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CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

"Beyond three drugs: Next-generation antiretroviral strategies for HIV treatment: an overview of novel ART therapeutic strategies for HIV"

3rd SAHCS Long-acting HIV Treatment and Prevention Conference

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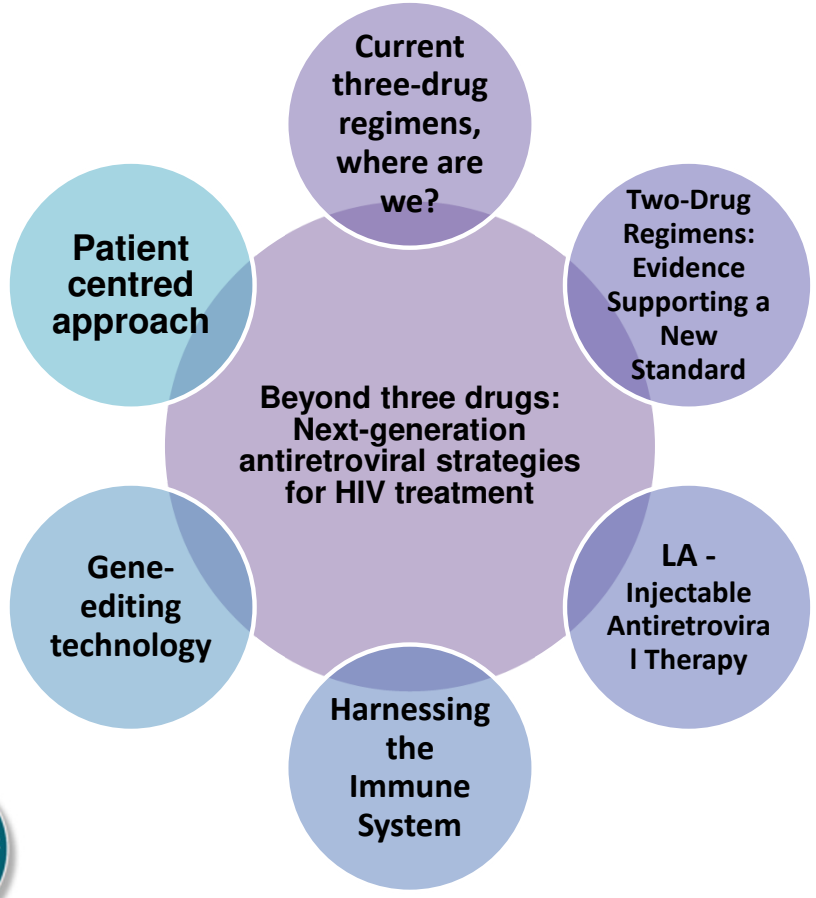
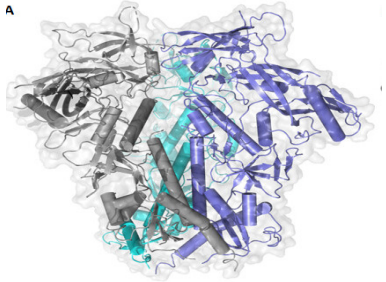
University of the Western Cape

Beyond three drugs . . .





Local HIV Epidemic and statistics

7.9 million PLWH

70.7 % on ART; AVLS 91,4%

KZN	FS	MP	EC	NW	GP	NC	LP	WC
78.8 % on ART	75.6% on ART	75.2% on ART	70.2 on ART	68.1% on ART	66.2% on ART	66.0% on ART	62.7% on ART	61.1% on ART
93.7% AVLS	93.4% AVLS	93% AVLS	92.9% AVLS	91.9% AVLS	91.8% AVLS	91.5% AVLS	90.5% AVLS	84.4% AVLS
73.8% CVLS	81.2% CVLS	66.5% CVLS	62.4% CVLS	62.3% CVLS	65.6% CVLS	20% CVLS	57.6% CVLS	52.2% CVLS

- Number of new infections are high – 230 000
- Highest number of new infections in women
- HIV-related deaths are a concern
- In eThekwini Municipality, 3.9 million PLWH have access to ART and are in follow-up

HST. District Health Barometer 2023/24. Durban: Health Systems Trust; . Westville, Durban, South Africa; 2025 March 2025 .

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

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Why was the historical three-drug combination effective?

- High viral replication
- Rapid mutation
- Low genetic barrier of early drugs ⟶ Combination ART
- Modern ART has changed the equation: Highly potent INSTIs (dolutegravir / bictegravir)

  High genetic barrier

  Improved pharmacokinetics

  Better tolerability

  More durable suppression

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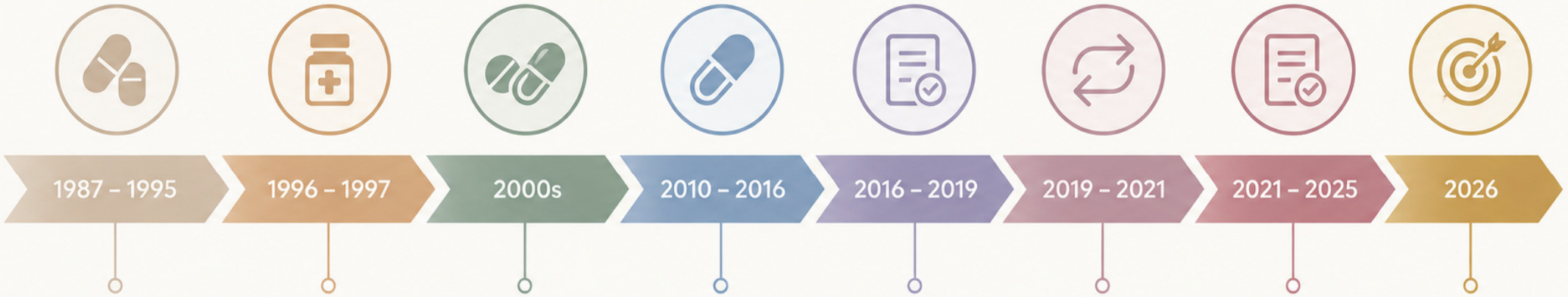
The Evolution of Two-Drug ART

FROM EARLY CONCEPTS TO GLOBAL GUIDELINES



1987 – 1995

Early monotherapy and dual-NRTI therapy

Zidovudine(AZT)
AZT + ddI
AZT + ddC
AZT + 3TC

1996 – 1997

The HAART era

Two NRTIs + a third active drug
TDF/3TC + EFV
TDF/3TC + DTG.

2000s

The first modern dual-maintenance concepts

Boosted PI + lamivudine
DRV/r + 3TC
INSTI + NNRTI,
DTG + RPV.

2010 – 2016

Dolutegravir + rilpivirine becomes a major proof of concept

SWORD-1 and SWORD-2 trials

2016 – 2019

DTG/3TC moves from concept to first-line evidence

GEMINI-1 and GEMINI-2 Trials
*Dovato

2019 – 2021

Switch trials establish treatment simplification

TANGO:
TAF to DTG/3TC
SALSA:
3 or 4 drug regimen to DTG/3TC

2021 – 2025

Two-drug ART becomes incorporated into major guidelines

DTG/3TC
DTG/RPV
Boosted PI + 3TC

2026

The current position

In South Africa:
TLD remains
*DTG/3TC under recommendation

Can we achieve the same virological outcomes with fewer drugs and what is the scientific rationale?

First, modern antiretroviral agents have much greater antiviral potency than earlier drugs.

Second, improved pharmacokinetics allow more consistent drug exposure throughout the dosing interval.

Third, integrase inhibitors exhibit high resistance barriers, meaning multiple mutations are generally required before clinically significant resistance develops.

Fourth, long-term stable viral suppression may no longer require lifelong exposure to three fully **active** drugs → reduced drug exposure → reduced adverse effects.

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Two-Drug Regimens: Evidence Supporting a *"New Standard of Care"*

Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment–Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials
Pedro Cahn et al.

IDSA
Infectious Diseases Society of America

Efficacy and Safety of Switching to Dolutegravir/Lamivudine Fixed-Dose 2-Drug Regimen vs Continuing a Tenofovir Alafenamide–Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults Living With Human Immunodeficiency Virus Type 1: Phase 3, Randomized, Noninferiority TANGO Study
Jean van Wyk et al

Patient-Reported Outcomes After Switching to a 2-Drug Regimen of Fixed-Dose Combination Dolutegravir/Lamivudine: 48-Week Results from the SALSA Study
Princy Kumar et al

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Two-drug combined oral regimens in a South African context

- Not yet SOC, used under recommendation
- Formal guideline required for a South African context
- Hepatitis B concern in the absence of TDF: WHO's position is more cautious than the US or European regulatory position.
- 2025 WHO recommendation supports DTG + 3TC for treatment simplification in adults and adolescents with undetectable viral load on three-drug ART and **without active HBV**.
- Aging population with HIV may benefit (bone density / renal impairment / metabolic benefits)
- Cost effectiveness
- Possible alternative treatment in the face of TLD stock shortages

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Comparative analysis of TLD vs DTG/3TC for a Southern African context

Feature	TLD	DTG/3TC
Number of drugs	3	2
Classes	NRTI+NRTI+INSTI	NRTI+INSTI
HBV activity	Yes	No, not adequate alone
Initial treatment	Broadly suitable SOC	Selective patients
Switching suppressed patients	Effective	Evidence for simplification
Resistance barrier	Strong overall	DTG high barrier, 3TC low barrier
Renal/bone considerations	TDF – problematic	Better outcomes
TB/Rifampicin	DTG dose adjustment, FDC, problematic	
Cost & availability	Well established in SA	Limited
Programme suitability	Excellent	Requires guideline development
Main clinical advantage	Robust, scalable, HBV active	TDF sparing, simplified treatment
Clinical limitations	TDF renal/bone disease	HBV, resistance, eligibility

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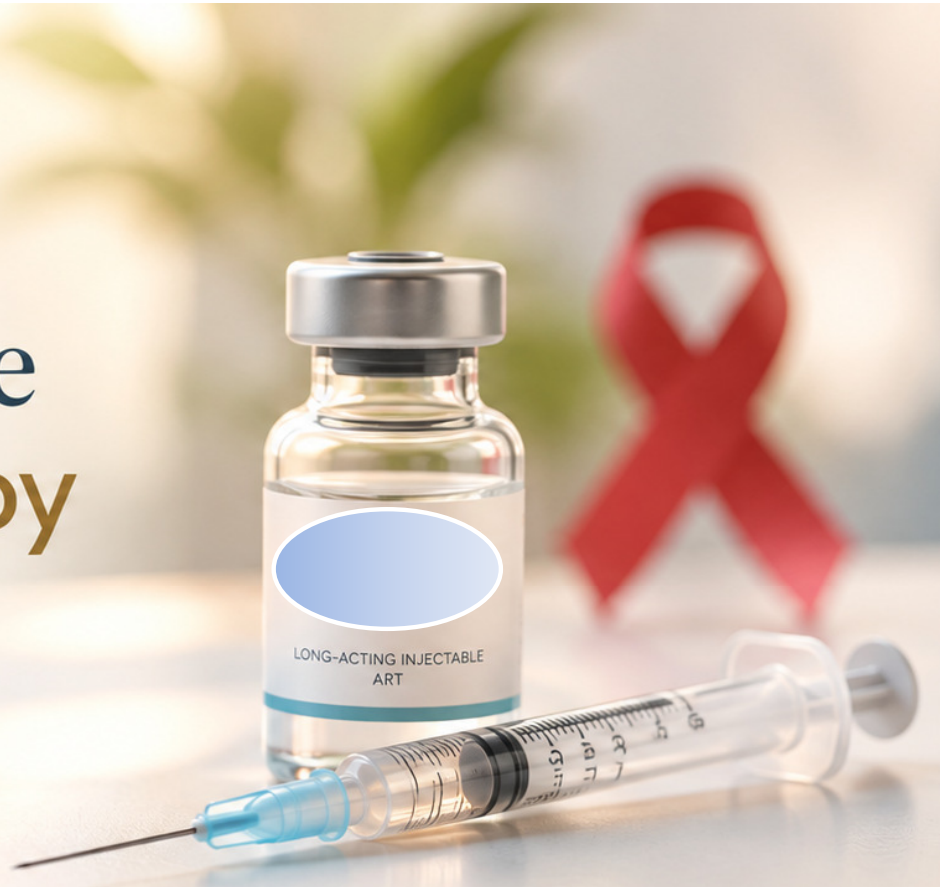
Long-Acting Injectable Antiretroviral Therapy

LONGER ACTING • SIMPLER • BRIGHTER FUTURES



LESS FREQUENT DOSING

IMPROVED ADHERENCE

BETTER OUTCOMES

Why should we consider LA-ART?

The clinical problem:

- Daily oral ART is highly effective, but daily pill-taking is not equally feasible for everyone.
- Treatment may be affected by:
- Forgetting doses
- Pill fatigue
- Stigma and fear of disclosure
- Unstable housing or mobility
- Depression, substance use, or competing priorities
- Difficulty engaging consistently with healthcare
- Some patients remain at risk of viraemia despite access to effective oral regimens.

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Long-acting injectable ART: what does the evidence say?

THE LANCET HIV

Initiation of long-acting cabotegravir plus rilpivirine as direct-to-injection or with an oral lead-in in adults with HIV-1 infection: week 124 results of the open-label phase 3 FLAIR study
Prof Chloe Orkin et al; 2021

Clinical Infectious Diseases

Long-Acting Cabotegravir and Rilpivirine Dosed Every 2 Months in Adults With Human Immunodeficiency Virus 1 Type 1 Infection: 152-Week Results From ATLAS-2M, a Randomized, Open-Label, Phase 3b, Noninferiority Study
Edgar T Overton et al; 2023

Efficacy and Safety of Long-acting Injectable Cabotegravir and Rilpivirine in Improving HIV-1 Control in sub-Saharan Africa: Protocol for a Phase 3b Open-Label Randomized Controlled Trial (IMPALA)
Victoria Babirye Tumusiime et al; 2025

nature medicine

Cabotegravir and rilpivirine for treatment of HIV infection in Africa: week 96 results from the phase 3b randomized, open-label, noninferiority CARES trial
Cissy Kityo et al; 2025

Subcutaneous Lenacapavir in People With Multidrug-Resistant HIV-1: 156 Week Results of the CAPELLA Study
Onyema Ogbuagu et al; 2025

Eligibility and implementation concerns from clinical trials

ELIGIBILITY

- Hepatitis B infection / reinfection
- TB co-infection
- NNRTI resistance (except for K103N)
- Estimated creatinine clearance <50 mL/minute (min)/1.73 meter square (m^2)
- History of mono HIV-1 therapy (including peri-partum period)
- Hepatic impairment (cirrhosis)
- Risk of seizures (carbamazepine/phenytoin)
- Pregnancy

IMPLEMENTATION

- Long pharmacokinetic-tail
- Nursing time for injection administration
- Hepatitis B vaccination
- Oral bridging(missed visits)

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Potential benefits in Sub-Saharan Africa

- Reduced daily pill burden
- Potentially improved discretion and treatment satisfaction
- Overcomes drug holidays (transient viraemia risk)
- Alternative for selected patients with difficulty sustaining oral ART
- Reduced exposure to tenofovir in appropriate CAB/RPV candidates
- Differentiated service delivery through scheduled injection visits.
- Opportunity to integrate ART delivery with other chronic-care services.
- Improved treatment experience for patients who prefer injections.

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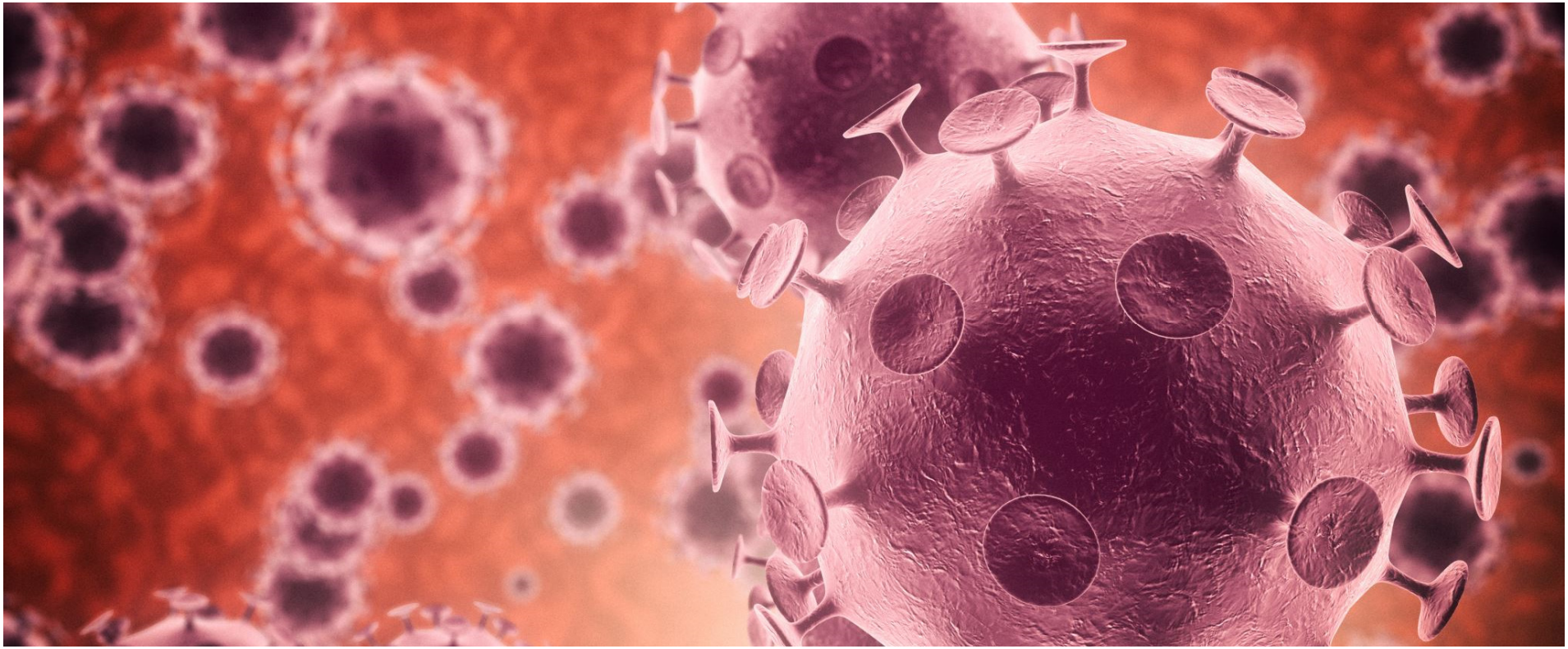
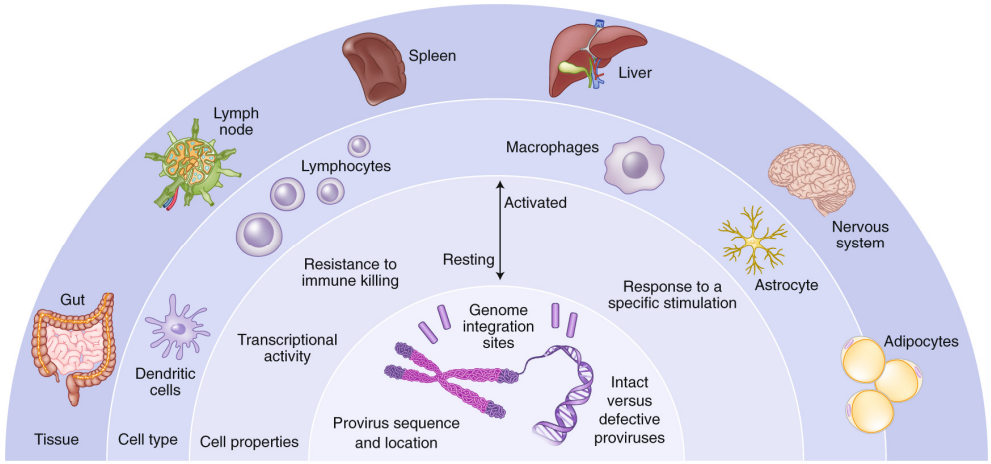
Harnessing the Immune System



The “HIV reservoir”

- Group of immune system cells in the body that are infected with HIV but are **not actively producing new virus particles**.
- Some CD4 cells with HIV go into a **latent state** and do not produce new virus particles or viral products.
- HIV can hide inside these cells for years, forming a **latent HIV reservoir**.
- Cells in the latent reservoir can become **active again at any time and start making more virus particles**.
- **ART does NOT target the HIV reservoir.**



Landscape of the HIV reservoir

Ref: Deeks, S.G., Archin, N., Cannon, P. *et al.* Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021. *Nat Med* **27**, 2085–2098 (2021).

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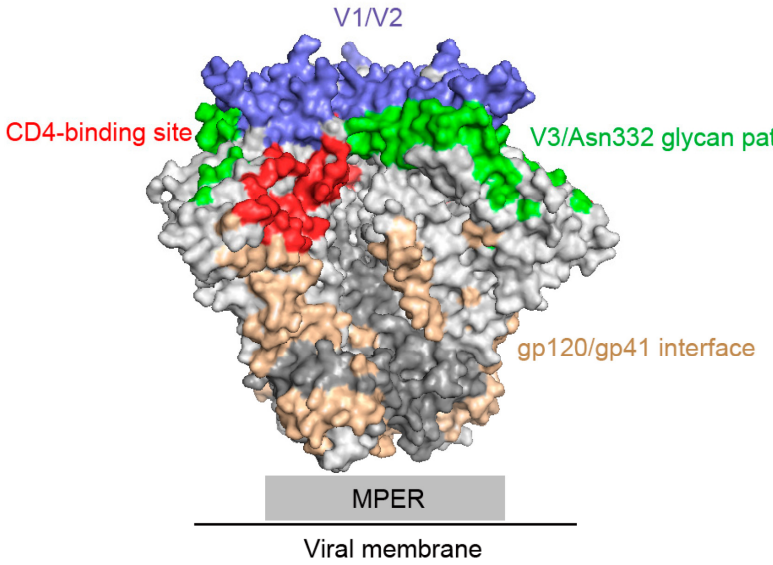
Broadly Neutralising Antibodies for therapeutic HIV intervention and cure

What exactly is a bNAb?

- An antibody which recognizes a “conserved” part of the HIV envelope and can neutralize it.
- Ab’s generated following HIV acquisition are strain-specific.
- The virus, changes its envelope continuously → escape from antibody responses.



CD4-binding site
b12, VRC01, VRC07, NIH45-46, 3BNC117, VRC-PG04

V1/V2
PG9, PG16, CH01-04, PGT141-145, PGDM1400

V3/Asn332 glycan patch
PGT121-123, PGT125-131, PGT135, 10-1074, 2G12

gp120/gp41-interface
PGT151, 35O22, 8ANC195

MPER
2F5, 4E10, 10E8

Ref: Zhang, Z., Li, S., Gu, Y., & Xia, N. (2016). Antiviral Therapy by HIV-1 Broadly Neutralizing and Inhibitory Antibodies. International Journal of Molecular Sciences, 17(11), 1901. https://doi.org/10.3390/ijms17111901

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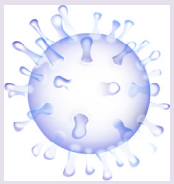
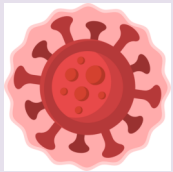
The Evolution of bNAbs



1990's

Early bNAb discovery



2009 - 2011

Target site ID

- VRC01 – CD4 binding site
- 3BNC117 – CD4 binding site
- 10-1074- V3 glycan
- PGT121 –V3 glycan
- CAP 256V2 – V2 apex

2012 - 2014

South Africa (CAP 002)

CAP 256

CAP 256V2

CAP256V2LS

2017- 2019

Therapeutic cocktail

3BNC117

+

10-1074

*baseline viral resistance

2023

LA –bNAbs

CAP 012 C trial

(prevention)

CAP256V2LS
3BNC117-LS
VRC07-523LS
10-1074-LS

2024 - 2025

Teatment & cure research

CAP 095 (NeutART)

CAP 079 (RENEW-CAP)

HVTN 806

2026

bNAbs + Lenacapavir

LEN
+
3BNC117-LS
+10-1074-LS

Limitations and next steps for therapeutic bNAb and vaccine intervention

- **Pre-existing viral resistance against bNAbs**
- **High bNAb concentrations required over a long period of time**
- **HIV subtype diversity**
- **Trial phase**
- **Cost of manufacture**
- **Next generations bNAbs:** greater breadth, longer half-life, improved tissue penetration, combined resistance pathway coverage, HIV-1 subtypes
- **Independent epitope targeting:** 3BNC117 and 10-1074
- **Combination cure therapy**

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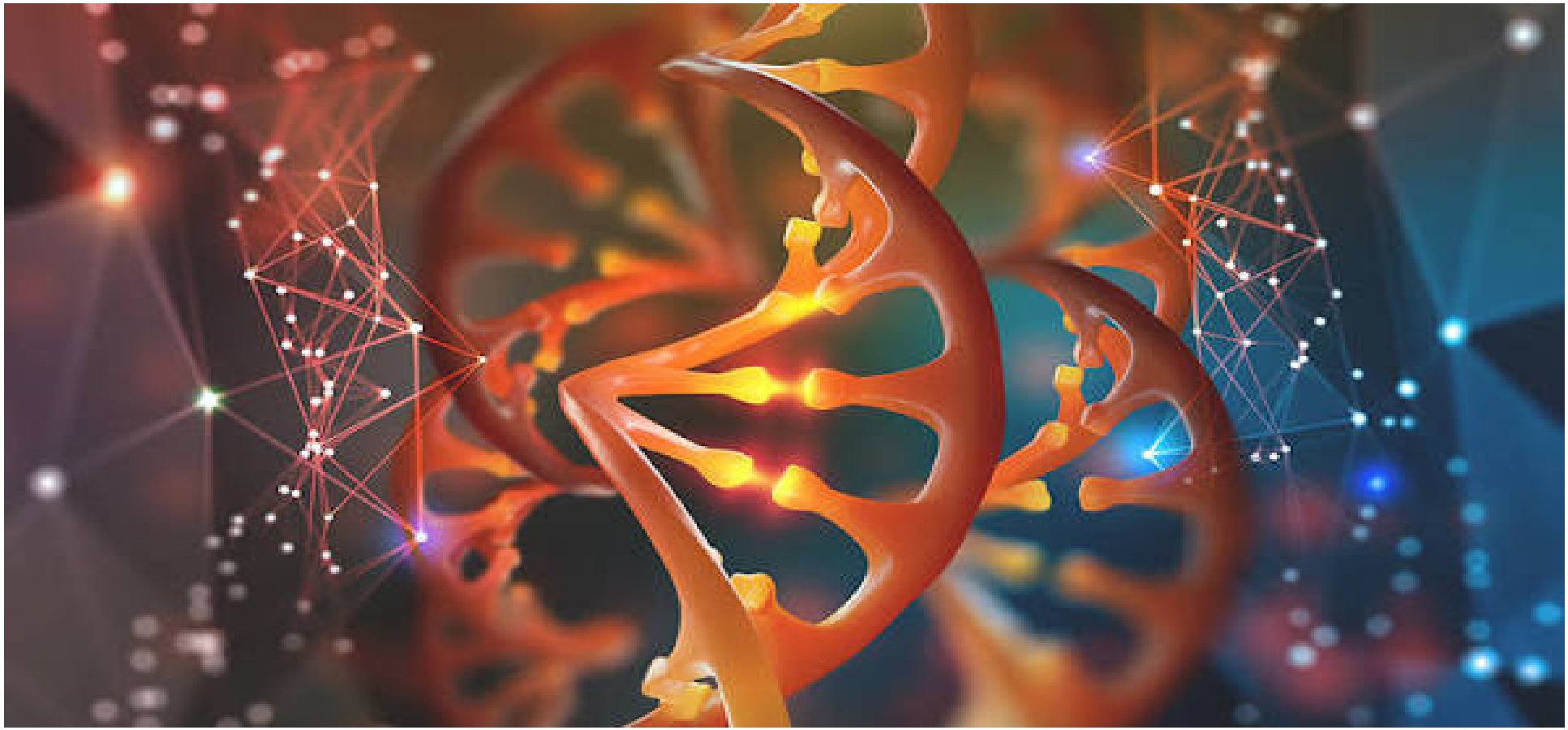
Gene editing technology in HIV cure



Gene editing

- Chronic HIV infection is associated with T-cell exhaustion, causing increased expression of inhibitory receptors such as PD-1 on HIV-specific CD4+ and CD8+ T cells.
- By reversing immune exhaustion, checkpoint inhibitors may restore antiviral immune function and potentially contribute to long-term viral control.
- Current antiretroviral therapy effectively suppresses viral replication but cannot eliminate the latent viral reservoir.
- HIV reservoir: eliminating or permanently controlling this reservoir remains the greatest challenge in HIV cure research.
- Gene-editing technologies such as CRISPR-Cas9 are being investigated to directly excise integrated HIV proviral DNA from infected cells or to modify host genes required for viral entry.

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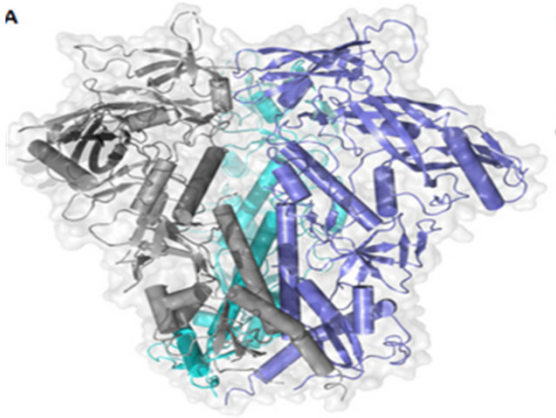
Current clinical trial evidence

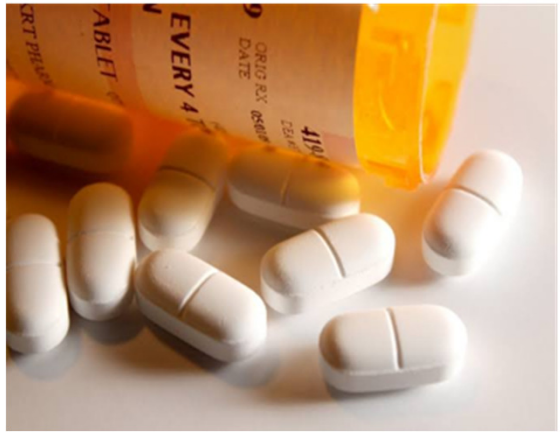
Summary of selected clinical and preclinical trials involving gene therapy approaches for HIV treatment.

Trial Title	Gene therapy type	Phase	Status	Key results	NCT Number / reference
Safety of CCR5 Gene-Edited Autologous CD4 + T Cells in HIV	ZFN-mediated CCR5 disruption	Phase I/II	Completed	Safe with partial HIV control in some patients	NCT00842634
Evaluation of Lentiviral Vector Modified T Cells (Cal-1)	Lentiviral vector (CCR5-RNAi + C46 fusion inhibitor)	Phase I	Completed	Cells persisted long-term; well tolerated	NCT01734850
CRISPR CCR5-modified HSPC[1] Transplant in HIV/AML Patient	CRISPR/Cas9 (CCR5 knockout in HSPCs)	Case Study	Completed	Partial HIV suppression, not cured due to low editing	37
Zinc Finger CCR5 T Cell Infusion for HIV	ZFN-modified CCR5 T cells	Phase I	Completed	Functional HIV control in some participants	NCT01252641
Lentiviral Vector Transduced CD4 + T Cells (AGT103-T)	Lentivirus expressing antisense genes	Phase I	Ongoing	Early data suggest HIV suppression	NCT03215004
DermaVir Patch: Nanoparticle-Based Therapeutic Vaccine	DNA plasmid nanoparticles targeting dendritic cells	Phase II	Completed	Induced long-term memory T cell responses; reduced HIV load in reservoirs	PMC4910962
OZ1: Ribozyme Gene Therapy in CD34 + Cells	Anti-HIV ribozyme delivered to autologous CD34 + cells	Phase II	Completed	Induced long-term memory T cell responses; reduced HIV load in reservoirs	PMC4910962

Ref: Maryam Fattahi et al. Next-generation gene therapy for infectious disease: Advances, challenges, and future directions, Journal of Infection and Public Health,Volume 19, Issue 4, 2026

Patient centered Approach





The right treatment for the right patient:

“What is the best regimen for the individual sitting in front of me?”

- Individualized, longer-acting, integrated HIV treatment options
- Personalised treatment options: age, comorbidities, lifestyle, reporoductive/family planning, preference, drug-drug interactions
- Resistance profiling
- The question?

??Rather than asking whether a regimen is superior overall, we may ask which regimen is most appropriate for a specific individual.

This represents a fundamental shift in HIV medicine from standardized treatment toward truly personalized care.

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“Beyond three drugs”

- For nearly thirty years, success was defined by suppressing viral replication through lifelong daily triple therapy.
- Today, success also includes reducing treatment burden, minimizing toxicity, improving quality of life, supporting healthy ageing, and empowering patients with treatment choices that align with their individual lives.
- Two-drug regimens have demonstrated that less can indeed be more for carefully selected patients.
- Long-acting injectable therapies have shown that daily treatment is no longer the only effective option. Weekly oral regimens promise to further simplify therapy.
- Broadly neutralizing antibodies introduce entirely new mechanisms for controlling HIV through immune modulation.
- Gene editing, therapeutic vaccines, and reservoir-targeting strategies remind us that the pursuit of a functional cure continues.
- As clinicians and researchers, we have the privilege of witnessing and contributing to one of the most exciting periods in the history of HIV medicine.

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Final Take-Home Messages

- Triple-drug ART remains the standard for many patients, but it is no longer the only effective strategy.
- Evidence from landmark trials supports two-drug regimens in carefully selected individuals, with efficacy comparable to three-drug therapy.
- Long-acting oral and injectable ART is transforming adherence and patient experience by reducing dosing frequency from daily to every two months, with even longer intervals on the horizon.

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