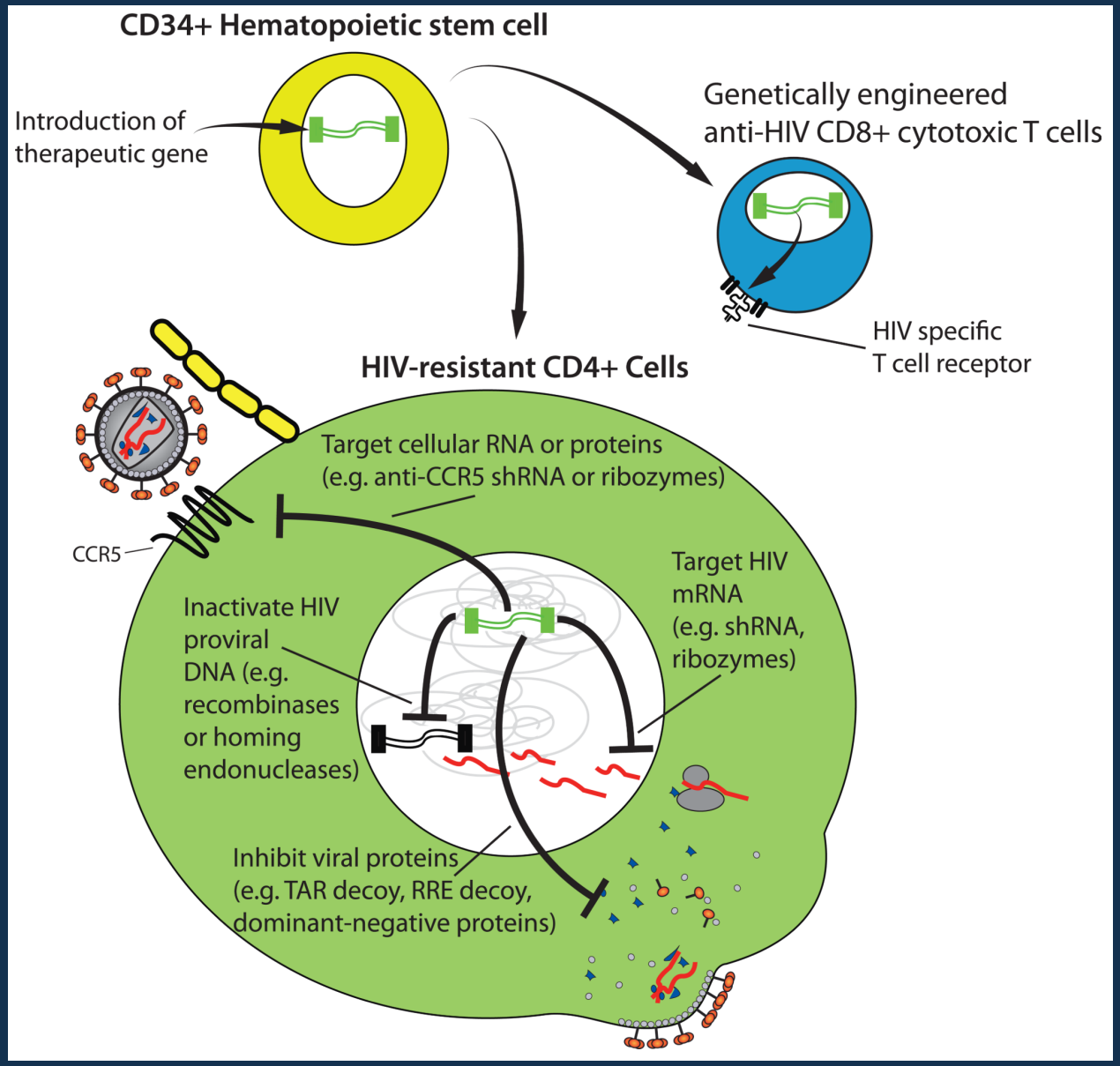
four steps

1. ART is used to make sure HIV is undetectable
2. Two vaccines are then used to train the immune system to recognise cells that will be activated
3. Vorinostat is used to wake and activate the sleeping HIV containing cells
4. The immune system, boosted by the vaccines, attacks and kills the newly activated cells

Recruitment started in December 2015 and closed in February 2017

Sarah Fidler

Gene therapy approaches for eliminating HIV



Bioorg Med Chem Lett. 2013 July 15; 23(14): 4003–4010

Cell therapy

February 22–25, 2016 | Boston, Massachusetts

Abstract Number:
358LB

T-Cell Homeostasis and CD8 Responses Predict Viral Control Post SB-728-T Treatment

18 **ART treated subjects** with CD4 counts above 500 were preconditioned with Cytoxan prior to **infusion of SB-728-T**. Subjects initiated TI at 6 weeks post infusion.

Of the 9 subjects pre-conditioned with 1.0 and 1.5 g/m2 Cytoxan, **6 subjects** demonstrated **durable control** of viremia (VL<10,000) in extended TI (duration= 14-26 months), with **2 subjects** showing **consistent ongoing VL** measurements <1000 (duration= 17 & 20 months).

Results indicate that **higher CD4 TSCM levels**, along with **greater** polyfunctional anti-HIV gag **CD8 response** during TI (p=0.04) were **associated with reduced viral load**.

"2 pazienti australiani"

1 trapiantato nel 2011 con midollo con 1 delle coppie geniche mutata per CCR5 e 1 trapiantato nel 2012 con midollo "normale": apparente assenza di virus in 2014 ma sospetto attività HAART

"2 pazienti di Boston"

Trapianto midollo nel 2008 e 2010; ricomparsa HIV dopo 12 e 32 settimane da interruzione HAART

Dr. Lambros Kordelas et al. (New England Journal of Medicine 2014) described the case of a **patient with T-cell lymphoma and HIV** who also was given a **stem cell transplant** from a homozygous **CCR5 delta 32** donor.

After the stem cell transplant, the **HIV** in his body **shifted its** mode of **attack from** entry via the **CCR5** receptor **to** entry via the **CXCR4** receptor.

The genotypic analyses showed a **shift from** a dominantly **R5-tropic HIV toward an X4-tropic HIV** after transplantation, probably driven by transplantation with stem cells homozygous for the CCR5 delta32 mutation.

This case highlights the fact that **viral escape mechanisms might jeopardize CCR5-knockout strategies** to control HIV infection."

Vaccines in study

AGS-004 (personalized immunotherapy) *Argos Therapeutics* Treatment

GOVX-B11 (clade B) (DNA/MVA vaccine) *Geovax* Prevention

HIV recombinant vaccine *GSK* Immunotherapy

HIV recombinant vaccine *GSK* Prevention

HIV vaccine *Novartis* Treatment

HIV vaccine (Ad4-EnvC 150) *PaxVax*

HIV vaccine (Ad4-mGag) *PaxVax*

} Prevention

HIV vaccine (SAV001) *Sumagen* Prevention

HIVAX™ replication-defective HIV-1 vaccine *GeneCure* Treatment

LFn-p24-B-C (HIV therapeutic vaccine) *Haikou VTI Biological Institute* Treatment

PBSVax™ HIV-MAG DNA vaccine *Profectus Bioscience* Prevention

Pennvax®-B DNA vaccine (clade B) *Inovio Pharmaceuticals*

Pennvax®-G DNA vaccine (clades A, C, D)

} Prevention/ Treatment

Remune® HIV vaccine *Immuneresponse Biopharma*

RemuneX® HIV combination vaccine

} Treatment

vacc-4x (intradermal vaccine) *BionorPharma*

} treatment combined with Revlimid®
treatment combined with Istodax®

Ensoli *et al. Retrovirology* (2016) 13:34
DOI 10.1186/s12977-016-0261-1

Retrovirology

RESEARCH Open Access

HIV-Tat immunization induces cross-clade neutralizing antibodies and CD4^{+} T cell increases in antiretroviral-treated South African volunteers: a randomized phase II clinical trial

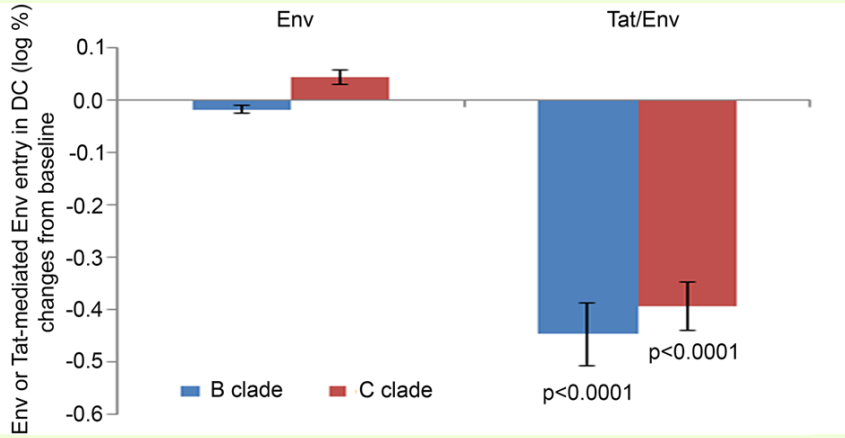


Fig. 6 Neutralization of B- and C-clade Tat/Env complex entry in DC in vaccinees. Neutralization of B- (n = 13) and C- (n = 10) clade Env entry in DC in the presence or absence of (B- or C-clade) Tat by sera of Ab-positive vaccinees, measured at week 20 or week 48 after immunization. Data are presented as mean values with standard errors. Student's t test for paired data was used for the analyses

Conclusions: The data indicate that **Tat vaccination** can **restore the immune system** and induces cross-clade neutralizing anti-Tat antibodies **in patients with** different genetic backgrounds and **infecting viruses**, supporting the conduct of phase III studies in South Africa.

Trial registration ClinicalTrials.gov NCT01513135, 01/23/2012